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Original Communication

Negative Association between Vitamin E Intake and Remnant Cholesterol: The National Health and Nutrition Examination Survey 2007–2020

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Abstract

Background: Remnant cholesterol (RC) is a risk factor for the development of atherosclerosis. Vitamin E has antioxidant properties, making it a potentially effective management tool for preventing cardiovascular disease (CVD). However, the relationship between vitamin E intake and RC remains unclear. **Methods:** We conducted a cross-sectional study using data from the National Health and Nutrition Examination Survey (NHANES) Survey 2007–2020. 11,585 participants (aged ≥20, 48% male) were included. Information on vitamin E intake (dietary vitamin E intake and total vitamin E intake) was collected. RC was defined as serum total cholesterol minus high-density lipoprotein and low-density lipoprotein cholesterol. Survey-weighted linear regression models and a restricted cubic spline (RCS) were used to test the relationship between vitamin E intake and RC. Subgroup analyses and interaction tests were also performed to verify the robustness of the results. **Results:** After adjusting for all potential confounders (demographics, socioeconomic status, lifestyle, diet, and comorbidities), dietary vitamin E intake was negatively associated with RC (β = –0.21, 95% CI: (–0.29, –0.12), $p < 0.0001$), and this negative association was also present between total vitamin E intake and RC (β = –0.12, 95% CI: (–0.18, –0.06), $p < 0.0001$). The RCS analysis revealed a nonlinear negative association between vitamin E intake and RC. The negative correlation existed in different subgroups, with no interaction except for the "use of vitamin E supplements" subgroup. **Conclusion**: Vitamin E intake showed a protective association with RC. The results suggest that increasing dietary vitamin E intake may help reduce RC levels and CVD risk.

Keywords: remnant cholesterol; cardiovascular disease; vitamin E; cross-sectional study; NHANES

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death globally, causing approximately 19.8 million deaths worldwide in 2022 [1]. According to a report from the American Heart Association in 2019, 48% (about 121.5 million) of adults in the United States (US) suffer from cardiovascular disease (including coronary heart disease, heart failure, stroke or hypertension) [2]. In recent years, remnant cholesterol (RC) has been recognized as a direct factor in the development of atherosclerosis. Elshazly *et al.* [3] reported that RC, compared with serum low-density lipoprotein cholesterol (LDL-C), correlated more significantly with the progression of coronary atherosclerosis in statin-treated patients. Moreover, high levels of RC, but not serum LDL-C, were associated with increased all-cause mortality in patients with ischaemic heart disease [4]. RC is a triglyceride-rich lipoprotein cholesterol that consists of serum very low-density lipoprotein cholesterol in the fasting state, intermediate-density lipoprotein cholesterol, and cholesterol in the celiac residue in the postprandial state [5]. As an independent lipid risk marker, RC has been suggested as a therapeutic target for the clinical development of novel anti-atherosclerotic drugs and CVD prevention [3,6].

To date, no guidelines or consensus exists on reducing RC levels. Despite achieving desirable serum LDL-C levels, intensive lipid-lowering therapy does not eliminate the residual risk of recurrent atherosclerotic cardiovascular events [7,8]. Several international lipid management and treatment guidelines recognize the importance of diet and lifestyle in CVD prevention [9,10]. Thus, early management of CVD by preventing and treating risk factors through behavioral changes (i.e., weight management, healthy diet, physical activity, and smoking cessation) is essential to reduce the risk of developing CVD [11,12]. Lipid peroxidation is central to the pathogenesis of CVD [13], and vitamin E has anti-inflammatory and antioxidant properties.

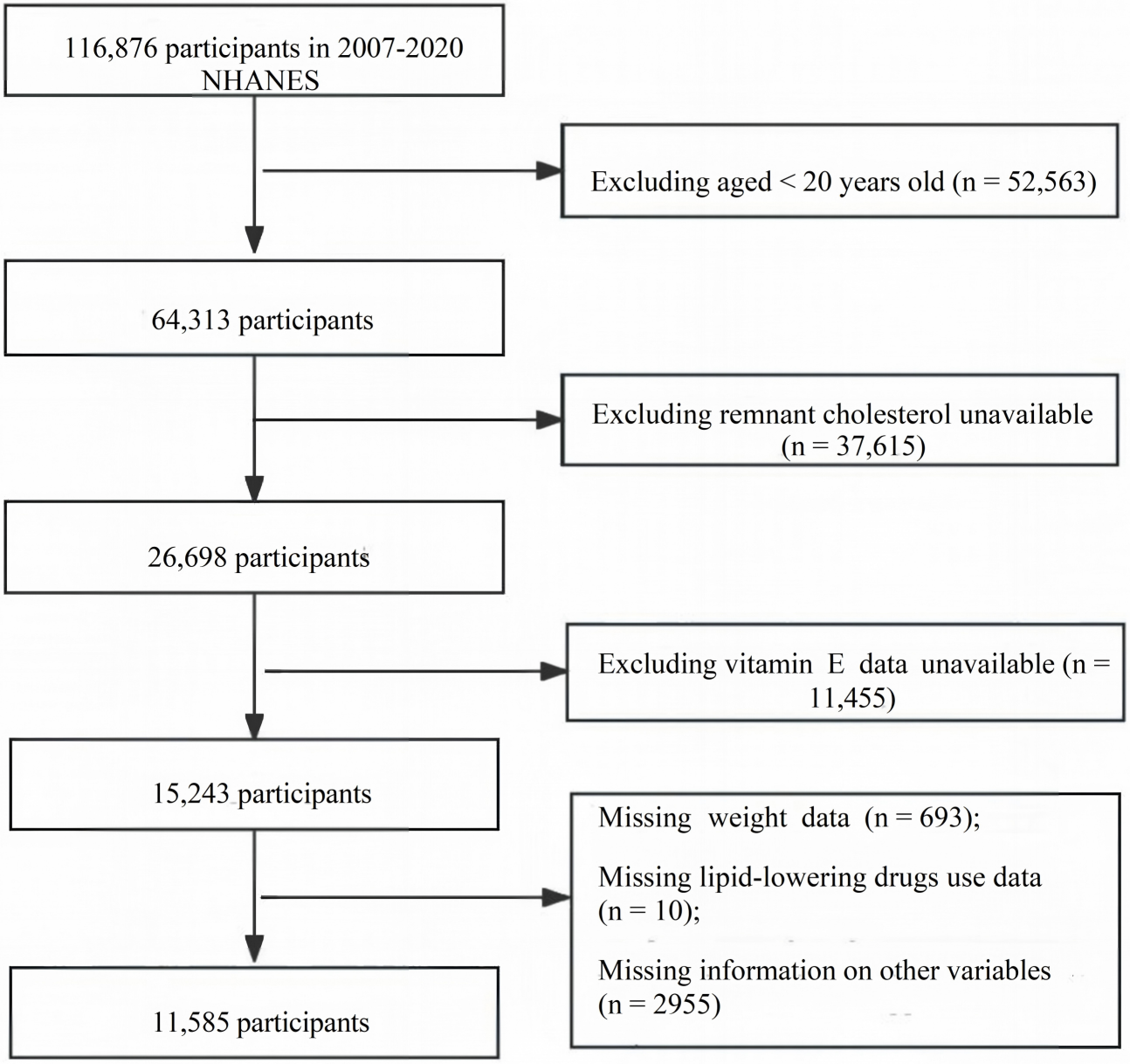

Fig. 1. Flowchart of the standard for participants enrolled in the study.

Therefore, dietary vitamin E may be an effective management strategy for preventing CVD.

Vitamin E includes tocopherols and tocotrienols, both of which have four isomers: α, β, γ, and δ. Among these, α-tocopherol is the predominant form. Vitamin E is a potent fat-soluble antioxidant derived primarily from nuts, vegetable oils, olives, wheat germ, and green leafy vegetables [14]. Epidemiological studies have shown that vitamin E intake protects against nonalcoholic fatty liver disease, hyperuricemia, cognitive dysfunction, depression, and persistent high-risk human papillomavirus infection [15–19]. A cohort study showed that dietary vitamin E intake was inversely associated with CVD risk [20]. However, this study did not consider the effects of factors such as supplement intake, socioeconomic level, ethnicity, and comorbidities. Moreover, large epidemiological studies that comprehensively investigate the association between dietary vitamin E levels and RC are lacking. To fill these gaps, we investigated the relationship between vitamin E intake and RC among adults in the US.

2. Materials and Methods

Participants

The National Health and Nutrition Examination Survey (NHANES) is a large epidemiological survey database administered by the National Center for Health Statistics (NCHS) dedicated to investigating the nutritional and health status of US citizens. The survey utilized a multistage sampling design and collected data every two years.

In this cross-sectional study, we use publicly available data for seven cycles: 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016, 2017–2018, and 2019–2020. The study included 116,876 potential participants. Participants under 20 years of age (n = 52,563), lacking RC data (n = 37,615), and deficient in vitamin E intake (n = 11,455) were excluded. Participants with missing weights were excluded (n = 693). Participants with incomplete data were excluded (n = 2965). A total of 11,585 participants aged ≥20 years were ultimately included, the details of which are presented in Fig. 1.

3. Variables

3.1 Assessment of Vitamin E Intake

Participants' dietary consumption, including food composition, nutrient content, and caloric intake, was calculated according to the study protocol. The diet interview was conducted with the United States Department of Agriculture and the United States Department of Health and Human Services (DHHS). DHHS's National Center for Health Statistics is responsible for sample design and data collection; and the US Department of Agriculture's Dietary Research Food and Nutrition Database is used to encode individual foods and portion sizes reported by participants, process data, and calculate the nutritional value of nutritional intake. The staff is professionally trained and the data is reviewed to ensure quality. Data is collected every 2 years. The dietary interviews were conducted in two sessions. The first interview was conducted face-to-face, and the second was conducted by phone 3-10 days later. Dietary vitamin E intake could only be derived from food intake data and did not include supplemental use. According to previously published literature [15,19], 24-hour dietary vitamin E intake and vitamin E supplements were calculated by averaging two 24-hour dietary recall interviews, and total vitamin E intake equaled the sum of dietary vitamin E and vitamin E supplements. The detailed data processing and calculation methods are publicly available at https://wwwn.cdc.gov/Nchs/Data/Nhanes/Public/2007/DataFiles/dr1tot_e.htm#DR1TATOC.

3.2 Assessment of RC

According to previous studies [21–23], RC levels were calculated as serum total cholesterol (TC) minus high-density lipoprotein cholesterol (HDL-C) and LDL-C. The Friedewald equation was used to calculate serum LDL-C as recommended by the guidelines [11].

3.3 Covariates

Based on previously published literature [15,16,19], we collected potential covariates which included demographics, socioeconomic status, lifestyle, diet, and comorbidities. Demographics included sex, age, and race. The socioeconomic factors included education level, marriage status, body mass index (BMI), and family income-poverty ratio (PIR). PIR was categorized as <1, 1–3, or ≥3. Lifestyle factors included smoking, alcohol consumption, and recreational activities. The dietary factors included dietary inflammatory index (DII), use of vitamin E supplements, dietary vitamin C intake, dietary fiber intake, total energy intake, and whether lipid-lowering medications were taken. The DII is a scoring system used to assess the potential level of inflammation associated with dietary components [24]. Our study used 28 nutrients to calculate the DII score. Supplemental use was examined based on responses to the question, "Any Dietary Supplements Taken?" It was recorded as "No" or "Yes". Dietary vitamin C intake, dietary fiber intake, and total energy intake were estimated from the mean of two 24-hour dietary recall interviews. The comorbidities included hypertension, diabetes mellitus (DM), and CVD. The detailed categorization is presented in Table 1. Other detailed assessment approaches are shown in the **Supplementary Material.**

3.4 Statistical Analysis

We weighted the data using sampling weights (WTSA2YR) to represent US citizens nationally. Categorical variables are presented as counts (weighted percentages) and were analyzed using survey-weighted chi-square tests. Continuous variables are displayed as weighted means (standard errors) and were analyzed using weighted one-way ANOVA. Weighted linear regression models were used to analyze the association between vitamin E intake and RC. Three models were developed. Model 1 did not adjust for covariates. Model 2 was adjusted for age, sex, and race. Model 3 was adjusted for age, sex, race, education, marriage status, BMI, PIR, smoking status, alcohol consumption, recreational activity, use of vitamin E supplements, lipid-lowering drug use, DII, total energy intake, vitamin C intake, dietary fiber intake, hypertension, CVD, and DM. We examined the dose-response relationships between dietary and total vitamin E and RC concentrations using a restricted cubic spline (RCS). In addition, we performed subgroup analyses and interaction tests. All analysis steps were performed using the R software package (version 4.2.2, http://www.R-project.org). p-values < 0.05 were considered to indicate statistical significance.

4. Results

The baseline characteristics of all participants are presented in Table 1. The percentage of participants with obesity, comorbid hypertension, DM, and CVD were 37.99%, 37.13%, 15.50%, and 8.89%, respectively. Those with higher levels of RC tended to have the following characteristics compared to those with lower RC: greater prevalence at 40–60 years of age, greater prevalence of male sex, obesity, comorbid hypertension, DM, and CVD; and lower proportions of participation in recreational activities. It showed that dietary vitamin E intake (8.72 mg/day) and total vitamin E intake (9.49 mg/day) are below the estimated average requirement (12 mg/day) [25].

Table 1. Features of the study population, weighted (n = 11,585).

Variables	Total	Q1 [2, 15]	Q2 (15, 25]	Q3 (25, 80]	*p*-value
Age (years), n (%)					<0.0001
<40	3701 (35.61)	1661 (46.14)	1116 (32.52)	924 (27.63)	
40–60	3949 (37.37)	1202 (32.35)	1373 (38.01)	1374 (42.07)	
≥60	3935 (27.02)	1036 (21.50)	1541 (29.47)	1358 (30.30)	
Gender, n (%)					<0.0001
Female	6021 (51.86)	2283 (58.38)	2055 (51.63)	1683 (45.13)	
Male	5564 (48.14)	1616 (41.62)	1975 (48.37)	1973 (54.87)	
Race, n (%)					<0.0001
Non-Hispanic Black	2370 (10.59)	1192 (16.18)	796 (9.92)	382 (5.34)	
Non-Hispanic White	5148 (69.71)	1544 (65.95)	1810 (70.70)	1794 (72.68)	
Mexican American	1616 (7.61)	368 (5.82)	588 (7.72)	660 (9.41)	
Other Hispanic	1137 (5.11)	304 (4.72)	414 (5.27)	419 (5.35)	
Other Race	1314 (6.98)	491 (7.33)	422 (6.39)	401 (7.23)	
Education level, n (%)					<0.0001
<High School	2317 (13.22)	563 (9.47)	843 (14.19)	911 (16.20)	
High School	2623 (22.85)	814 (20.02)	935 (23.66)	874 (25.01)	
>High School	6645 (63.93)	2522 (70.51)	2252 (62.15)	1871 (58.79)	
Marital status, n (%)					<0.0001
Never married	2066 (17.87)	953 (22.92)	634 (16.42)	479 (14.00)	
Married/Living with a partner	7008 (64.27)	2208 (61.74)	2463 (64.75)	2337 (66.46)	
Widowed/Divorced/Separated	2511 (17.86)	738 (15.34)	933 (18.83)	840 (19.53)	
PIR, n (%)					0.01
<1	2186 (12.76)	684 (12.14)	775 (13.21)	727 (12.96)	
1–3	4860 (35.50)	1571 (33.17)	1679 (36.09)	1610 (37.38)	
≥3	4539 (51.73)	1644 (54.70)	1576 (50.70)	1319 (49.66)	
BMI (kg/m^2), n (%)					<0.0001
<25	3217 (29.38)	1619 (45.32)	1028 (26.58)	570 (15.28)	
25–30	3783 (32.63)	1166 (29.71)	1406 (35.87)	1211 (32.28)	
≥30	4585 (37.99)	1114 (24.97)	1596 (37.54)	1875 (52.44)	
Smoke status, n (%)					<0.0001
Former	2884 (25.84)	846 (23.35)	1008 (25.57)	1030 (28.80)	
Never	6531 (56.61)	2455 (62.65)	2262 (56.52)	1814 (50.23)	
Now	2170 (17.55)	598 (13.99)	760 (17.90)	812 (20.98)	
Alcohol consumption, n (%)					<0.001
No	2952 (20.98)	869 (18.21)	1047 (22.13)	1036 (22.69)	
Yes	8633 (79.02)	3030 (81.79)	2983 (77.87)	2620 (77.31)	
Lipid-lowering drugs, n (%)					<0.0001
No	9036 (79.99)	3295 (86.26)	3086 (79.36)	2655 (73.96)	
Yes	2549 (20.01)	604 (13.74)	944 (20.64)	1001 (26.04)	
Recreational activity, n (%)					<0.0001
No	5757 (43.93)	1651 (36.22)	2072 (45.75)	2034 (50.24)	
Yes	5828 (56.07)	2248 (63.78)	1958 (54.25)	1622 (49.76)	
Hypertension, n (%)					<0.0001
No	6735 (62.87)	2640 (74.32)	2284 (61.49)	1811 (52.08)	
Yes	4850 (37.13)	1259 (25.68)	1746 (38.51)	1845 (47.92)	
DM, n (%)					<0.0001
No	7120 (67.39)	2986 (81.65)	2441 (67.37)	1693 (52.11)	
Borderline	2053 (17.11)	477 (10.97)	741 (18.04)	835 (22.70)	
Yes	2412 (15.50)	436 (7.38)	848 (14.58)	1128 (25.19)	
CVD, n (%)					<0.0001
No	10,307 (91.11)	3580 (94.02)	3552 (91.04)	3175 (88.07)	
Yes	1278 (8.89)	319 (5.98)	478 (8.96)	481 (11.93)	

Table 1. Continued.

Variables	Total	Q1 [2, 15]	Q2 (15, 25]	Q3 (25, 80]	*p*-value
Use of vitamin E supplements, n (%)					<0.001
No	9565 (81.13)	3133 (78.31)	3362 (82.05)	3070 (83.17)	
Yes	2020 (18.87)	766 (21.69)	668 (17.95)	586 (16.83)	
Dietary vitamin E intake (mg/day)	8.72 (0.08)	9.48 (0.14)	8.38 (0.12)	8.28 (0.13)	<0.0001
Total vitamin E intake (mg/day)	9.49 (0.11)	10.38 (0.20)	9.12 (0.17)	8.93 (0.16)	<0.0001
Fast triglyceride (mg/dL)	113.81 (1.00)	56.36 (0.33)	100.28 (0.32)	189.94 (1.64)	<0.0001
Fast total cholesterol (mg/dL)	190.74 (0.59)	176.02 (0.83)	191.21 (0.83)	206.02 (0.92)	<0.0001
HDL-C (mg/dL)	54.53 (0.25)	62.79 (0.41)	54.43 (0.32)	45.79 (0.31)	<0.0001
LDL-C (mg/dL)	113.45 (0.46)	101.98 (0.70)	116.72 (0.68)	122.24 (0.80)	<0.0001
DII	1.42 (0.04)	1.26 (0.05)	1.52 (0.05)	1.48 (0.05)	<0.0001
Dietary vitamin C intake (g/day)	78.76 (1.14)	82.82 (1.99)	77.01 (1.47)	76.30 (1.43)	0.02
Dietary fiber intake (g/day)	17.13 (0.16)	17.72 (0.27)	16.63 (0.19)	17.03 (0.21)	0.001
Energy intake (kcal/day)	2095.02 (9.61)	2096.27 (14.05)	2076.10 (15.91)	2114.00 (19.88)	0.32

Continuous variables were expressed as weighted mean (standard error), categorical variables as counts (weighted percentage). Abbreviations: n, numbers; PIR, poverty income ratio; BMI, body mass index; DM, diabetes mellitus; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; DII, dietary inflammatory index; RC, remnant cholesterol. Q1–3 respectively represent the groups divided according to the tertiles of remnant cholesterol.

Table 2. Univariate analysis between variables and RC, weighted (n = 11,585).

Variables	β (95% CI)	*p*-value
Age		
<40	ref	ref
40–60	4.30 (3.50, 5.10)	<0.0001
≥60	3.45 (2.62, 4.28)	<0.0001
Gender		
Female	ref	ref
Male	2.77 (2.10, 3.45)	<0.0001
Race		
Non-Hispanic Black	ref	ref
Non-Hispanic White	5.62 (4.91, 6.33)	<0.0001
Mexican American	7.51 (6.33, 8.69)	<0.0001
Other Hispanic	5.48 (4.38, 6.58)	<0.0001
Other Race	5.56 (4.26, 6.86)	<0.0001
Education level		
<High School	ref	ref
High School	–1.42 (–2.34, –0.50)	0.003
>High School	–3.06 (–3.78, –2.33)	<0.0001
Marital status		
Never married	ref	ref
Married/Living with a partner	2.78 (1.90, 3.65)	<0.0001
Widowed/Divorced/Separated	3.25 (2.18, 4.32)	<0.0001
PIR		
<1	ref	ref
1–3	0.10 (–0.78, 0.97)	0.83
≥3	–0.75 (–1.64, 0.14)	0.10
BMI		
<25	ref	ref
25–30	5.85 (5.11, 6.60)	<0.0001
≥30	8.70 (7.98, 9.43)	<0.0001

Table 2. Continued.

Variables	β (95% CI)	p-value
Smoke status		
Former	ref	ref
Never	–2.07 (–2.80, –1.34)	<0.0001
Now	1.19 (0.09, 2.29)	0.03
Alcohol consumption		
No	ref	ref
Yes	–1.05 (–1.68, –0.43)	0.001
Lipid-lowering drugs		
No	ref	ref
Yes	3.74 (2.88, 4.60)	<0.0001
Recreational activity		
No	ref	ref
Yes	–2.92 (–3.54, –2.31)	<0.0001
Hypertension		
No	ref	ref
Yes	5.15 (4.43, 5.87)	<0.0001
DM		
No	ref	ref
Borderline	5.37 (4.52, 6.23)	<0.0001
Yes	8.20 (7.27, 9.13)	<0.0001
CVD		
No	ref	ref
Yes	3.53 (2.39, 4.67)	<0.0001
Use of vitamin E supplements		
No	ref	ref
Yes	–1.90 (–2.72, –1.09)	<0.0001
Dietary vitamin E intake	–0.17 (–0.23, –0.12)	<0.0001
Total vitamin E intake	–0.12 (–0.17, –0.08)	<0.0001
DII	0.18 (–0.01, 0.36)	0.06
Dietary vitamin C intake	0.07 (0.06, 0.08)	0.08
Dietary fiber intake	–0.02 (–0.05, 0.02)	0.30
Energy intake	0.00 (0.00,0.00)	0.14

Abbreviations: RC, remnant cholesterol; PIR, poverty income ratio; BMI, body mass index; DM, diabetes mellitus; CVD, cardiovascular disease; DII, dietary inflammatory index; ref, reference.

Table 2 shows that dietary vitamin E intake and total vitamin E intake were all negatively associated with RC, with β = –0.17, 95% confidence intervals [CI]: (–0.23, –0.12), $p < 0.001$; and β = –0.12, 95% CI: (–0.17, –0.08), $p < 0.001$, respectively.

Table 3 displays the multivariate linear regression relationship between vitamin E intake and RC. In Model 3, the β (95% CI, p) values for the continuous and highest quartiles of dietary vitamin E intake were –0.21 (–0.29, –0.12, $p < 0.0001$) and –3.24 (–4.47, –2.02, $p < 0.0001$) respectively. The p for trend was less than 0.0001. The β (95% CI, p) values for the continuous and highest quartiles of total vitamin E intake were –0.12 (–0.18, –0.06, $p <$ 0.0001) and –3.07 (–4.23, –1.91, $p < 0.0001$), respectively. The p for trend was less than 0.0001.

After adjusting for all potential variables, nonlinear inverse relationships with RC were found to exist in dietary vitamin E intake (Fig. 2A), total vitamin E intake (Fig. 2B), and different subgroups (Fig. 3). There was no interaction between the subgroups except for the "use of vitamin E supplements" subgroup.

5. Discussion

In this cross-sectional study, we assessed the relationship between vitamin E intake and RC. Our findings revealed that vitamin E deficiencies are prevalent among adults in the US aged 20 years or older. The average dietary (8.72 mg/day) and total vitamin E intakes (9.49 mg/day) were lower than the recommended intake (15 mg/day) for adults in the US [26]. Previous studies have yielded similar conclusions. A micronutrient intake survey of 26,282

Table 3. Association between vitamin E intake and RC, weighted (n = 11,585).

	Model 1		Model 2		Model 3	
	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
Dietary vitamin E intake	–0.17 (–0.23, –0.12)	<0.0001	–0.24 (–0.30, –0.18)	<0.0001	–0.21 (–0.29, –0.12)	<0.0001
Categories						
Q1 [0.06, 4.84]	ref	ref	ref	ref	ref	ref
Q2 (4.84, 7.06]	–0.41 (–1.16, 0.35)	0.29	–0.88 (–1.61, –0.14)	0.02	–0.69 (–1.40, 0.02)	0.06
Q3 (7.06, 10.1]	–1.40 (–2.34, –0.45)	0.004	–2.03 (–2.93, –1.13)	<0.0001	–1.97 (–2.94, –1.00)	<0.001
Q4 (10.1, 77.88]	–2.20 (–3.15, –1.24)	<0.0001	–3.39 (–4.30, –2.48)	<0.0001	–3.24 (–4.47, –2.02)	<0.0001
p for trend	<0.0001		<0.0001		<0.0001	
Total vitamin E intake	–0.12 (–0.17, –0.08)	<0.0001	–0.16 (–0.20, –0.12)	<0.0001	–0.12 (–0.18, –0.06)	<0.0001
Categories						
Q1 [0.06, 4.88]	ref	ref	ref	ref	ref	ref
Q2 (4.88, 7.17]	–0.27 (–1.02, 0.47)	0.47	–0.76 (–1.49, –0.03)	0.04	–0.56 (–1.26, 0.14)	0.12
Q3 (7.17, 10.46]	–1.53 (–2.49, –0.57)	0.002	–2.14 (–3.04, –1.25)	<0.0001	–2.02 (–2.98, –1.06)	<0.0001
Q4 (10.46, 136.69]	–2.12 (–3.10, –1.29)	<0.0001	–3.31 (–4.18, –2.45)	<0.0001	–3.07 (–4.23, –1.91)	<0.0001
p for trend	<0.0001		<0.0001		<0.0001	

Model 1, variables unadjusted;

Model 2, gender, age, and race were adjusted;

Model 3, gender, age, race, education, marriage, BMI, PIR, smoking status, alcohol consumption, recreational activity, use of vitamin E supplements, lipid-lowering drug use, DII, total energy intake, dietary fiber intake, vitamin C intake, hypertension, CVD, and DM were adjusted.

95% CI, 95% confidence interval; RC, remnant cholesterol; PIR, poverty income ratio; BMI, body mass index; DII, dietary inflammatory index; CVD, cardiovascular disease; DM, diabetes mellitus; Q1–4 respectively represent the groups divided according to the quartiles of vitamin E intake.

adults (>19 years of age) from the 2005–2016 NHANES database revealed that 84% of US residents were generally deficient in vitamin E [25]. In addition, vitamin E levels were lower in patients with metabolic syndrome than in healthy controls [27]. Studies have confirmed that only one-fifth of the global population has optimal vitamin E levels [28]. The optimal daily intake of vitamin E needed to maintain immune health is higher in older individuals (134 mg/day) [29]. After adjusting for potential confounders, we found that dietary and total vitamin E intakes were nonlinearly and negatively associated with RC. Stratified analyses confirmed that vitamin E intake was negatively associated with RC across ethnicities, economic levels, and comorbidities. These results may have public health implications, suggesting that a diet rich in vitamin E can help reduce RC levels.

The possible mechanisms by which α-tocopherol affects lipids and atherosclerosis have been investigated in the field of clinical and experimental studies. Several animal experiments have shown that α-tocopherol inhibits cholesterol-induced atherosclerotic plaque progression in rabbits by decreasing protein kinase C activity, jnk1-mediated c-jun phosphorylation, MMP-9 levels, and CD36 mRNA production [30–32]. High-density lipoprotein and vitamin E combination significantly inhibited foam cell formation, attenuated oxidative stress, and reduced apoptosis in the RAW264.7 mouse macrophage line [33]. Long-term vitamin E supplementation in mice lacking LDL receptors reduced atherosclerotic lesions, but not when fed Western style diet [34]. Vitamin E inhibits lipid peroxidation by disrupting chain proliferation *in vitro* and *in vivo* [35].

Vitamin E has a protective association with new-onset hypertension (reverse J-shaped association) and type 2 diabetes (by reducing insulin resistance) [36,37]. Moreover, *in vivo* and *in vitro* studies have confirmed that vitamin E can reduce the risk of CVD and mortality [20,38,39], by lowering serum cholesterol and triglyceride levels [40]. Several studies have shown that α-tocopherol benefits atherosclerosis by reducing oxidized serum LDL uptake, thereby reducing foam cell formation [41–43]. Tocotrienols in animal cells have been shown to inhibit serum cholesterol biosynthesis by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase, a key enzyme in the steroidogenic pathway, leading to decreased serum cholesterol produced by hepatocytes [44]. Furthermore, low-dose tocotrienol combined with lovastatin is an effective cholesterol-lowering agent that prevents some of the adverse effects of statins [45]. However, another *in vitro* study revealed that α - tocopherol does not prevent lipoprotein lipid oxidation in atherosclerotic vessel walls [46]. A recent study investigated the relationship between dietary vitamin E and RC [47], however, it did not consider the effects of total vitamin E intake on RC after using vitamin E supplements. The study excluded individuals using statins, but it did not consider the impact of other lipid-lowering drugs on RC. To further comprehensively analyze this association, our study con-

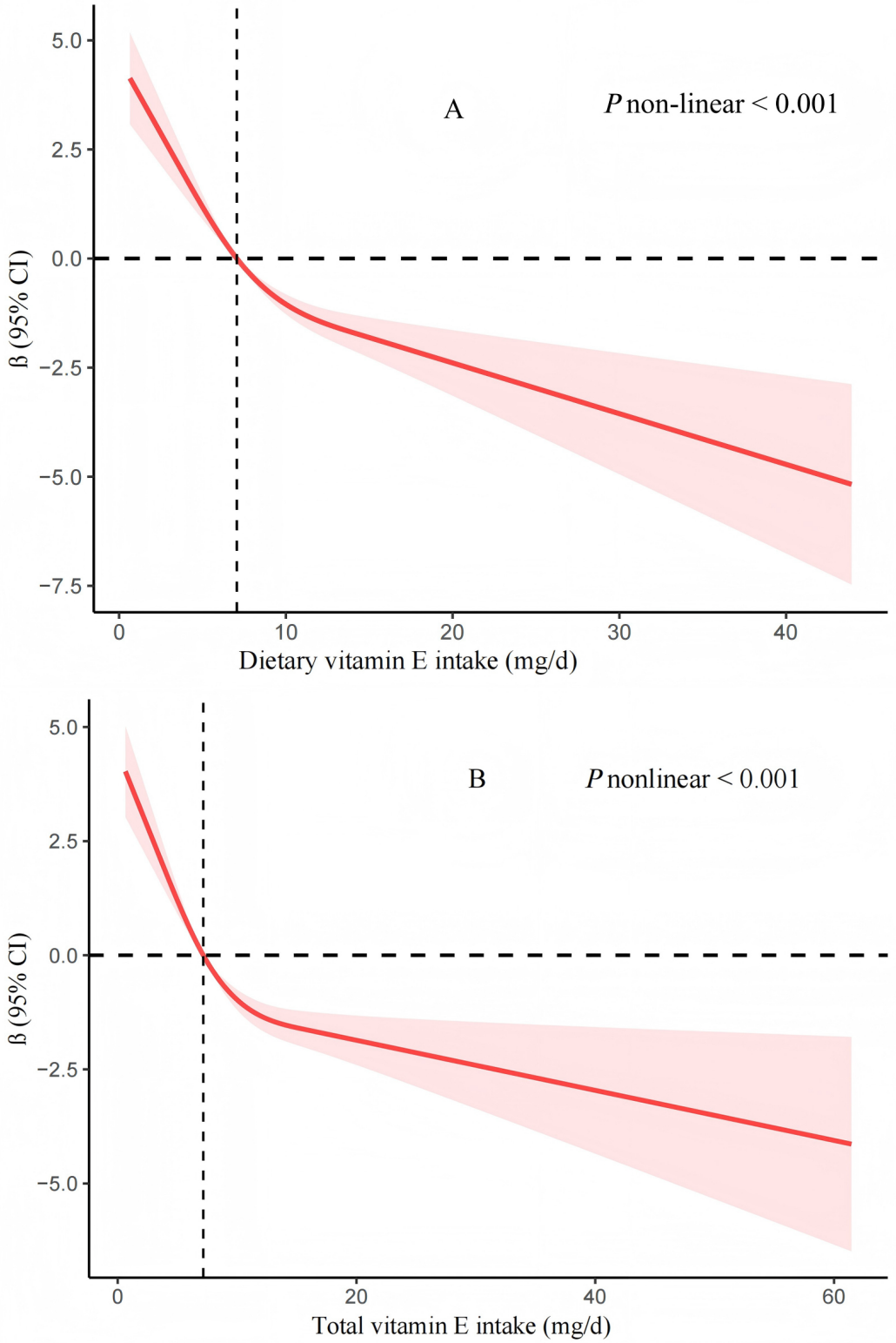

Fig. 2. Restricted cubic spline curves of both dietary vitamin E intake (A) and total vitamin E intake (B) with remnant cholesterol (n =11,585). Adjusted for gender, age, race, education, marriage status, BMI, PIR, smoking status, alcohol consumption, recreational activity, use of vitamin E supplements, lipid-lowering drug use, DII, total energy intake, dietary fiber intake, vitamin C intake, hypertension, CVD, and DM. Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; PIR, Ratio of family income to poverty; DM, diabetes mellitus; DII, dietary inflammatory index; CVD, cardiovascular disease.

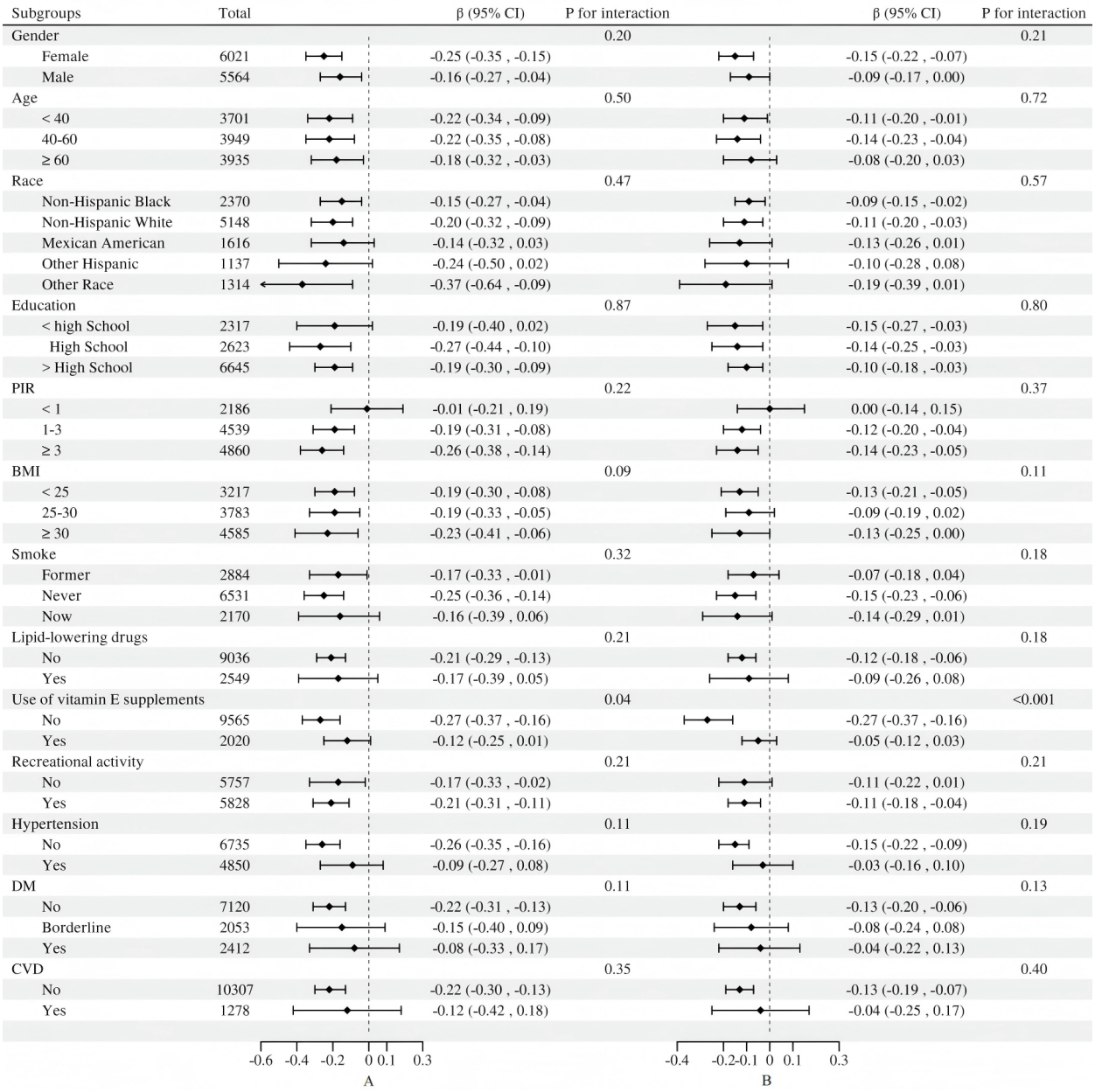

Fig. 3. Stratified analyses between dietary vitamin E intake (A) and total vitamin E intake (B) and remnant cholesterol (n = 11,585). Adjusted for gender, age, race, education, marriage status, BMI, PIR, smoking status, alcohol consumption, recreational activity, use of vitamin E supplements, lipid-lowering drug use, DII, total energy intake, dietary fiber intake, vitamin C intake, hypertension, CVD, and DM except for the stratification variable. Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; PIR, Ratio of family income to poverty; DII, dietary inflammatory index; CVD, cardiovascular disease; DM, diabetes mellitus.

sidered the use of key influencing factors, such as vitamin E supplements and lipid-lowering drugs (including statins, fenofibrate, ezetimibe, gemfibrozil, colestipol, and niacin). Subgroup analysis showed that the effect values of vitamin E supplementation and RC in the dietary and total vitamin E intake groups were –0.12 and –0.05, respectively, suggesting that vitamin E supplementation can reduce the risk of RC. High doses of γ-tocotrienols (6 mg/g) in the rice bran oil diet will increase serum HDL-C levels, lower serum cholesterol, and reduce the ratio of serum TC to HDL-C in rats with type 2 diabetes [48]. However, few studies have studied the association between vitamin E supplements and RC, and further research is needed on the association and underlying mechanisms.

This study has several strengths. In this epidemiologic survey, we aimed to assess the association between vitamin E intake and RC with a large sample size, multiple adjusted variables, and weighted analyses representing the national US populations. Consuming more vitamin E may help reduce RC and cardiovascular risks. Nonetheless, this study

had several limitations. First, the cross-sectional design does not yield causal relationships; therefore, further longitudinal studies are required to verify these findings. Second, dietary data were self-reported and might have been subject to recall bias. Third, the population of this study was adults aged 20 years or older of the US, and it is not possible to generalize the results to other age groups or populations outside of the US. Further studies are necessary to validate our findings and explore the potential relationships between vitamin E intake and RC using more comprehensive designs.

The 2020–2025 Dietary Guidelines in the US recommend that nutritional needs should be met primarily through foods and beverages [49]. We recommend following the current nutritional guidelines to obtain adequate vitamin E from food to reduce RC levels. Our findings can be significant for developing public health policies and treatment practices.

6. Conclusion

This cross-sectional study revealed a protective association between vitamin E intake and serum RC. We speculate that vitamin E-rich diets can be used as part of dietary management and may contribute to lowering serum RC concentrations, thereby helping to control the risk of CVD. Furthermore, longitudinal studies should be conducted to verify causality and observe the effects of dietary vitamin E intervention.

Availability of Data and Materials

Original contributions are included in the article/supplementary material, which can be further queried by the corresponding author. This data can be found at: https://wwwn.cdc.gov/nchs/nhanes/.

Author Contributions

SZ and HY designed the research. SZ performed the research. YX provided help and advice on the study. JC and YS analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

NHANES was approved by the National Center for Health Statistics (NCHS). Ethics Review Board approved the study protocol (Continuation of Protocol #2005-06; Protocol #2011-17; Continuation of Protocol #2011-17; Protocol #2018-01). All participants provided written informed consent. All methods were carried out in accordance with relevant guidelines and regulations (Declarations of Helsinki).

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/IJVNR26882.

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