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Association between fat-soluble vitamins and metabolic syndromes in US adults: a cross-section study from NHANES database

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Abstract

Background Previous studies have shown significant associations between individual fat-soluble vitamins (FSVs) and metabolic syndromes (MetS). However, evidence on the multiple FSVs co-exposure and MetS odds is limited. Given that individuals are typically exposed to different levels of FSVs simultaneously, and FSVs can interact with each other. It's necessary to explore the association between multiple FSVs co-exposure and MetS odds. This study aims to address this gap in general U.S. adults aged ≥ 20 years.

Methods We conducted a cross-sectional study utilizing data from the National Health and Nutrition Examination Surveys (NHANESs) 2003–2006 and 2017–2018. Three FSV, including vitamin A (VA), vitamin E (VE), and vitamin D (VD), and MetS diagnosed according to the ATP III guidelines were selected as exposure and outcome, respectively. Multivariable-adjusted logistic model was used to explore the associations of individual FSV exposure with MetS odds and MetS components. Restricted cubic splines were performed to explore the dose–response relationships among them. The quantile g-computation method was adopted to explore the associations of multiple FSVs co-exposure with MetS odds and MetS components.

Results The presented study included a total of 13,975 individuals, with 2400 (17.17%) were diagnosed with MetS. After adjusting for various confounders, a positive linear pattern was observed for serum VA and VE and MetS associations. Serum VD was found to be negatively associated with MetS in a linear dose–response way. For each component of MetS, higher serum VA and VE were associated with higher triglyceride and high-density lipoprotein; higher serum VD was negatively associated with triglyceride, blood pressure, and fasting plasma glucose. MetS odds increased by 15% and 13%, respectively, in response to one quartile increase in FSVs co-exposure index (qgcomp) in the conditional model (OR = 1.15, 95%CI: 1.06, 1.24) and the marginal structural model (OR = 1.13, 95%CI: 1.06, 1.20). Besides, co-exposure to VA, VE, and VD was positively associated with triglyceride, high-density lipoprotein, and blood pressure levels.

Conclusion Findings in the present study revealed that high serum VA and VE levels were associated with elevated MetS odds, while serum VD was inversely associated with MetS odds. FSVs co-exposure was positively associated with MetS odds.

Keywords Fat-soluble vitamin, Metabolic syndrome, Quantile g-computation, Co-exposure, Dose–response relationship

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Introduction

Metabolic syndrome (MetS) represents a complex cluster of interconnected metabolic abnormalities, including central obesity, impaired glucose metabolism, dyslipidemia, and hypertension, which collectively pose a significant threat to human health [1]. The diagnostic criteria for MetS was firstly established in 1998 [2]. The NCEP: ATP III made several revisions, formulating the definition of MetS that is most widely adopted in clinical practices [3]. MetS has emerged as a major public health challenge globally, affecting both developed and developing nations [4]. It is estimated that approximately one in four to five people worldwide experience MetS [4]. The prevalence of MetS exhibits considerable regional variation. A cross-sectional analysis of the National Health and Nutrition Examination Surveys (NHANESs) 2011–2016 data revealed a weighted MetS prevalence of 34.7% among American adults aged > 20 years [5]. In contrast, a study reported an estimated MetS prevalence of 15.5% in China in 2017 [6]. The rapid urbanization and economic growth in many countries have precipitated a nutritional transition characterized by increased intake of fast foods and ultra-processed foods [6, 7]. This dietary shift, marked by high intake of saturated fats and added sugars, and low dietary fiber content, coupled with increasingly sedentary lifestyle and reduced physical activity levels, will significantly increase the MetS risk. Moreover, the global demographic transition towards ageing population further exacerbates this trend, as the aging process shares common biochemical alterations with MetS [8]. The implications of this escalating MetS prevalence are substantial, not only for individual well-being but also for societal health and economic prosperity. MetS not only diminishes individual health outcomes but also imposes a substantial societal burden through the loss of a productive workforce and escalating healthcare expenditures.

Fat-soluble vitamins (FSVs) comprise a group of essential micronutrients that are soluble in lipids or fat solvents but not in water. These vitamins play crucial roles in various physiological processes, including metabolism, growth, and development. The FSV family includes vitamin A (VA), vitamin D (VD), vitamin E (VE), and vitamin K (VK), each with distinct biological functions. Deficiency in VA, VD, VE, and VK can lead to specific health issues, i.e., night blindness, bone disease, nerve damage, and spontaneous bleeding [9–12]. Accumulating evidence suggested a potential association between FSVs and MetS. A cross-sectional study in China demonstrated a dose-dependent positive association between serum VA levels and MetS [13], with similar findings reported in a Korean population study [14]. Waniek et al. conducted a study in Northern German, concluding that elevated α-tocopherol levels were associated with hypertriglyceridemia, low high-density lipoprotein (HDL), and increased odds of MetS [15]. Furthermore, a significant association between VD and MetS odds has been reported [16]. However, the existing evidence presented some inconsistencies regarding these associations [17–20]. Furthermore, dietary diversity inherently exposes individuals to multiple vitamins simultaneously, and interactions among FSVs can occur at the intestinal level, influencing absorption and metabolism [21]. Consequently, exploring the association between co-exposure to multiple FSVs and health outcomes is more valuable and may provide a more comprehensive understanding of their associations. While Pei et al. investigated the association between co-exposure to multiple water-soluble vitamins and MetS risk [22], evidence on the association between multiple FSVs co-exposure and MetS odds was still limited.

To address this knowledge gap, we conducted a cross-sectional study. Data from the NHANESs 2003–2006 and 2017–2018 was used. Our objective was to investigate the associations of exposure to serum FSVs (i.e., VA, VD, VE) with MetS odds and each MetS component in a representative sample of American adults. Additionally, we also explored potential dose–response relationships among them.

Participants and methods

Study design and participants

Data from three NHANES rounds, specifically the periods of 2003–2004, 2005–2006, and 2017–2018, was analyzed. Briefly, about 5,000 individuals were recruited from representative regions across America per year to assess the health and nutritional status of the civilian population. Details could be found in NHANES official website. The NHANES was approved by the National Center for Health Statistics Research Ethics Review Board, with written informed consent was obtained from all participants.

A total of 29,724 individuals were involved across the three NHANES rounds. There were 1427, 13,517, and 805 participants were excluded from our analysis, respectively, because they did not undergo a physical examination, under the age of 20, and lacked serum data for VA, VE, VD, and MetS. Consequently, the final study consisted of 13,975 U.S. adults aged > 20 years.

Exposure measurement

FSV family typically includes VA, VE, VD and VK (33549284). Unfortunately, data on VK was not available across all three NHANES rounds. Thus, the other three kinds of FSV, including VA (retinol), VE (α-tocopherols), and VD (25(OH)D) were selected as exposures in this study. Regarding VA and VE, they were measured using

high performance liquid chromatography with multi-wavelength photodiode-array absorbance detection in NHANES 2003–2004 (https://wwwn.cdc.gov/Nchs/Nhanes/2003-2004/L45VIT_C.htm), and using high performance liquid chromatography with photodiode array detection in NHANES 2005–2006 (https://wwwn.cdc.gov/Nchs/Nhanes/2005-2006/VITAEC_D.htm) and 2017–2018 (https://wwwn.cdc.gov/Nchs/Nhanes/2017-2018/VITAEC_J.htm). NHANES has made corresponding correction for measurements of different survey cycles to ensure that they can be combined for analysis. VD was measured primarily using the DiaSorin RIA kit (Stillwater MN) in NHANES 2003–2006 (https://wwwn.cdc.gov/nchs/nhanes/vitamind/analyticalnote.aspx?b=2003&e=2004&d=VID_C&x=htm), and using high performance liquid chromatography-tandem mass spectrometry (HPLC–MS/MS) method in NHANES 2017–2018 (https://wwwn.cdc.gov/Nchs/Nhanes/2017-2018/VID_J.htm). Meanwhile, NHANES officially reported the LC_MS/MS-equivalent data of VD and highly recommended that researchers use the equivalent data for all analyses.

Outcome measurement

MetS was assessed using by five variables, including waist circumference (WC), triglyceride (TG), high-density lipoprotein (HDL), blood pressure, and fasting glucose (FG). Based on ATP III guidelines, MetS is diagnosed when three or more of the following criteria are met: (1) abdominal obesity (WC > 40/ > 35 inches in men/women; (2) TG ≥ 150 mg/dL; (3) HDL < 40/ < 50 mg/dL in men/women; (4) systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mmHg; and (5) FG ≥ 110 mg/dL.

To comprehensively evaluate the associations between FSVs and MetS, each component of MetS was also categorized into two groups (low and high) based on the ATP III guidelines, which were used as secondary outcomes.

Covariates

Referring previous studies, we selected age, sex, race, education background, marital status, family poverty income ratio (PIR), body mass index, smoking status, drinking status, physical activity, and dietary total energy as covariates (37251666). Age was categorized into three groups: 20–39, 40–59, and ≥ 60 years. Race included Mexican American, Hispanics, non-Hispanic White, non-Hispanic Black, and others. Education background was described as < high school, high school or equivalent, and > high school. Marital status was classified as married/living with a partner, widowed/separated/devoiced, and never married. BMI was calculated by using weight (Kg) divided by the square of height (m), and was categorized into four groups: underweight (< 18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obesity (≥ 30 kg/m^2). Smoking and drinking status were described as never, ever, and current. We firstly calculated the metabolic equivalent (MET)-minutes per week based on the time and MET scores of vigorous and moderate leisure-time physical activities reported in the NHANES. Then physical activity was classified as sedentary (MET = 0), insufficient (0 < MET ≤ 500), moderate (500 < MET ≤ 1000), and high (MET > 1000).

Statistical analysis

All participants were grouped into MetS and non-MetS groups, and we then described the distribution of each variable separately. Prior to the statistical description, we used the Kolmogorov–Smirnov test to examine whether continuous variables followed a normal distribution. We also constructed quantile–quantile plots and bar charts to visualize their distributions. Mean ± standard deviation (SD) and median (interquartile range) were employed to describe continuous variables with and without a normal distribution, respectively. And we used the t-test or Wilcoxon rank-sum test for between-group comparisons. Categorical variables were described as n (%) and chi-square test was adopted for between-group differences.

Considering the complex design of the NHANES, we mainly employed weighted multivariable-adjusted logistic regression model to investigate the associations between exposure to single serum FSVs and the odds of MetS and each MetS component. To facilitate interpretation and comparison across different exposure levels, we categorized FSVs into four groups based on corresponding quartiles, with the first quartile serving as the reference. We conducted two models with adjustment for different covariates: model 1 adjusted for age, sex, race, education background, marital status, BMI, and family PIR, and model 2 further adjusted for physical activity, smoking and drinking status, and dietary total energy in addition to those in model 1. Furthermore, to test the robustness of the results, we also examined the aforementioned associations using continuous FSVs as exposures. Given the possibility of non-linear associations, we performed restricted cubic spline analysis with full covariate adjustment.

We used the quantile g-computation method to explore the associations between co-exposure to all studied FSVs and the odds of MetS and each MetS component. All FSVs were performed with log-transformation and standardization to ensure normal distributions and eliminate the influence of units. The "qgcomp.noboot" function of R "qgcomp" package was employed to obtain the contribution of each FSV in the association between co-exposure to multiple FSVs and MetS odds and MetS components, as well as conditional ORs and 95% confidence intervals

(Cis) of the overall associations. The "qgcomp.boot" function of R "qgcomp" package was used to assess the dose–response relationship and get marginal ORs and 95% CIs.

The SAS 9.4 and R 4.3.1 software were used for analyses and figure production. All analyses were two-sided, and a P value < 0.05 indicated statistical significance.

Results

General characteristics

Of the 13,975 participants, 2,400 (17.2%) were diagnosed with MetS. Table 1 illustrated significant differences between the MetS and non-MetS groups regarding age, race, education background, marital status, BMI, physical activity, drinking and smoking status, family PIR and dietary total energy.

Serum VA and VE concentrations were significantly higher in the MetS group (VA: median = 1.99, IQR: 1.63, 2.41 μmol/L); VE: median = 29.49, IQR: 23.92, 38.08 μmol/L) compared to the non-MetS group (VA: median = 1.88, IQR: 1.54, 2.27 μmol/L; VE: median = 26.47, IQR: 21.50, 33.44 μmol/L). Conversely, serum VD concentration was significantly lower in MetS group (median = 55.90, IQR: 40.90, 72.90 nmol/L) than in the non-MetS group (median = 59.20, IQR: 43.40, 76.20 nmol/L) (all P < 0.05).

Association of individual FSV with MetS odds and each component

Table 2 presented the weighted multivariable-adjusted logistic regression analysis results. In the full adjustment model (model 2), the third (OR = 1.46, 95%CI: 1.09, 1.97) and highest quartiles (OR = 1.53, 95%CI: 1.10, 2.14) of VA, as well as the third (OR = 2.21, 95%CI: 1.63, 2.98) and the highest quartiles (OR = 2.79, 95%CI: 1.94, 4.03) of VE, were positively associated with the odds of MetS compared to their respective lowest quartiles. In contrast, the second (OR = 0.76, 95%CI: 0.60, 0.98), third (OR = 0.75, 95%CI: 0.56, 0.99) and highest quartiles (OR = 0.52, 95%CI: 0.37, 0.73) of VD were associated with 24%, 25% and 48% reductions in the odds of MetS, respectively. Analyses using continuous variables of VA, VE, and VD yielded similar trends.

Table S1 delineated the associations between individual FSV and MetS components. After controlling for all covariates (model 2), elevated serum VA and VE were associated with higher TG levels. The highest quartile of VA (OR = 0.67, 95% CI: 0.50, 0.89) and VD (OR = 0.54, 95% CI: 0.39, 0.73), and the second quartile of VE (OR = 0.74, 95% CI: 0.59, 0.93) were associated with higher HDL levels compared to their lowest quartiles. Additionally, higher VD levels were associated with lower blood pressure and lower FG.

Dose–response relationship between individual FSV and MetS odds

Figures 1, 2 and 3 illustrated the dose–response relationships between serum VA, VE and VE concentrations and MetS odds, as assessed using restricted cubic spline analyses. We found the odds of MetS increased with elevated VA and VE in a linear dose–response manner. Notably, the CIs for the association between VA levels below the reference point and MetS odds included the null value, while the CIs for VE levels below the reference point excluded the null. Conversely, a negative linear dose–response relationship was observed between VD concentration and MetS odds.

Associations of multiple FSVs co-exposure with MetS odds and each component

After adjusting for potential confounders, the FSV co-exposure index demonstrated a significant association with increased MetS odds. A one-quartile increase in the index corresponded to a 15% and 13% increase in MetS odds in the conditional model (OR = 1.15, 95%CI: 1.06, 1.24) and the marginal structural model (OR = 1.13, 95%CI: 1.06, 1.20), respectively (Table 3 and Fig. 4B). VE and VA contributed 61% and 39%, respectively, to this positive association (Fig. 4A and Table 4).

The relationships between multiple FSV co-exposure and individual MetS components were presented in Table 3 and Figures S1-S5 B. FSVs co-exposure was positively associated with TG, HDL, and blood pressure. The relative contribution of each FSV to these association were detailed in Table 4 and Figure S1-S5 A.

Discussion

In this cross-sectional study of a nationally representative U.S. adults, we investigated the associations between individual and combined FSVs (specifically VA, VD, VE) exposures and the odds of MetS, as well as its individual components. We also examined the dose–response relationships among them. After adjusting for various confounders, our findings revealed that serum VA and VE concentrations were positively associated with MetS odds in a linear dose–response manner, while serum VD levels exhibited an inverse relationship with MetS odds. Elevated serum VA and VE levels were positively associated with TG and HDL levels. Conversely, higher serum VD concentrations were associated with increased HDL and decreased TG, blood pressure, and FG levels. Furthermore, MetS odds increased by 15% and 13% in response to a one-quartile increase in the FSV co-exposure index in the conditional model and marginal structural model,

Table 1 General characteristics of participants in NHANES 2003–2006 and 2017–2018

Variables	Non-MetS (*n* = 11 575)	MetS (*n* = 2 400)	*P*
Age*, years, n (%)			< 0.0001
20–39	4386 (37.89)	366 (15.25)	
40–59	3429 (29.62)	806 (33.58)	
≥ 60	3760 (32.48)	1228 (51.17)	
Sex*, n (%)			0.0508
Men	5619 (48.54)	1112 (46.33)	
Women	5956 (51.46)	1288 (53.67)	
Race*, n (%)			< 0.0001
Mexican American	2005 (17.32)	489 (20.38)	
Other Hispanic	607 (5.24)	143 (5.96)	
Non-Hispanic White	5270 (45.53)	1146 (47.75)	
Non-Hispanic Black	2582 (22.31)	416 (17.33)	
Others	1111 (9.60)	206 (8.58)	
Education*, n (%)			< 0.0001
Under high school	2792 (24.16)	758 (31.61)	
High school or equivalent	2771 (23.98)	606 (25.27)	
Above high school	5991 (51.85)	1034 (43.12)	
Marital status*, n (%)			< 0.0001
Married/cohabiting	7048 (60.94)	1456 (60.69)	
Widowed/divorced/separated	2461 (21.28)	687 (28.64)	
Never married	2056 (17.78)	256 (10.67)	
BMI*, kg/m^2, n (%)			< 0.0001
< 18.5	209 (1.84)	2 (0.08)	
18.5–24.9	3613 (31.81)	157 (6.60)	
25.0–29.9	3978 (35.02)	686 (28.84)	
≥ 30.0	3559 (31.33)	1534 (64.48)	
Physical activity*, n (%)			< 0.0001
Sedentary	2065 (24.03)	604 (35.20)	
Insufficient	3054 (35.54)	621 (36.19)	
Moderate	1258 (14.64)	242 (14.10)	
High	2216 (25.79)	249 (14.51)	
Drinking status*, n (%)			< 0.0001
Never	1309 (22.51)	338 (23.47)	
Ever	1397 (24.03)	433 (30.07)	
Current	3108 (53.46)	669 (46.46)	
Smoking status*, n (%)			< 0.0001
Never	6297 (54.44)	1195 (49.81)	
Ever	2829 (24.46)	748 (31.18)	
Current	2441 (21.10)	456 (19.01)	
Family PIR*, median (IQR)	2.29 (1.22, 4.22)	2.02 (1.16, 3.71)	< 0.0001
Total total energy#, kcal/day, median (IQR)	1953.00 (1473.00, 2552.00)	1815.50 (1373.50, 2376.50)	< 0.0001
Vitamin A#, μmol/L, median (IQR)	1.88 (1.54, 2.27)	1.99 (1.63, 2.41)	< 0.0001
Vitamin E#, μmol /L, median (IQR)	26.47 (21.50, 33.44)	29.49 (23.92, 38.08)	< 0.0001
Vitamin D#, nmol/L, median (IQR)	59.20 (43.40, 76.20)	55.90 (40.90, 72.90)	< 0.0001

Physical activity was categorized into four groups based on metabolic equivalent (MET)-minutes per week: sedentary (MET = 0), insufficient (0 < MET < 500), moderate (500 ≤ MET < 1000), and high (MET ≥ 1000). But no participant was categorized into "sedentary" group

NHANES the National Health and Nutrition Examination Survey, *BMI* Body mass index, *Family PIR* ratio of family income to poverty, *IQR* Interquartile range, *MetS* Metabolic syndromes

* *P* values were calculated using t-test

P values were calculated using Wilcoxon rank-sum test

Table 2 Associations of serum fat-soluble vitamins with metabolic syndromes in NHANES 2003–2006 and 2017–2018 participants

Vitamin	Quantile 1	Quantile 2	Quantile 3	Quantile 4	$P_{continuous}$
Model1					
Vitamin A	1.00	1.19 (0.89, 1.58)	1.40 (1.05, 1.89)	1.46 (1.06, 2.02)	0.0087
Vitamin E	1.00	1.20 (0.87, 1.65)	2.23 (1.65, 3.01)	2.71 (1.89, 3.87)	< 0.0001
Vitamin D	1.00	0.78 (0.63, 0.97)	0.73 (0.55, 0.97)	0.52 (0.37, 0.71)	0.0009
Model2					
Vitamin A	1.00	1.20 (0.89, 1.63)	1.46 (1.09, 1.97)	1.53 (1.10, 2.14)	0.0055
Vitamin E	1.00	1.17 (0.85, 1.63)	2.21 (1.63, 2.98)	2.79 (1.94, 4.03)	< 0.0001
Vitamin D	1.00	0.76 (0.60, 0.98)	0.75 (0.56, 0.99)	0.52 (0.37, 0.73)	0.0013

All estimates were calculated by the multivariable logistic regression model, and results were expressed as odds ratio (95% confidence interval). Covariates adjusted in model 1 included age, sex, race, education, marital status, body mass index, and ratio of family income to poverty. Covariates adjusted in model 2 included leisure time physical activity, dietary energy, drinking status, and smoking status in addition to those in model 1

NHANES the National Health and Nutrition Examination Survey

$P_{continuous}$ meant the *P* value of the multivariable logistic regression model using continuous vitamin levels as exposure

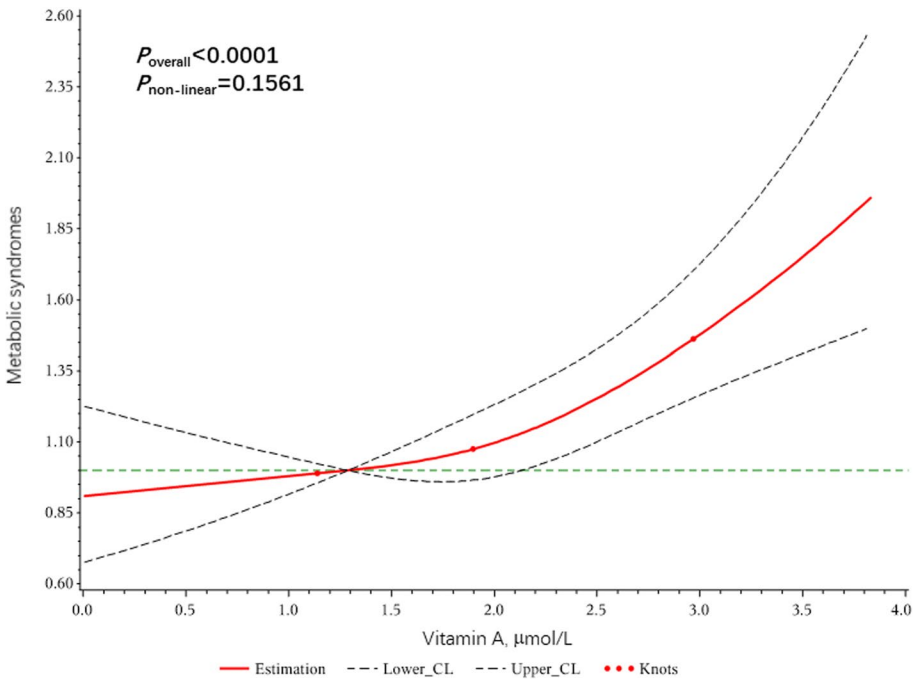

Fig. 1 The dose–response relationship between serum Vitamin A and metabolic syndrome risk

respectively. Also, co-exposure to VA, VE, and VD was positively associated with TG, HDL, and blood pressure levels.

Our findings demonstrated a positive, linear dose–response relationship between serum VA concentrations and MetS odds. And elevated serum VA levels were associated with increased TG and HDL. VA encompasses various compounds, including retinol, retinal, retinoic acid, and carotenoids, with retinol being the predominant retinoid found abundantly in animal-derived foods [23]. Our results aligned with previous research. A study of 606 adults from the European Health Examination Survey reported an association between increased VA levels and elevated MetS odds in women [24]. Similarly, Kim et al. using data from the Korea National Health and Nutrition

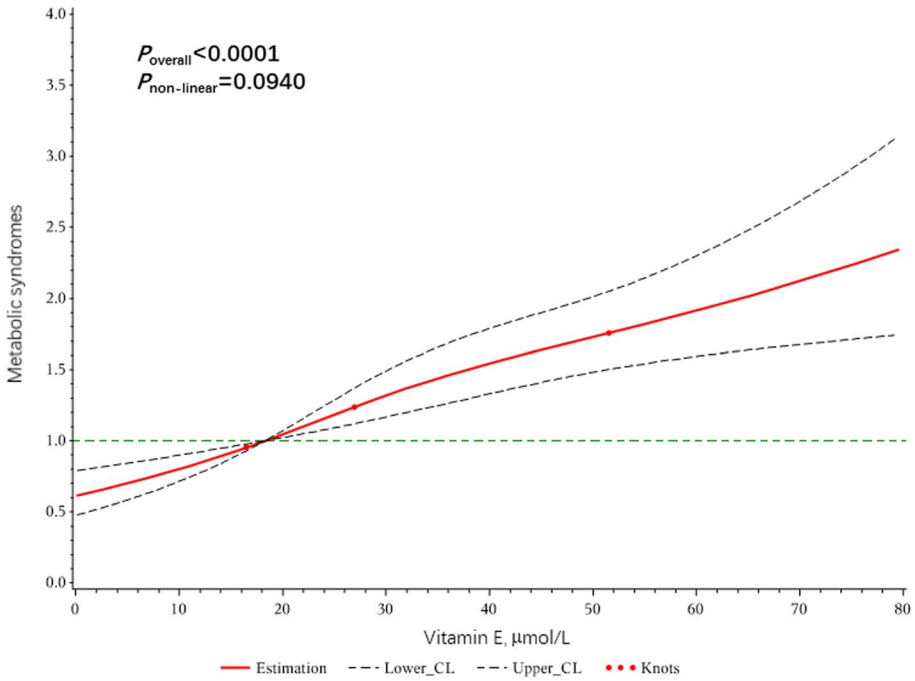

Fig. 2 The dose–response relationship between serum Vitamin E and metabolic syndrome risk

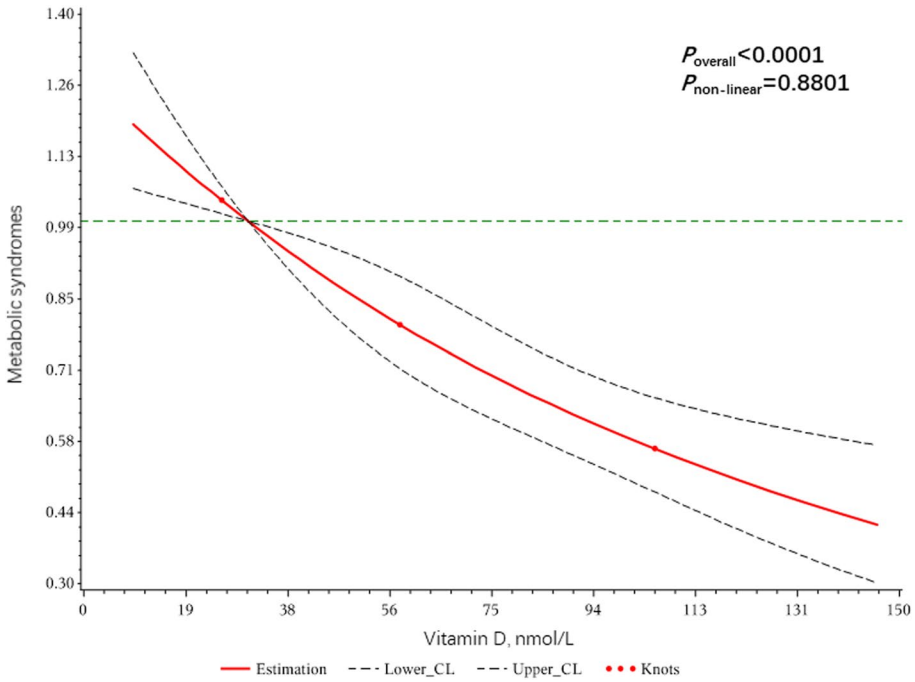

Fig. 3 The dose–response relationship between serum Vitamin D and metabolic syndrome risk

Examination Survey, observed that participants with higher retinol levels exhibited increased MetS odds, as well as elevated FG, blood pressure, and TG [14]. Some other studies also drew the same conclusions [13, 25]. The proposed mechanism underlying this association is oxidative stress. Elevated retinol levels may enhance

Table 3 Association of multiple fat-soluble vitamins co-exposure and metabolic syndromes and each component

Models	OR (95% CI)	*P* value
Metabolism syndromes		
Conditional model	1.15 (1.06, 1.24)	0.0003
Marginal structural model	1.13 (1.06, 1.20)	0.0004
Waist Circumference		
Conditional model	1.07 (0.98,1.17)	0.1469
Marginal structural model	1.03 (0.99, 1.06)	0.1852
Triglyceride		
Conditional model	2.74 (2.46, 3.04)	< 0.0001
Marginal structural model	2.42 (2.20, 2.66)	< 0.0001
High-density lipoprotein		
Conditional model	0.83 (0.78, 0.89)	< 0.0001
Marginal structural model	0.85 (0.80, 0.90)	< 0.0001
Blood pressure		
Conditional model	1.13 (1.06, 1.20)	0.0002
Marginal structural model	1.10 (1.04, 1.17)	0.0005
Fasting plasma glucose		
Conditional model	1.05 (0.95, 1.16)	0.3413
Marginal structural model	1.04 (0.96, 1.12)	0.3235

Concentrations of serum Vitamin A, Vitamin E, and Vitamin D were log-transformed and then standardized

Each component of metabolism syndromes was categorized based on NCEP: ATP III guidelines. Waist circumference was categorized into low (< 102 cm in men or < 88 cm in women) and high (≥ 102 cm in men or ≥ 88 cm in women) groups, and the low group was used as the reference; triglyceride was categorized into low (< 150 mg/dL) and high (≥ 150 mg/dL) groups, and the low group was used as the reference; high-density lipoprotein was categorized into low (< 40 mg/dL in men or < 50 mg/dL in women) and high (≥ 40 mg/dL in men or ≥ 50 mg/dL in women) groups, and the high group was used as the reference; blood pressure was categorized into low (systolic blood pressure < 130 mmHg and diastolic blood pressure < 85 mmHg) and high (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg) groups, and the low group was used as the reference; fasting plasma glucose was categorized into low (< 110 mg/dL) and high (≥ 110 mg/dL) groups, and the low group was used as the reference

OR Odds ratio, *CI* Confidence interval

the activity of antioxidant enzymes such as catalase, superoxide dismutase, and glutathione peroxidase, potentially affecting metabolic processes [14]. Dietary patterns may also contribute to this relationship, as VA is primarily obtained from animal-based foods rich in fat, such as meat, dairy products, and oils. However, inconsistent evidence existed. A meta-analysis reported a significant inverse association between serum retinyl esters and MetS odds, while finding no significant association serum retinol and MetS odds [17]. Additionally, Park et al. observed that the interaction between total VA and vitamin C intake may reduce MetS risk in women in women [26]. This discrepancy could be attributed to differences in study population, study design and adjustments for confounders.

Our findings demonstrated that serum VE levels was positively associated with MetS odds, as well as TG and HDL. Epidemiological evidence regarding this association remained controversial. A large-scaled study of 5,885 Korean adults reported a dose-dependent positive association between α-tocopherol levels and MetS odds [14]. Similarly, another cross-sectional study suggested that elevated α-tocopherol levels were associated with increased visceral adipose tissue, TG and MetS odds [15]. Conversely, a comprehensive review of animal and human studies concluded that VE could potentially mitigate MetS symptom [27]. A meta-analysis conducted by Zhang et al. reported a weak inverse association between circulating VE and MetS [28]. Furthermore, some studies have found significant effect of VE supplementation on MetS [29]. Circulating VE levels reflect the net balance of replenishment, absorption, and excretion processes. Evidence suggested that MetS patients exhibit slower catabolism of α-tocopherol and reduced VE excretion compared to healthy individuals [30], potentially resulting in elevated serum VE levels. Additionally, the increased oxidative and inflammatory stressors associated with MetS patients might necessitate higher VE levels to counteract these deleterious effect [30]. Interestingly, our findings revealed that VE might be a protective factor against MetS within a specific dose range, highlighting its antioxidant properties. However, the optimal serum VE range for metabolic health requires further investigation.

Consistent with numerous previous studies, our findings demonstrated an inverse association between serum VD concentration and MetS odds. This association was further reflected in the observed relationships between higher VD levels and lower TG, blood pressure, and FG. VD, a unique FSV, can be endogenously synthesized in the skin upon ultraviolet radiation exposure [31]. A dose–response meta-analysis including 16 cross-sectional studies reported a 13% reduction in MetS odds for every 25 nmol/L increment in serum VD levels [32]. However, this study also showed no significant association between VD and MetS odds in pooled longitudinal studies. But this conclusion was limited due to the inclusion of only one cohort study and one nested case–control study. Buchmann et al. corroborated these findings, concluding that VD deficiency was associated with increased MetS odds, independent of obesity and insulin resistance [33]. Similar conclusions have been reported in other studies [34, 35]. Several mechanisms may explain these associations: (1) MetS patients may engage in less outdoor activity, resulting in reduced sunlight exposure and consequently lower VD synthesis; (2) MetS is often associated with

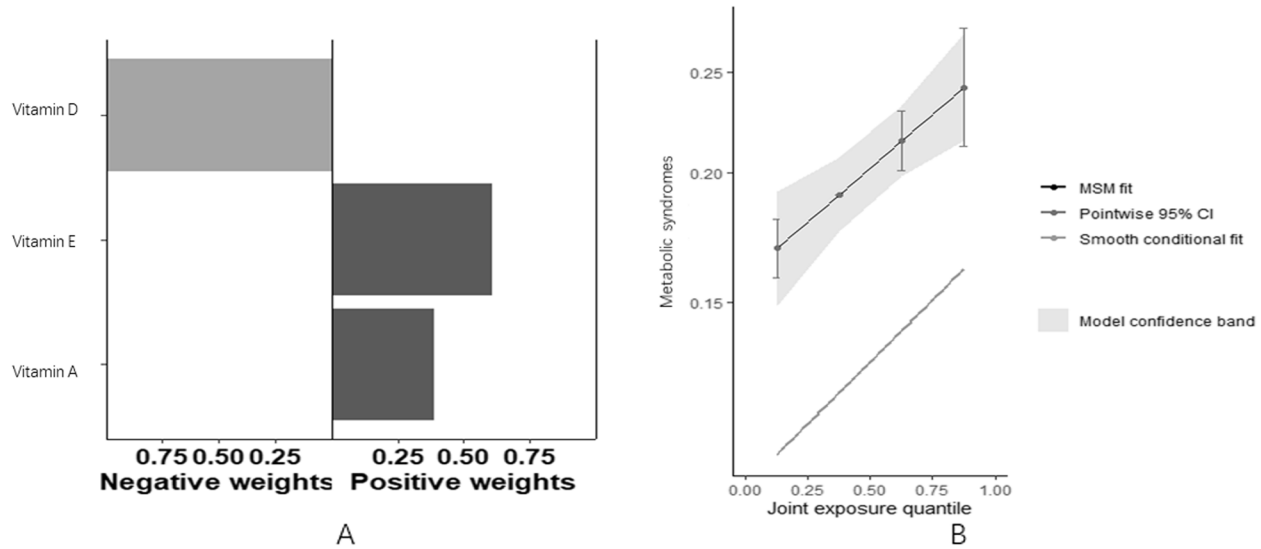

Fig. 4 Quantile g-computation model regression index weighs (**A**) and joint effect (**B**) (95% confidence interval) of fat-soluble vitamins (i.e., Vitamin A, Vitamin E, and Vitamin D) on metabolic syndrome

increased body mass, potentially leading to a dilution effect of VD; (3) VD deficiency may influence fat metabolism by modulating insulin secretion and sensitivity [36].

A notable finding of our study is the significant positive association between co-exposure to VA, VD and VE and MetS odds, as well as TG, HDL, and blood pressure. Our analysis revealed that VE was the primary contributor to this association, followed by VA. The interplay between FSVs during intestinal absorption may explain these observations. Aurélie Goncalves et al. demonstrated that medium–high VE status significantly enhanced VA uptake by 40%, while medium–high VA and high VE status significantly reduced VD uptake [21]. These interactions may account for the concurrent elevated serum VA and VE levels and lower serum VD levels observed in the MetS group in our study. Furthermore, epidemiological evidence suggested that while VD was negatively associated with cardiovascular disease mortality, this inverse association may be attenuated by circulating VA levels [37]. The molecular structure of VA derivatives may allow them to form heterodimers with receptors, potentially increasing the catabolism of VD [38]. Despite so, each FSV possesses specific roles in human physiology and development. The positive association between FSV co-exposure and MetS odds need more studies to prove and find out an appropriate exposure dose.

We noted that the prevalence of MetS in our study differed significantly from that reported in the study by Hirode et al. [5], despite both studies utilizing NHANES data. This discrepancy could be attributed to two explanations. First, the prevalence of MetS increases over time due to socio-economic development and population aging. The study by Hirode et al. used NHANES data from 2011–2016, while our study included NHANES rounds from 2003–2006 and 2017–2018. The combination of earlier NHANES rounds (2003–2004 and 2005–2006) may have led to an underestimation of the overall MetS prevalence in our study. Second, our study specially focused on participants with available data on both serum vitamins A, E and D and MetS. This selection criteria may have introduced a bias in our study population, resulting in a lower prevalence of MetS compared to the overall population.

Our study has several strengths. First, our study is the first to explore the associations between multiple FSVs co-exposure and MetS odds, as well as MetS components. Second, the quantile g-computation method is a new method that combined weighted quantile sum regression and Bayesian Kernel Machine regression, and it is very computationally efficient [39]. At the meantime, some limitations also should be noted. First, the present study is a cross-sectional study that cannot determine causality. Second, the single serum concentration measurement of FSVs could not represent the long-term exposure status. Third, we did not include Vitamin K due to the unavailable data. At last, we only included the U.S. population, thus the extrapolation of the conclusion would be limited.

Table 4 Weights of each serum vitamin in the association of multiple fat-soluble vitamins co-exposure with metabolic syndromes and each component

Fat-soluble Vitamins	Positive weight	Negative weight
Metabolism syndromes		
Vitamin A	0.390	0
Vitamin E	0.610	0
Vitamin D	0	1.000
Waist Circumference		
Vitamin A	0	0.307
Vitamin E	1.000	0
Vitamin D	0	0.693
Triglyceride		
Vitamin A	0.238	0
Vitamin E	0.762	0
Vitamin D	0	1.000
High-density lipoprotein		
Vitamin A	0	0.134
Vitamin E	1.000	0
Vitamin D	0	0.866
Blood pressure		
Vitamin A	0.400	0
Vitamin E	0.600	0
Vitamin D	0	1.000
Fasting plasma glucose		
Vitamin A	0.907	0
Vitamin E	0.093	0
Vitamin D	0	1.000

Concentrations of serum Vitamin A, Vitamin E, and Vitamin D were log-transformed and then standardized

Each component of metabolism syndromes was categorized based on NCEP: ATP III guidelines. Waist circumference was categorized into low (< 102 cm in men or < 88 cm in women) and high (≥ 102 cm in men or ≥ 88 cm in women) groups, and the low group was used as the reference; triglyceride was categorized into low (< 150 mg/dL) and high (≥ 150 mg/dL) groups, and the low group was used as the reference; high-density lipoprotein was categorized into low (< 40 mg/dL in men or < 50 mg/dL in women) and high (≥ 40 mg/dL in men or ≥ 50 mg/dL in women) groups, and the high group was used as the reference; blood pressure was categorized into low (systolic blood pressure < 130 mmHg and diastolic blood pressure < 85 mmHg) and high (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg) groups, and the low group was used as the reference; fasting plasma glucose was categorized into low (< 110 mg/dL) and high (≥ 110 mg/dL) groups, and the low group was used as the reference

Conclusion

Our study showed that serum VA and VE levels were positively associated with MetS odds, while high serum VD level was associated with decreased MetS odds. Co-exposure to FSVs (i.e. VA, VE, and VD) was positively associated with MetS odds. More prospective and experimental studies are needed to confirm our findings and elucidate the underlying mechanisms.

Abbreviations

BMI	Body mass index
FG	Fasting glucose
Family PIR	Family poverty income ratio
FSV	Fat-soluble vitamin
HDL	High-density lipoprotein
MET	Metabolic equivalent
MetS	Metabolic syndrome
NHANES	The National Health and Nutrition Examination Survey
TG	Triglyceride
VA	Vitamin A
VD	Vitamin D
VE	Vitamin E
WC	Waist circumference
WHO	The World Health Organization

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Disclosure statement

The authors have nothing to disclose.

Authors' contributions

D.J clarified the research concepts and methods.M.L and S.J performed the data curation, formal analysis and wrote the manuscript. M.L, C.D and D.J reviewed and edited papers. All authors read, reviewed and approved the final manuscript.

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Availability of data and materials

All data used in this study came from the NHANES, a publicly accessed database. All data can be viewed online or downloaded for analysis through the following link: http://www.cdc.gov/nchs/nhanes/index.htm, without any accession number.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The National Center for Health Statistics Research Ethics Review Board approved the protocol of the NHANES (NCHS IRB/ERB Protocol Number: Protocol #98–12, Protocol #2005–06, Continuation of Protocol #2011–17, and Protocol #2018–01). Each participant signed the informed consent form. We conducted a secondary data analysis using NHANES data, which can be accessed by the public. No further ethical approval and informed consent are required.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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