BMC Gastroenterology

RESEARCH

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Association between vitamin C, D, and K intake and inflammatory bowel disease risk: findings from 2009 to 2010 NHANES

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Abstract

Background Micronutrient deficiency is commonly observed in patients with inflammatory bowel disease (IBD), yet the role of certain dietary trace elements in the risk of IBD development remains unclear.

Objectives This study aimed to investigate the relationship between vitamin C, D, and K intake and IBD risk.

Methods This study included 3,591 participants from the 2009–2010 National Health and Nutrition Examination Survey (NHANES). Multivariable logistic regression were conducted to assess associations between vitamin C, D, and K intake and IBD risk while controlling for multiple confounders. Subgroup analyses were employed to test the robustness of the associations across participants with various characteristics. Additionally, restricted cubic spline (RCS) analysis was conducted to investigate potential nonlinear relationships.

Results In the fully adjusted model, each 1 mcg increase in vitamin D intake was linked to an approximately 51% decrease in IBD risk (adjusted OR = 0.49, 95% CI: 0.25–0.98, $p = 0.045$). The benefit appeared stronger in women, individuals without hypertension, and non-smokers. No statistically significant associations were found between vitamin C or vitamin K intake and IBD risk. However, among individuals without diabetes, each 1 mcg increase in vitamin K intake was associated with an approximate 67% reduction in IBD risk (adjusted OR = 0.33, 95% CI: 0.12–0.94, $p = 0.039$). RCS analysis suggested a linear relationship between dietary micronutrient intake and IBD risk (vitamin D: p for nonlinearity = 0.127, p for overall = 0.015; vitamin C: p for nonlinearity = 0.984, p for overall = 0.937; vitamin K: p for nonlinearity = 0.736, p for overall = 0.434).

Conclusion Increased vitamin D intake may reduce the risk of IBD, with more pronounced benefits in certain subgroups, highlighting the potential of vitamin D supplementation as a novel therapeutic approach for IBD prevention and management. Future well-designed studies should further test the therapeutic effects of vitamin D supplementation and investigate the associations of other dietary trace elements with IBD risk to better inform prevention and treatment approaches.

Keywords Dietary trace elements, Vitamin D, Vitamin C, Vitamin K, Inflammatory bowel disease, Inflammatory bowel disease (IBD), NHANES

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Introduction

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is a chronic inflammatory disorder of the gastrointestinal tract affecting 4.9 million people worldwide [1]. The past few decades have seen a rising global burden of IBD, characterized by sharp increases in incidence, prevalence, mortality, and disability-adjusted life-years (DALYs) in both developed and developing countries [2]. China and the United States (US) have the largest number of prevalent cases, mortality, and DALYs of IBD in the world, with substantial healthcare and societal burdens [1]. Identifying modifiable causes and risk factors of IBD is crucial in guiding further prevention and intervention programs to reduce the disease burden.

Research highlights that diet, lifestyle, environmental exposures, genetic predisposition, and gut microbiota significantly influence IBD development [2]. In recent years, dietary trace elements, such as vitamins C, D, and K, have garnered increasing research interest due to the commonly observed nutritional deficiency in IBD patients [3, 4]. These vitamins are considered to be beneficial to health due to their antioxidant, immune-regulatory, and anti-inflammatory effects, and their deficiency may be related to various inflammatory diseases, including IBD [3, 5]. For instance, vitamin D is a well-established immune modulator involved in immune cell differentiation, T-cell antigen receptor signaling, gut microbiota modulation, gene transcription, and barrier integrity [6]. Both animal models and epidemiological studies have consistently shown a significant association between low vitamin D levels and increased IBD [6, 7]. These findings suggest that vitamin D may be a contributing factor to IBD development, and vitamin D supplementation may be a cost-effective approach for IBD treatment [7, 8].

While vitamin D's role in IBD development is well-established, the clinical relevance of vitamins C and K remains less clear. Vitamin C is an antioxidant that can prevent free radical damage and reduce extracellular oxidants, which is vital for collagen synthesis and immune defense [9]. Vitamin C deficiency is more commonly observed in IBD patients than in the general population, mainly due to inadequate consumption and malabsorption of vitamin C in these patients [10, 11]. However, the association between vitamin C and IBD risk remains inconclusive, with some studies showing that a decreased level of vitamin C was associated with an increased risk of IBD [12–14], while others showed a non-significant association between them [15–17]. Therefore, more evidence is needed to confirm the role of vitamin C in IBD development.

The role of Vitamin K in IBD development has been studied even less. Vitamin K is a fat-soluble vitamin involved with multiple body functions, including blood coagulation, bone metabolism, and modulation of inflammatory responses [18]. Apart from its anti-hemorrhagic role, emerging evidence has shown that VitK can affect intestinal flora and gut permeability, which are essential in the development of IBD [19]. In addition, VitK exerts antioxidant, anti-inflammatory, and anti-atherosclerotic functions through the carboxylation of Gla-rich proteins [20]. Matrix Gla protein (MGP), a vitamin K-dependent protein, has demonstrated immunoregulatory properties by suppressing cell proliferation and cytokine production in T cells, which alleviated the clinical and histopathological severity of IBD in mouse models [20, 21]. However, more epidemiological and clinical studies are needed to explore the role of vitamin K in IBD development further.

To address the research gaps, we investigated the relationship between vitamin C, D, and K intake and IBD risk in American adults aged 20–60 using data from the National Health and Nutrition Examination Survey (NHANES). Additionally, we analyzed the influence of age, gender, physical activity, and chronic disease on these associations to test the robustness of such associations. Clarifying the impact of these vitamins on IBD development can guide dietary adjustments, serving as potential preventive or therapeutic strategies for IBD management.

Materials and methods

Study population

The NHANES, conducted by the National Center for Health Statistics (NCHS), assesses the health and nutritional status of non-institutionalized adults and children across the United States. This study analyzed data from the 2009–2010 NHANES cycle, including 10,537 participants. Applying strict exclusion criteria, 6,946 individuals were removed from the sample, resulting in a final sample of 3,591 participants. We excluded individuals who (1) were over 60 years old ($n = 731$), (2) lacked information on IBD status ($n = 5,441$), (3) lacked data on vitamin C, D, or K intake ($n = 339$), (4) lacked data on covariates including family income to poverty ratio (PIR), body mass index (BMI), alcohol consumption, diabetes, hypertension, and cardiovascular disease (CVD) ($n = 435$) (Fig. 1).

Measurements

Vitamins C, D, and K intake

Data on dietary intake of vitamins C, D, and K were collected through NHANES Day 1 and Day 2 dietary interviews. Each participant's total dietary intake was recorded over two non-consecutive 24-hour periods: the first interview was conducted during the Medical Executive Committee (MEC) visit and the second via telephone a few days later. Both interviews were performed by trained dietitians using the Automated Multiple-Pass

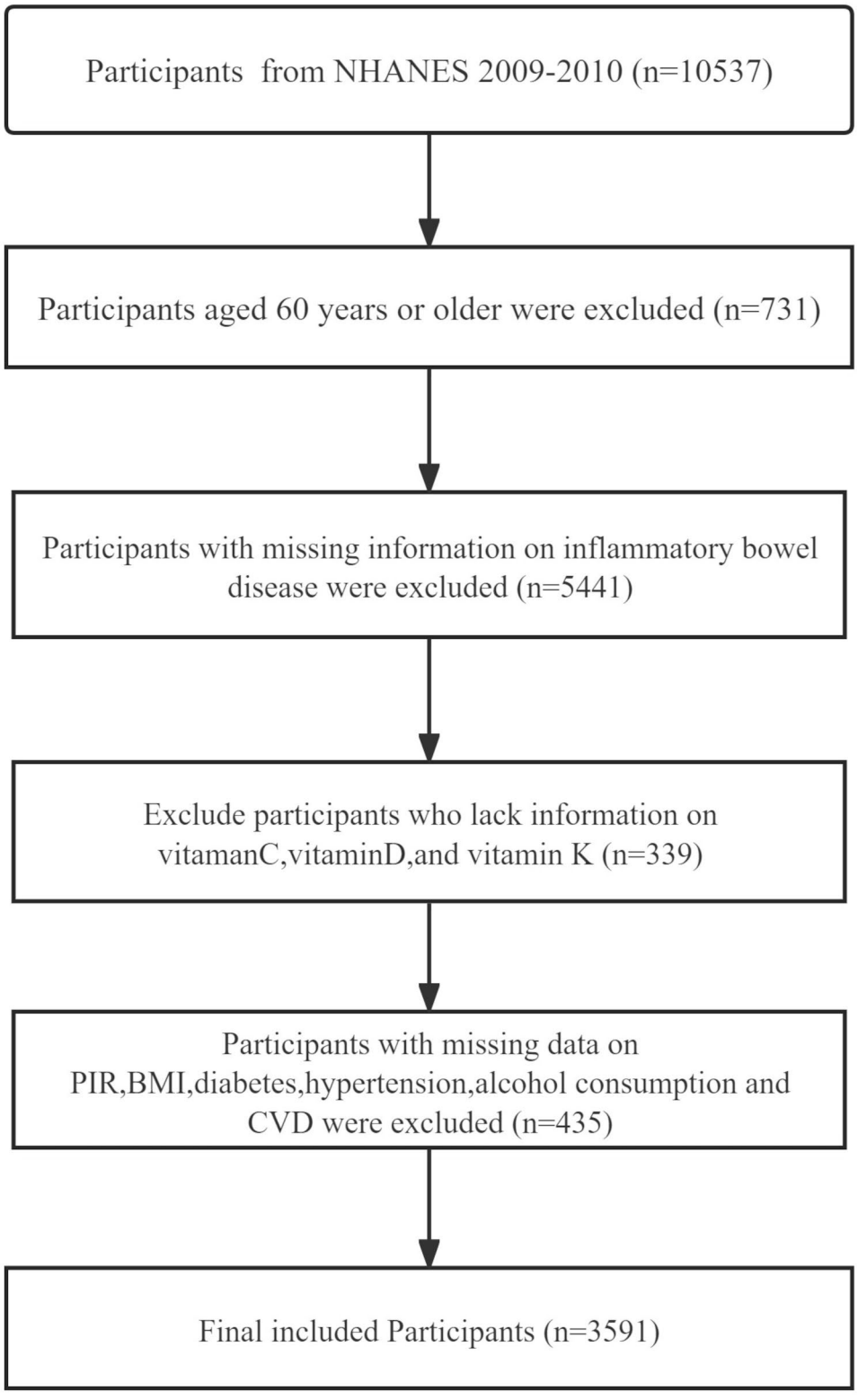

Fig. 1 Flow chart of participant selection in this study, NHANES 2009–2010

Method (AMPM) to ensure accurate reporting of all food and drink consumption. After collecting details about the portion sizes and preparation methods of food and drinks from two 24-hour dietary recalls, we further matched the food and drinks to entries in the USDA National Nutrient Database to determine their vitamin contents. We also collected participants' dietary supplement usage, including types and frequency of vitamin consumption, over the past month through additional questionnaires to calculate overall vitamin intake. Finally, we used statistical models to estimate "usual" vitamin intake, accounting for recall variability and sampling design.

IBD

In the 2009–2010 NHANES cycle, IBD status was assessed through the "arthritis" questionnaire, which identified participants with Crohn's disease (CD) or ulcerative colitis (UC). Participants who answered "yes" to the question, "Have you ever been told you had Ulcerative Colitis or Crohn's disease?" were classified as having IBD.

$$PA\,(MET - \min/week) = MET \times Duration \times Weekly\,frequency\,Co\,\mathrm{var}\,iates$$

Sociodemographic characteristics, lifestyle factors, and other chronic diseases were included as study covariates. These variables encompassed age, sex, race/ethnicity (categorized as Mexican American, Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other Race), education level (< 9th grade, 9–11th grade, high school diploma/general educational development [GED], some college/Associate of Arts [AA] degree, and ≥ college graduate), PIR, BMI, smoking, alcohol use, physical activity (PA), hypertension, diabetes, and CVD.

PIR was calculated by dividing family income by poverty guidelines specific to the survey year, which was further categorized into low (PIR ≤ 1), middle (1 < PIR < 4), and high (PIR ≥ 4) household income [22]. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). According to smoking status, participants were classified into non-smokers (never smoked or quit over one year ago) and current smokers (recent or resumed smoking). According to alcohol use status, participants were categorized as non-drinkers (fewer than 12 drinks of alcohol during their lifetime) and current drinkers (at least 12 drinks of alcohol per year or six drinks in the past 12 months).

Physical activity (PA) was evaluated based on participants' self-reported data using the Global Physical Activity Questionnaire. Metabolic Equivalent (MET), a measure of relative energy expenditure across activities, was calculated from MET values, frequency of exercise per week, and duration. Participants were categorized as inactive if their PA was < 600 MET-min/week and as active if their PA was ≥ 600 MET-min/week. The calculation formula of PA is as follows:

$$PA\,(MET - min/week) = MET \times Duration \times Weekly\,frequency$$

Hypertension was defined as either a history of high blood pressure or current use of prescribed antihypertensive medications. Diabetes was determined by a doctor's diagnosis, two-hour glucose (OGTT) ≥ 11.1 mmol/L, or fasting glucose ≥ 7.0 mmol/L. At the same time, prediabetes was defined by a prior diagnosis, two-hour glucose (OGTT) between 7.8 and 11.1 mmol/L, or fasting glucose between 6.1 and 6.9 mmol/L. CVD was determined by one self-reported question in the Medical Conditions Questionnaire. Participants who answered "yes" to the question, "Have you ever been told you had congestive heart failure, coronary heart disease, angina, heart attack, or stroke?" were classified as having CVD.

Statistical analyses

All statistical analyses adhered to NHANES guidelines. Final weights were assigned according to NHANES data analysis recommendations for the 2009–2010 cycle, with each weighted sample representing approximately 40,580 Americans. Continuous variables were summarized as means with standard deviations (SD), and categorical variables as counts with weighted percentages. Group differences were assessed using chi-square tests for categorical variables and Student's t-tests for continuous variables.

Multivariable logistic regression was used to examine associations between vitamin intake and IBD, adjusting for potential confounders. Model 1 involved unadjusted univariate analysis; Model 2 adjusted for age, sex, race/ethnicity, education, PIR, and BMI; Model 3 further adjusted for alcohol use and smoking, hypertension, and diabetes; and Model 4 additionally adjusted for CVD and PA. Restricted cubic spline (RCS) analysis was conducted to evaluate nonlinear relationships between vitamin intake and IBD risk. Subgroup and interaction analyses were conducted across participants with various characteristics. Missing data were handled using multiple imputations, preserving sample size and reducing potential bias. Data were processed and analyzed using IBM SPSS Statistics (version 24.0) and R software (version 4.3.0), with statistical significance set at a two-sided p-value < 0.05.

Results

Characteristics of participants by IBD status

This study included 3,591 participants from the NHANES 2009–2010 cycle, with a mean age of 39.90

years (SD = 11.83). Among these, 1,824 were female (50.79%) and 1,767 were male (49.21%). Thirty-six participants were diagnosed with IBD, with an average age of 45.72 years (SD = 11.95). Table 1 shows the comparison of baseline characteristics between participants with and without IBD. Compared to healthy participants, those with IBD tended to be older (mean age 45.72 vs. 39.84, $p = 0.003$) and were more likely to have hypertension (52.78% vs. 47.22%, $p < 0.001$). No statistically significant differences in dietary intake of vitamin C (mean 161.64 vs. 161.45, $p = 0.994$), vitamin D (mean 8.11 vs. 9.40, $p = 0.353$), or vitamin K (mean 179.78 vs. 176.17, $p = 0.920$) were observed between participants with and without IBD. Intake distributions for all three micronutrients were tested for normality; as vitamin C, D, and K intakes were skewed, logarithmic transformations were applied to normalize these distributions (Fig. 2).

Relationship between vitamin intake and IBD risk

Table 2; Fig. 3 present associations between each vitamin intake and IBD risk. In the unadjusted model, vitamin D intake was inversely associated with IBD risk (OR = 0.51, 95% CI: 0.26–0.97, $p = 0.040$), vitamin C intake showed a non-significant positive association (OR = 1.25, 95% CI: 0.61–2.57, $p = 0.534$), and vitamin K intake showed a non-significant inverse association (OR = 0.57, 95% CI: 0.25–1.30, $p = 0.184$). After adjusting for confounders in Model 4, the inverse association for vitamin D intake and IBD risk remained significant (adjusted OR = 0.49, 95% CI: 0.25–0.98, $p = 0.045$). Notably, each 1 mcg increase in vitamin D intake was associated with a 51% reduction in IBD risk. After adjustments, neither vitamin C intake (adjusted OR = 1.25, 95% CI: 0.57–2.75, $p = 0.579$) nor vitamin K intake (adjusted OR = 0.53, 95% CI: 0.21–1.34, $p = 0.182$) showed statistically significant associations with IBD risk. Participants were categorized into quartiles by vitamin intake levels, and adjusted comparisons across quartiles showed no statistically significant association with IBD risk for any of the nutrients (Fig. 4). Trend tests across quartiles for each micronutrient also yielded no statistically significant results ($p > 0.05$).

Subgroup analysis of the relationship between vitamin intake and IBD risk

Subgroup analysis examined whether associations between vitamin intake and IBD risk varied across participants with various characteristics. An inverse association between vitamin D intake and IBD risk was observed among female participants (adjusted OR = 0.39, 95% CI: 0.17–0.92, $p = 0.032$), non-hypertensive individuals (adjusted OR = 0.33, 95% CI: 0.13–0.81, $p = 0.016$), and non-smokers (adjusted OR = 0.44, 95% CI: 0.19–0.99, $p = 0.032$). An inverse association between vitamin K intake and IBD risk was observed in individuals without diabetes (adjusted OR = 0.33, 95% CI: 0.12–0.94, $p = 0.039$). Vitamin C intake was not significantly associated with IBD risk in any subgroup. Interaction tests showed significant interactions between diabetes status and both vitamin C (p for interaction = 0.009) and vitamin K (p for interaction < 0.001) in relation to IBD risk (Fig. 5).

Linear and nonlinear relationships between vitamin intake and IBD risk

RCS analysis illustrated the relationship between vitamin intake and IBD risk. Figure 6 presents the RCS analysis results for each vitamin. In the unadjusted model, a linear relationship was found between each vitamin and IBD risk (vitamin D: p for nonlinear = 0.186, p for overall = 0.019; vitamin C: p for nonlinear = 0.931, p for overall = 0.919; vitamin K: p for nonlinear = 0.846, p for overall = 0.518). After adjusting for confounders, the linear relationships remained consistent (vitamin D: p for nonlinear = 0.127, p for overall = 0.015; vitamin C: p for nonlinear = 0.948, p for overall = 0.937; vitamin K: p for nonlinear = 0.736, p for overall = 0.434).

Discussion

This study examined the relationship between dietary intake of vitamins C, D, and K and the risk of IBD in U.S. adults aged 20–60. A notable finding was the inverse association between vitamin D intake and IBD risk, with each 1 mcg increase in vitamin D intake linked to a 51% reduction in IBD risk, even after adjusting for confounders. In contrast, vitamins C and K showed no statistically significant associations with IBD risk. Subgroup analyses revealed that the protective effect of vitamin D intake on IBD risk was particularly pronounced among women, non-smokers, and individuals without hypertension. Additionally, vitamin K intake was significantly associated with a reduced IBD risk among those without diabetes.

Our findings were consistent with previous research, which supports the protective role of vitamin D in modulating immune function and reducing inflammatory responses. Studies have shown that higher serum vitamin D levels are associated with a lower risk of IBD [23]. This protective relationship may be attributed to vitamin D's role in maintaining the integrity of the intestinal epithelial barrier and dampening inflammation [24, 25]. Vitamin D has been shown to support the intestinal mucosa by modulating the expression of tight junction proteins, such as claudin-4, claudin-7, and claudin-2, within intestinal epithelial cells [26]. Additionally, vitamin D may improve gut health and reduce IBD risk by positively influencing gut microbiota composition [6]. In a cross-sectional study of 567 elderly male participants, random forest analysis indicated that higher vitamin D and its

Table 1 Characteristics of NHANES (2009–2010) participants aged 20 to 60 years with IBD (*N* = 3591)

Variables	Total (*n* = 3591)	No IBD (*n* = 3555)	IBD (*n* = 36)	*P*
Age(year)[a], Mean ± SD	39.90 ± 11.83	39.84 ± 11.81	45.72 ± 11.95	0.003
Sex[b], *n*(%)				0.056
Female	1824 (50.79)	1800 (50.63)	24 (66.67)	
Male	1767 (49.21)	1755 (49.37)	12 (33.33)	
Race/ethnicity[b], *n*(%)				0.544
Mexican American	717 (19.97)	708 (19.92)	9 (25.00)	
Other Hispanic	393 (10.94)	389 (10.94)	4 (11.11)	
Non-Hispanic White	1624 (45.22)	1606 (45.18)	18 (50.00)	
Non-Hispanic Black	653 (18.18)	648 (18.23)	5 (13.89)	
Other Race	204 (5.68)	204 (5.74)	0 (0.00)	
Education[b], *n*(%)				0.044
< 9th grade	347 (9.66)	342 (9.62)	5 (13.89)	
9–11th grade	568 (15.82)	559 (15.72)	9 (25.00)	
High school diploma/GED	847 (23.59)	844 (23.74)	3 (8.33)	
Some College/AA degree	1061 (29.55)	1046 (29.42)	15 (41.67)	
≥College graduate	768 (21.39)	764 (21.49)	4 (11.11)	
Family income to poverty ratio[a], Mean ± SD	2.42 ± 1.58	2.42 ± 1.58	2.25 ± 1.50	0.515
BMI[a], Mean ± SD	29.21 ± 7.12	29.22 ± 7.12	28.78 ± 6.29	0.714
Hypertension[b], *n*(%)				< 0.001
No	2767 (77.05)	2750 (77.36)	17 (47.22)	
Yes	824 (22.95)	805 (22.64)	19 (52.78)	
Diabetes[b], *n*(%)				0.822
No	2822 (78.59)	2794 (78.59)	28 (77.78)	
Yes	293 (8.16)	291 (8.19)	2 (5.56)	
Borderline	476 (13.26)	470 (13.22)	6 (16.67)	
Drinking status[b], *n*(%)				0.711
No	381 (10.61)	376 (10.58)	5 (13.89)	
Yes	3210 (89.39)	3179 (89.42)	31 (86.11)	
Smoking status[b], *n*(%)				0.820
No	2653 (73.88)	2627 (73.90)	26 (72.22)	
Yes	938 (26.12)	928 (26.10)	10 (27.78)	
Cardiovascular disease[b], *n*(%)				0.461
No	3432 (95.57)	3399 (95.61)	33 (91.67)	
Yes	159 (4.43)	156 (4.39)	3 (8.33)	
Physical activity[b], *n*(%)				0.274
No	1284 (35.76)	1268 (35.67)	16 (44.44)	
Yes	2307 (64.24)	2287 (64.33)	20 (55.56)	
Vitamin C (mg)[a], Mean ± SD	161.45 ± 155.51	161.45 ± 155.72	161.64 ± 134.30	0.994
Vitamin C group[b], *n*(%)				0.525
Q1	897 (24.98)	887 (24.95)	10 (27.78)	
Q2	897 (24.98)	891 (25.06)	6 (16.67)	
Q3	899 (25.03)	887 (24.95)	12 (33.33)	
Q4	898 (25.01)	890 (25.04)	8 (22.22)	
Vitamin D (mcg)[a], Mean ± SD	9.39 ± 8.26	9.40 ± 8.27	8.11 ± 7.54	0.353
Vitamin D group[b], *n*(%)				0.192
Q1	876 (24.39)	863 (24.28)	13 (36.11)	
Q2	902 (25.12)	897 (25.23)	5 (13.89)	
Q3	910 (25.34)	899 (25.29)	11 (30.56)	
Q4	903 (25.15)	896 (25.20)	7 (19.44)	
Vitamin K (mcg)[a], Mean ± SD	176.21 ± 214.12	176.17 ± 212.04	179.78 ± 370.34	0.920
Vitamin K group[b], *n*(%)				0.667
Q1	898 (25.01)	887 (24.95)	11 (30.56)	
Q2	896 (24.95)	887 (24.95)	9 (25.00)	

Table 1 (continued)

Variables	Total ($n=3591$)	No IBD ($n=3555$)	IBD ($n=36$)	*P*
Q3	899 (25.03)	889 (25.01)	10 (27.78)	
Q4	898 (25.01)	892 (25.09)	6 (16.67)	

a: Student t-test, b: Chi-square test, SD: standard deviation

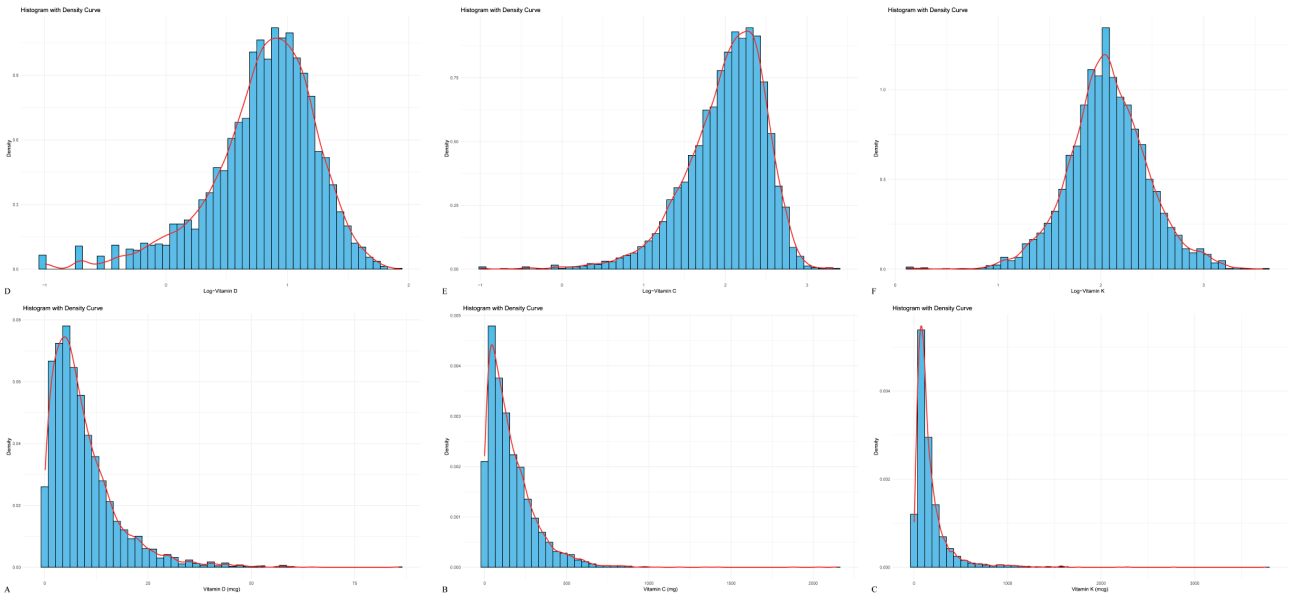

Fig. 2 Normality test of the distribution of different dietary trace elements (vitamin C, vitamin D, vitamin K)

metabolites were associated with an increased abundance of beneficial gut bacteria [27]. Further research suggests that higher vitamin D intake may enhance treatment outcomes and prognosis in cancer patients [28]. Notably, a bidirectional relationship exists between vitamin D and the gut microbiota, as the microbiota can influence both vitamin D absorption and its function [8]. Noteworthily, the inverse association between vitamin D intake and IBD risk observed in this cross-sectional study may be interpreted as a bidirectional relationship, suggesting that vitamin D deficiency may be both a cause and a consequence of IBD [6]. These findings suggest the potential of vitamin D supplementation in the prevention and treatment of IBD [8].

Vitamin K, a fat-soluble vitamin, plays a crucial role in coagulation, bone health, nervous system function, and metabolism [29–31]. Beyond its role in coagulation, vitamin K also exerts anti-inflammatory, antioxidant, and immune-regulatory effects, which may influence IBD risk. Research suggested that vitamin K-dependent proteins (VKDPs) may have mediated these effects, contributing to anti-inflammatory, anti-tumor, and immune-modulating actions [32, 33]. For instance, growth arrest-specific gene 6 (Gas6) is a widely expressed vitamin K-dependent protein that can regulate homeostasis and inflammation by inhibiting the production of pro-inflammatory cytokines (e.g., TNF, IL-6, and IL-1β), promoting phagocytosis of apoptotic cell debris, and protecting cells from stress-induced apoptosis [34, 35]. Additionally, vitamin K helps prevent IBD by reducing gut inflammation and oxidative stress, enhancing the composition of the gut microbiota, and modulating microbial metabolites [36, 37]. These mechanisms align with findings from prior research, further supporting the potential protective role of vitamin K in IBD prevention.

Our results showed a positive, though not statistically significant, correlation between vitamin C intake and IBD risk, which was partially in agreement with previous studies. While some studies in Japan and Iran showed that increasing vitamin C intake could reduce the risk of IBD [12–14], other studies in European countries and Israel showed no significant association between vitamin C intake and IBD risk [15–17]. Vitamin C is generally considered to have anti-inflammatory properties, and research has demonstrated that vitamin C can enhance immune cell function and modulate immune responses, influencing anti-tumor, antioxidant, and anti-inflammatory pathways [38, 39]. However, high doses of vitamin C may potentially exacerbate inflammation by stimulating immune cell activity, especially in inflammatory conditions with highly activated immune systems [14, 40, 41]. Patients with IBD already have a dysregulated immune system, and vitamin C's immune-stimulatory effects may potentially worsen inflammation. Studies show that

Table 2 Associations between dietary trace elements and IBD risk in NHANES participants aged 20–60 years (2009–2010)

Variables	Model1		Model2		Model3		Model4	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Log-Vitamin D	0.51 (0.26 ~ 0.97)	0.040	0.49 (0.25 ~ 0.97)	0.040	0.49 (0.24 ~ 0.97)	0.042	0.49 (0.25 ~ 0.98)	0.045
Log-Vitamin D group								
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	0.38 (0.13 ~ 1.07)	0.066	0.37 (0.13 ~ 1.04)	0.059	0.35 (0.12 ~ 0.99)	0.050	0.35 (0.12 ~ 1.01)	0.053
Q3	0.84 (0.37 ~ 1.89)	0.675	0.84 (0.37 ~ 1.90)	0.672	0.80 (0.35 ~ 1.84)	0.606	0.81 (0.35 ~ 1.86)	0.621
Q4	0.53 (0.21 ~ 1.34)	0.182	0.57 (0.22 ~ 1.44)	0.233	0.58 (0.22 ~ 1.48)	0.253	0.58 (0.22 ~ 1.49)	0.256
P for trend	0.271		0.327		0.332		0.341	
Log-Vitamin C	1.25 (0.61 ~ 2.57)	0.534	1.26 (0.59 ~ 2.71)	0.554	1.23 (0.56 ~ 2.70)	0.604	1.25 (0.57 ~ 2.75)	0.579
Log-Vitamin C group								
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	0.67 (0.24 ~ 1.88)	0.441	0.64 (0.22 ~ 1.83)	0.406	0.62 (0.22 ~ 1.80)	0.381	0.63 (0.22 ~ 1.81)	0.388
Q3	1.34 (0.56 ~ 3.19)	0.510	1.25 (0.51 ~ 3.07)	0.619	1.30 (0.53 ~ 3.22)	0.569	1.33 (0.53 ~ 3.30)	0.543
Q4	0.89 (0.34 ~ 2.31)	0.808	0.91 (0.34 ~ 2.44)	0.852	0.89 (0.32 ~ 2.43)	0.817	0.90 (0.33 ~ 2.47)	0.837
P for trend	0.869		0.864		0.868		0.845	
Log-Vitamin K	0.57 (0.25 ~ 1.30)	0.184	0.54 (0.22 ~ 1.34)	0.185	0.53 (0.21 ~ 1.33)	0.176	0.53 (0.21 ~ 1.34)	0.182
Log-Vitamin K group								
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	0.82 (0.34 ~ 1.98)	0.657	0.77 (0.31 ~ 1.90)	0.576	0.77 (0.31 ~ 1.92)	0.577	0.78 (0.31 ~ 1.93)	0.589
Q3	0.91 (0.38 ~ 2.15)	0.824	0.93 (0.38 ~ 2.27)	0.874	0.93 (0.38 ~ 2.30)	0.873	0.93 (0.37 ~ 2.29)	0.869
Q4	0.54 (0.20 ~ 1.47)	0.230	0.53 (0.18 ~ 1.50)	0.231	0.53 (0.18 ~ 1.53)	0.240	0.53 (0.18 ~ 1.55)	0.247
P for trend	0.275		0.294		0.305		0.313	

OR: Odds Ratio, CI: Confidence Interval

Model1: Crude

Model2: Adjust: Sex, Age, Race/ethnicity, Education, Family income to poverty ratio, BMI

Model3: Adjust: Sex, Age, Race/ethnicity, Education, Family income to poverty ratio, BMI, Drinking status, Smoking status, Hypertension, Diabetes

Model4: Adjust: Sex, Age, Race/ethnicity, Education, Family income to poverty ratio, BMI, Drinking status, Smoking status, Hypertension, Diabetes, Cardiovascular disease, Physical activity

vitamin C can exacerbate oxidative stress in IBD via activating redox-active metal ions, which activate the reactive oxygen and nitrogen species (RONS) and enhance the production of reactive oxygen and nitrogen species, leading to inflammation [42]. In addition, vitamin C supplementation is not recommended for IBD patients due to its digestive side effects, including gas, bloating, and diarrhea [43]. These findings suggest that the effect of vitamin C on IBD may vary according to doses, populations, and existing immunity conditions, which warrants caution and requires further research.

Our study also highlighted a gender-specific link between vitamin D intake and IBD risk, with a more pronounced association observed in female participants. Although the role of sex hormones in vitamin D metabolism is not fully understood, higher vitamin D levels among females may be linked to estrogen. Evidence suggests that estradiol may inhibit the enzyme responsible for degrading 1,25-dihydroxy vitamin D3, thereby influencing vitamin D status [44, 45]. Estrogen's role in IBD remains inconclusive; some studies propose that estrogen may impact the composition of gut microbiota, reinforce the intestinal epithelial barrier, and modulate immune responses in the gut, potentially influencing IBD development [46–48]. Other findings, however, indicate that estrogen may facilitate the onset and progression of IBD [49–51].

An additional finding was the protective effect of vitamin K against IBD, observed exclusively in the non-diabetic subgroup, suggesting a complex interaction between metabolic status and vitamin K. This effect may relate to vitamin K's involvement in insulin resistance and glucose metabolism [52, 53]. Lower vitamin K levels have been associated with increased insulin resistance, a hallmark of type II diabete [54]. Consequently, vitamin K may provide differential protective effects against IBD in diabetic and non-diabetic populations. Future research should investigate how metabolic conditions, such as diabetes, may influence the nutrition-disease association.

Noteworthily, we controlled a range of covariates that act as potential confounders, such as PIR and BMI, in the association between vitamin intake and IBD risk. PIR, an important indicator of income and poverty, has emerged as a critical social determinant of nutrition and health that draws increasing research attention [55]. A prospective cohort study based on the 2001–2018 NHANES showed that higher PIR was associated with a reduced risk of all-cause mortality in participants with

Fig. 3 Heat map of the relationship between different dietary trace elements and the risk of IBD

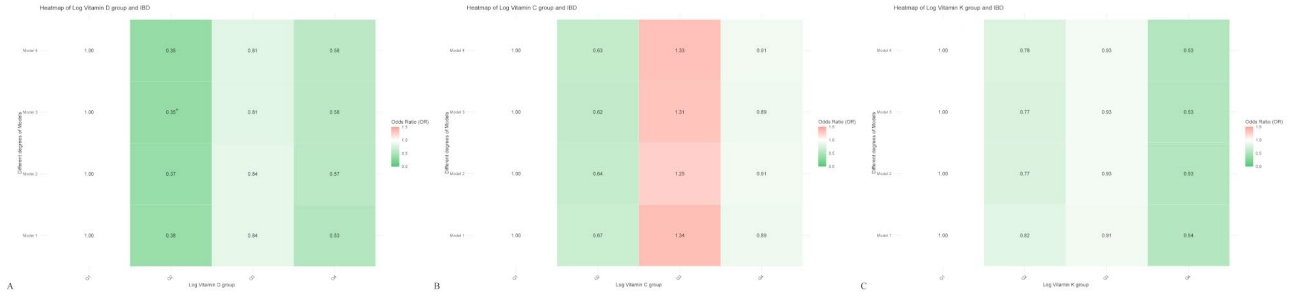

Fig. 4 Heat map of the relationship between dietary trace element intake in different quantiles and the risk of IBD

prediabetes and diabetes, and PIR mediated the association between healthy lifestyle and all-cause mortality [56]. BMI is another well-known factor that is linked to both diet and IBD. A systematic review of 15.6 million participants showed that both underweight and obesity were associated with an increased risk of IBD [57]. These confounding variables have significant implications in nutritional epidemiology studies, and future studies may consider further investigating their potential mediating or moderating roles in the association between vitamin intake and IBD development.

Despite these findings, several limitations must be noted. First, the cross-sectional design restricts causal inference between micronutrient intake and IBD risk, emphasizing the need for longitudinal studies to verify these associations. Second, we excluded participants with missing information on key study variables and covariates, which may introduce potential bias. For instance, CVD is a well-known confounder of various inflammatory conditions, including IBD. Our study excluded 16 participants whose CVD status remained unknown, which may potentially affect the observed association between vitamin intake and IBD risk. Third,

Subgroup analysis of the association between trace dietary elements and IBD risk in NHANES participants aged 20-60 years

Variables	n (%)	OR (95%CI)	*P*	Vitamin D	P for interaction	OR (95%CI)	*P*	Vitamin C	P for interaction	OR (95%CI)	*P*	Vitamin K	P for interaction
Sex					0.529				0.682				0.158
Female	1824 (50.79)	0.39 (0.17 ~ 0.92)	0.032			1.35 (0.47 ~ 3.85)	0.576			0.30 (0.09 ~ 1.00)	0.051		
Male	1767 (49.21)	0.69 (0.20 ~ 2.37)	0.554			0.97 (0.27 ~ 3.43)	0.958			1.13 (0.24 ~ 5.30)	0.874		
Age					0.873				0.509				0.493
<= 40	1720 (47.90)	0.63 (0.15 ~ 2.75)	0.540			1.81 (0.33 ~ 10.04)	0.499			0.26 (0.03 ~ 2.00)	0.196		
> 40	1871 (52.10)	0.46 (0.20 ~ 1.06)	0.068			0.97 (0.40 ~ 2.37)	0.944			0.65 (0.21 ~ 2.02)	0.453		
Hypertension					0.111				0.667				0.141
No	2767 (77.05)	0.33 (0.13 ~ 0.81)	0.016			1.26 (0.43 ~ 3.70)	0.680			0.28 (0.08 ~ 1.01)	0.052		
Yes	824 (22.95)	0.95 (0.30 ~ 2.97)	0.931			1.33 (0.39 ~ 4.54)	0.654			1.29 (0.31 ~ 5.36)	0.727		
Diabetes					0.688				0.009				<.001
No	2822 (78.59)	0.51 (0.23 ~ 1.14)	0.102			0.92 (0.40 ~ 2.13)	0.848			0.33 (0.12 ~ 0.94)	0.039		
Yes	293 (8.16)	0.00 (0.00 ~ Inf)	0.998			0.00 (0.00 ~ Inf)	0.998			0.00 (0.00 ~ Inf)	0.999		
Borderline	476 (13.26)	0.29 (0.01 ~ 9.32)	0.486			1238.70 (1.65 ~ 929213.42)	0.035			140.12 (2.58 ~ 7615.90)	0.015		
Smoke					0.627				0.338				0.656
No	2653 (73.88)	0.44 (0.19 ~ 0.99)	0.047			1.07 (0.41 ~ 2.80)	0.890			0.44 (0.14 ~ 1.43)	0.174		
Yes	938 (26.12)	0.67 (0.16 ~ 2.83)	0.590			1.86 (0.47 ~ 7.45)	0.378			0.81 (0.17 ~ 3.91)	0.794		
Drink					0.588				0.529				0.470
No	381 (10.61)	0.00 (0.00 ~ Inf)	0.995			0.00 (0.00 ~ Inf)	0.988			2.77 (0.00 ~ Inf)	0.799		
Yes	3210 (89.39)	0.54 (0.25 ~ 1.18)	0.124			1.37 (0.59 ~ 3.19)	0.461			0.46 (0.17 ~ 1.24)	0.124		
Physical activity					0.712				0.495				0.659
No	1284 (35.76)	0.45 (0.15 ~ 1.38)	0.163			1.61 (0.42 ~ 6.16)	0.483			0.74 (0.14 ~ 3.94)	0.721		
Yes	2307 (64.24)	0.40 (0.15 ~ 1.05)	0.064			1.15 (0.41 ~ 3.18)	0.791			0.44 (0.13 ~ 1.43)	0.172		
Cardiovascular disease					0.975				0.300				0.890
No	3432 (95.57)	0.50 (0.24 ~ 1.03)	0.061			1.10 (0.49 ~ 2.48)	0.812			0.50 (0.19 ~ 1.33)	0.167		
Yes	159 (4.43)	0.00 (0.00 ~ Inf)	1.000			0.00 (0.00 ~ Inf)	1.000			0.00 (0.00 ~ Inf)	1.000		

OR: Odds Ratio, CI: Confidence Interval

Fig. 5 Subgrop analysis of the association between trace dietary elements and IBD risk in NHANES participants aged 20–60 years

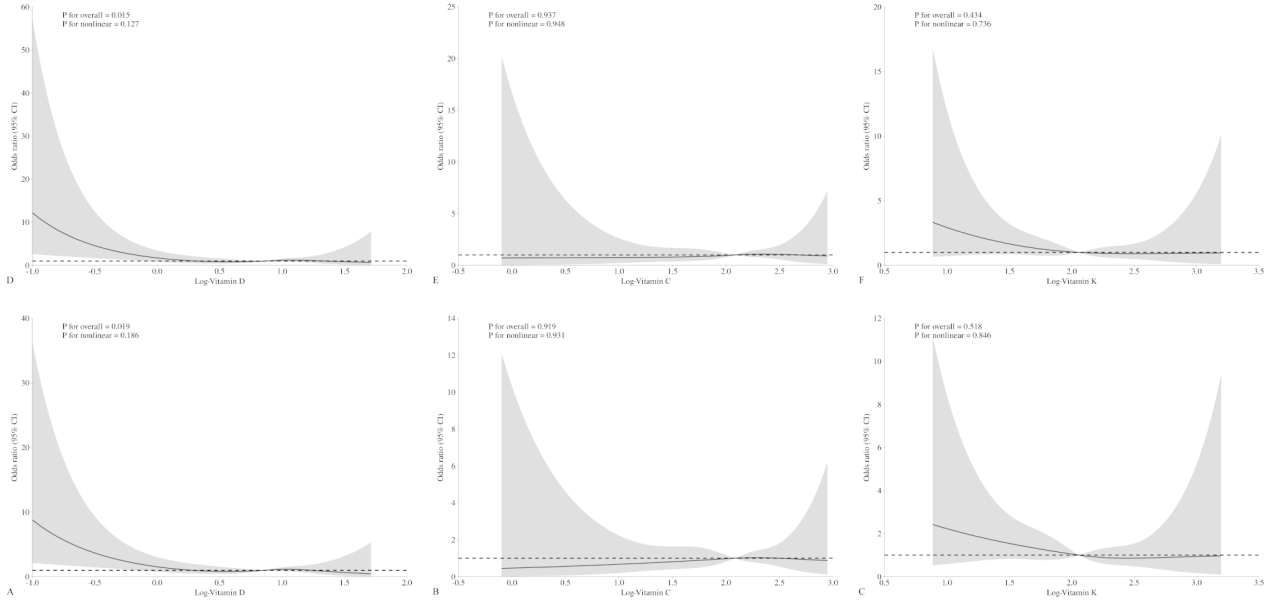

Fig. 6 RCS analysis of the relationship between different dietary trace element intakes and the risk of IBD

dietary intake was assessed based on two 24-hour dietary recalls using the AMPM method, which, although being a robust method, is subject to recall bias. For instance, participants may underreport or misreport certain foods and consumption frequency, which may affect the accuracy of the final calculation. Fourth, IBD status was determined based on one self-reported question from the participants, which is subject to potential bias. Future studies may consider using physician diagnosis or other more objective tools for IBD assessment. Fifth, although we adjusted for numerous potential confounders, unmeasured dietary variables may still impact our results. Sixth, IBD-related data were only collected during the NHANES 2009–2010 cycle, which could result in sample size discrepancies that may skew the associations, particularly regarding vitamins C and K. Finally, our study was focused on three vitamins, C, D, and K, which may not fully capture the role of dietary trace elements, especially fat-soluble vitamin (vitamin E), in the risk of IBD, which will be our next research step. Future studies with larger, more diverse IBD samples would improve the robustness of these findings.

Conclusion and implications

This study identified a significant inverse association between vitamin D intake and IBD risk, with this protective effect varying by gender, hypertension status, and smoking habits. No significant associations were found between vitamin C or vitamin K intake and overall IBD risk, though a significant inverse association between

vitamin K intake and IBD risk was observed in non-diabetic individuals. These findings highlight the complex relationship between dietary trace elements and IBD risk, potentially driven by diverse mechanisms.

Our findings offer fresh insights into the role of dietary trace elements in IBD development, which carry significant implications for the detection and management of IBD. First, the finding that vitamin D level was negatively associated with IBD risk in this observational study suggests that vitamin D deficiency may be both a cause and consequence of IBD. Therefore, serum Vitamin D may potentially serve as a biomarker for the screening and diagnosis of IBD, which is cheaper and less invasive than traditional endoscopy and biopsies. In addition, given the protective role of vitamin D in IBD, it is suggested that increasing vitamin D to an appropriate level through vitamin D supplementation may be a promising complementary therapy for IBD patients. Meanwhile, we still need more evidence, especially well-designed therapeutic studies, to test the therapeutic effects of vitamin D supplementation (and the appropriate doses) in the prevention and treatment of IBD, as well as the underlying mechanisms at the genetic, metabolic, and immunological levels. Furthermore, future studies should further investigate the associations of vitamin C, vitamin K, and other dietary trace elements with IBD risk to better inform prevention and treatment approaches.

Abbreviations

IBD	Inflammatory bowel disease
MEC	Medical Executive Committee
NHANES	National Health and Nutrition Examination Survey
RCS	Restricted cubic spline
NCHS	National Center for Health Statistics
VKDPs	Vitamin K-dependent proteins

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03747-9 .

Supplementary Table 1: Trend analysis between Log vitamin D and the risk of IBD

Supplementary Table 2: Trend analysis between Log vitamin C and the risk of IBD

Supplementary Table 3: Trend analysis between Log vitamin K and the risk of IBD

Acknowledgements

We acknowledged the staff of the National Center for Health Statistics at the CDC who designed, collected and managed the NHANES data and made the data sets of NHANES available on their website for the public.

Author contributions

XRH conceptualized the paper. HL performed statistical analysis and drafted the manuscript. WCL performed software and method validation. HL reviewed and edited the writing. All authors have read and approved the published version of the manuscript.

Funding

This study is funded by the Dongguan Science and Technology of Social Development Program (No. 20211800905222), Rural Science and Technology Special Agent Project (No. 20221800500302).

Data availability

Data are available from the NHANES (NHANES-National Health and Nutrition Examination Survey) Homepage (cdc.go) in 2009-2010.

Declarations

Ethics approval and consent to participate

The NHANES was approved by the Research Ethics Review Committee of the National Center for Health Statistics, and participants provided written informed consent (NHANES-NCHS Research Ethics Review Board Approval (cdc.gov).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 30 November 2024 / Accepted: 28 February 2025
Published online: 17 March 2025

References

1. Wang R, Li Z, Liu S, Zhang D. Global, regional and National burden of inflammatory bowel disease in 204 countries and territories from 1990 to 2019: a systematic analysis based on the global burden of disease study 2019. BMJ Open. 2023;13(3):e065186. https://doi.org/10.1136/bmjopen-2022-065186
2. Agrawal M, Jess T. Implications of the changing epidemiology of inflammatory bowel disease in a changing world. United Eur Gastroenterol J. 2022;10(10):1113–20. https://doi.org/10.1002/ueg2.12317
3. Thirumdas R, Kothakota A, Pandiselvam R, Bahrami A, Barba FJ. Role of food nutrients and supplementation in fighting against viral infections and boosting immunity: A review. Trends Food Sci Technol. 2021;110:66–77. https://doi.org/10.1016/j.tifs.2021.01.069
4. Jabłońska B, Mrowiec S. Nutritional status and its detection in patients with inflammatory bowel diseases. Nutrients. 2023;15(8):1991. https://doi.org/10.3390/nu15081991
5. Iddir M, Brito A, Dingeo G, Fernandez Del Campo SS, Samouda H, La Frano MR, Bohn T. Strengthening the immune system and reducing inflammation and oxidative stress through diet and nutrition: considerations during the COVID-19 crisis. Nutrients. 2020;12(6):1562. https://doi.org/10.3390/nu12061562
6. Battistini C, Ballan R, Herkenhoff ME, Saad SMI, Sun J. Vitamin D modulates intestinal microbiota in inflammatory bowel diseases. Int J Mol Sci 2020, 22(1):362https://doi.org/10.3390/ijms22010362
7. Fletcher J, Cooper SC, Ghosh S, Hewison M. The role of vitamin D in inflammatory bowel disease: mechanism to management. Nutrients. 2019;11(5):1019. https://doi.org/10.3390/nu11051019
8. Li J, Chen N, Wang D, Zhang J, Gong X. Efficacy of vitamin D in treatment of inflammatory bowel disease: A meta-analysis. Medicine. 2018;97(46):e12662. https://doi.org/10.1097/MD.0000000000012662
9. Granger M. P Eck 2018 Dietary vitamin C in human health. Adv Food Nutr Res 83 281–310 https://doi.org/10.1016/bs.afnr.2017.11.006
10. Dunleavy KA, Ungaro RC, Manning L, Gold S, Novak J, Colombel J-F. Vitamin C deficiency in inflammatory bowel disease: the forgotten micronutrient. Crohn's Colitis 360. 2021;3(1):otab009. https://doi.org/10.1093/crocol/otab009
11. Gordon BL, Galati JS, Yang S, Longman RS, Lukin D, Scherl EJ, Battat R. Prevalence and factors associated with vitamin C deficiency in inflammatory bowel disease. World J Gastroenterol. 2022;28(33):4834. https://doi.org/10.3748/wjg.v28.i33.4834
12. Iwakawa H, Fukui T, Fukuwatari T, Bamba S, Sasaki M, Tsujikawa T, Shibata K. Blood concentrations and renal clearance of water–soluble vitamins in outpatients with ulcerative colitis. Biomedical Rep. 2019;10(3):202–10. https://doi.org/10.3892/br.2019.1191

13. Rahmani J, Kord-Varkaneh H, Ryan PM, Rashvand S, Clark C, Day AS, Hekmatdoost A. Dietary total antioxidant capacity and risk of ulcerative colitis: A case-control study. J Dig Dis. 2019;20(12):636–41. https://doi.org/10.1111/1751-2980.12823
14. Miyake Y, Tanaka K, Nagata C, Furukawa S, Andoh A, Yokoyama T, Yoshimura N, Mori K, Ninomiya T, Yamamoto Y, et al. Dietary intake of vegetables, fruit, and antioxidants and risk of ulcerative colitis: A case-control study in Japan. Nutr (Burbank Los Angeles Cty Calif). 2021;91–92:111378. https://doi.org/10.1016/j.nut.2021.111378
15. Geerling B, Dagnelie P, Badart-Smook A, Russel M, Stockbrügger R, Brummer RM. Diet as a risk factor for the development of ulcerative colitis. Official J Am Coll Gastroenterology| ACG. 2000;95(4):1008–13. https://doi.org/10.1111/j.1572-0241.2000.01942
16. Hart AR, Luben R, Olsen A, Tjonneland A, Linseisen J, Nagel G, Berglund G, Lindgren S, Grip O, Key T. Diet in the aetiology of ulcerative colitis: a European prospective cohort study. Digestion. 2008;77(1):57–64. https://doi.org/10.1159/000121412
17. Ananthakrishnan AN, Khalili H, Song M, Higuchi LM, Richter JM, Nimptsch K, Wu K, Chan AT. High school diet and risk of Crohn's disease and ulcerative colitis. Inflamm Bowel Dis. 2015;21(10):2311–9. https://doi.org/10.1097/MIB.0000000000000501
18. Mladěnka P, Macáková K, Kujovská Krčmová L, Javorská L, Mrštná K, Carazo A, Protti M, Remião F, Nováková L, Researchers O, et al. Vitamin K–sources, physiological role, kinetics, deficiency, detection, therapeutic use, and toxicity. Nutr Rev. 2022;80(4):677–98. https://doi.org/10.1093/nutrit/nuab061
19. Lai Y, Masatoshi H, Ma Y, Guo Y, Zhang B. Role of vitamin K in intestinal health. Front Immunol. 2022;12:791565. https://doi.org/10.3389/fimmu.2021.791565
20. Feng Y, Liao Y, Huang W, Lai X, Luo J, Du C, Lin J, Zhang Z, Qiu D, Liu Q. Mesenchymal stromal cells-derived matrix Gla protein contribute to the alleviation of experimental colitis. Cell Death Dis. 2018;9(6):691. https://doi.org/10.1038/s41419-018-0734-3
21. Dong X-Y, Wu M-X, Zhang H-M, Lyu H, Qian J-M, Yang H. Association between matrix Gla protein and ulcerative colitis according to DNA microarray data. Gastroenterol Rep. 2020;8(1):66–75. https://doi.org/10.1093/gastro/goaa013
22. Odutayo A, Gill P, Shepherd S, Akingbade A, Hopewell S, Tennankore K, Hunn BH, Emdin CA. Income disparities in absolute cardiovascular risk and cardiovascular risk factors in the united States, 1999–2014. JAMA Cardiol. 2017;2(7):782–90. https://doi.org/10.1001/jamacardio.2017.1658
23. Ardesia M, Ferlazzo G, Fries W. Vitamin D and inflammatory bowel disease. Biomed Res Int. 2015;2015(1):470805. https://doi.org/10.1155/2015/470805
24. Hewison M. Vitamin D and immune function: an overview. Proc Nutr Soc. 2012;71(1):50–61. https://doi.org/10.1017/S0029665111001650
25. Del Pinto R, Pietropaoli D, Chandar AK, Ferri C, Cominelli F. Association between inflammatory bowel disease and vitamin D deficiency: a systematic review and meta-analysis. Inflamm Bowel Dis. 2015;21(11):2708–17. https://doi.org/10.1097/MIB.0000000000000546
26. Yang X, Zhu Q, Zhang L, Pei Y, Xu X, Liu X, Lu G, Pan J, Wang Y. Causal relationship between gut microbiota and serum vitamin D: evidence from genetic correlation and Mendelian randomization study. Eur J Clin Nutr. 2022;76(7):1017–23. https://doi.org/10.1038/s41430-021-01065-3
27. Thomas RL, Jiang L, Adams JS, Xu ZZ, Shen J, Janssen S, Ackermann G, Vanderschueren D, Pauwels S, Knight R, et al. Vitamin D metabolites and the gut Microbiome in older men. Nat Commun. 2020;11(1):5997. https://doi.org/10.1038/s41467-020-19793-8
28. Giampazolias E, Pereira da Costa M, Lam KC, Lim KHJ, Cardoso A, Piot C, Chakravarty P, Blasche S, Patel S, Biram A, et al. Vitamin D regulates microbiome-dependent cancer immunity. Sci (New York NY). 2024;384(6694):428–37. https://doi.org/10.1126/science.adh7954
29. Chen YC, Hung MS. Associations between vitamin A and K intake and lung function in the general US population: evidence from NHANES 2007–2012. Frontiers in nutrition 2024, 11:1417489https://doi.org/10.3389/fnut.2024.1417489
30. Ebid AI, Abdeen HA, Muhammed Maher R, Mohamed-Abdel-Motaleb SM. Cefoperazone-Sulbactam-Induced coagulopathy in critically ill Egyptian patients: role of vitamin K prophylactic doses. Hospital pharmacy 2024, 59(5):575–83https://doi.org/10.1177/00185787241238310
31. Friis Bryde Nielsen C, Møller Thysen S, Bach Kampmann F, Hansen TW, Jørgensen NR, Tofte N, Abitz Winther S, Theilade S, Rossing P, Frimodt-Møller M, et al. The associations between functional vitamin K status and all-cause mortality, cardiovascular disease and end-stage kidney disease in persons with type 1 diabetes. Diabetes Obes Metab. 2024. https://doi.org/10.1111/dom.16025
32. Lai Y, Masatoshi H, Ma Y, Guo Y, Zhang B. Role of vitamin K in intestinal health. Frontiers in immunology 2021, 12:791565https://doi.org/10.3389/fimmu.2021.791565
33. Xie Y, Li S, Wu D, Wang Y, Chen J, Duan L, Li S, Li Y. Vitamin K: infection, inflammation, and Auto-Immunity. J Inflamm Res. 2024;17:1147–60. https://doi.org/10.2147/jir.S445806
34. Bellan M, Cittone MG, Tonello S, Rigamonti C, Castello LM, Gavelli F, Pirisi M, Sainaghi PP. Gas6/TAM system: a key modulator of the interplay between inflammation and fibrosis. Int J Mol Sci. 2019;20(20):5070.
35. Goudarzi S, Montazerin SM, Najafi H, Shojaei F, Chi G. Effect of vitamins and dietary supplements on cardiovascular health. Crit Pathw Cardiol. 2020;19(3):153–9. https://doi.org/10.1097/HPC.0000000000000212
36. Hu J, Chen J, Xu X, Hou Q, Ren J, Yan X. Gut microbiota-derived 3-phenylpropionic acid promotes intestinal epithelial barrier function via AhR signaling. Microbiome. 2023;11(1):102. https://doi.org/10.1186/s40168-023-01551-9
37. Wang H, Liu Z, Zhan K, Ma Q, Xu L, Li Y, Liu Y. Vitamin K2 alleviates dextran sulfate sodium-induced colitis via inflammatory responses, gut barrier integrity, and the gut microbiota in mice. Int J Biol Macromol. 2024;280(Pt 4):136091. https://doi.org/10.1016/j.ijbiomac.2024.136091
38. Yue X, Samaniego-Castruita D, González-Avalos E, Li X, Barwick BG, Rao A. Whole-genome analysis of TET dioxygenase function in regulatory T cells. EMBO Rep. 2021;22(8):e52716. https://doi.org/10.15252/embr.202152716
39. Wang M, He J, Li S, Cai Q, Zhang K, She J. Structural basis of vitamin C recognition and transport by mammalian SVCT1 transporter. Nat Commun. 2023;14(1):1361. https://doi.org/10.1038/s41467-023-37037-3
40. Lu Q, Yang MF, Liang YJ, Xu J, Xu HM, Nie YQ, Wang LS, Yao J, Li DF. Immunology of inflammatory bowel disease: molecular mechanisms and therapeutics. J Inflamm Res. 2022;15:1825–44. https://doi.org/10.2147/jir.S353038
41. Sokal-Dembowska A, Jarmakiewicz-Czaja S, Ferenc K, Filip R. Can nutraceuticals support the treatment of MASLD/MASH, and thus affect the process of liver fibrosis?? Int J Mol Sci. 2024;25(10). https://doi.org/10.3390/ijms25105238
42. Fisher A, Naughton D. Vitamin C contributes to inflammation via radical generating mechanisms: a cautionary note. Med Hypotheses. 2003;61(5–6):657–60. https://doi.org/10.1016/s0306-9877(03)00271-8
43. Padayatty SJ, Levine M. Vitamin C: the known and the unknown and goldilocks. Oral Dis. 2016;22(6):463–93. https://doi.org/10.1111/odi.12446
44. Krishnan AV, Swami S, Feldman D. Vitamin D and breast cancer: Inhibition of Estrogen synthesis and signaling. J Steroid Biochem Mol Biol. 2010;121(1–2):343–8. https://doi.org/10.1016/j.jsbmb.2010.02.009
45. Li Y, Cook KL, Yu W, Jin L, Bouker KB, Clarke R, Hilakivi-Clarke L. Inhibition of Antiestrogen-Promoted Pro-Survival autophagy and Tamoxifen resistance in breast Cancer through vitamin D receptor. Nutrients. 2021;13(5). https://doi.org/10.3390/nu13051715
46. Baker JM, Al-Nakkash L, Herbst-Kralovetz MM. Estrogen-gut Microbiome axis: physiological and clinical implications. Maturitas. 2017;103:45–53. https://doi.org/10.1016/j.maturitas.2017.06.025
47. Pai AH, Wang YW, Lu PC, Wu HM, Xu JL, Huang HY. Gut Microbiome-Estrobolome profile in Reproductive-Age women with endometriosis. Int J Mol Sci. 2023;24(22). https://doi.org/10.3390/ijms242216301
48. Kumari N, Kumari R, Dua A, Singh M, Kumar R, Singh P, Duyar-Ayerdi S, Pradeep S, Ojesina AI, Kumar R. From gut to hormones: unraveling the role of gut microbiota in (Phyto)Estrogen modulation in health and disease. Mol Nutr Food Res. 2024;68(6):e2300688. https://doi.org/10.1002/mnfr.202300688
49. Jacenik D, Cygankiewicz AI, Mokrowiecka A, Małecka-Panas E, Fichna J, Krajewska WM. Sex- and Age-Related Estrogen signaling alteration in inflammatory bowel diseases: modulatory role of Estrogen receptors. Int J Mol Sci. 2019;20(13). https://doi.org/10.3390/ijms20133175
50. Xu L, Huang G, Cong Y, Yu Y, Li Y. Sex-related differences in inflammatory bowel diseases: the potential role of sex hormones. inflammatory bowel diseases 2022, 28(11):1766–75https://doi.org/10.1093/ibd/izac094
51. Pan J, Jiang W, Xin L, Wu J, Zhu S, Liu Z, Shen Z. The potential role of female sex hormones in patients with inflammatory bowel disease: A 2-Sample Mendelian randomization study. Clin Translational Gastroenterol. 2024;15(8):e00748. https://doi.org/10.14309/ctg.0000000000000748
52. Popa D-S, Bigman G, Rusu ME. The role of vitamin K in humans: implication in aging and age-associated diseases. Antioxidants. 2021;10(4):566. https://doi.org/10.3390/antiox10040566
53. Bourron O, Mohammedi K, De Keizer J, Schneider F, Hadjadj S, Saulnier PJ. A prospective observational study to evaluate a possible relationship between vitamin K antagonist therapy and risk of peripheral arterial disease in patients

with type 2 diabetes. Diabetes Obes Metab. 2024;26(8):3290–8. https://doi.org/10.1111/dom.15656
54. Yang L. Decreased serum levels of 25-OH vitamin D and vitamin K in patients with type 2 diabetes mellitus. Front Endocrinol. 2024;15:1412228. https://doi.org/10.3389/fendo.2024.1412228
55. Zhang Y-B, Chen C, Pan X-F, Guo J, Li Y, Franco OH, Liu G, Pan A. Associations of healthy lifestyle and socioeconomic status with mortality and incident cardiovascular disease: two prospective cohort studies. BMJ. 2021;373. https://doi.org/10.1136/bmj.n604
56. Li Z, Zhou L, Wu Y, Ding T, Gan Y, Fan X. Associations of healthy lifestyle and family income to poverty ratio with all-cause mortality among people with prediabetes and diabetes: a prospective cohort study. BMC Public Health. 2025;25(1):24. https://doi.org/10.1186/s12889-024-21206-0
57. Bhagavathula AS, Clark CC, Rahmani J, Chattu VK. Impact of body mass index on the development of inflammatory bowel disease: a systematic review and dose-response analysis of 15.6 million participants. In: Healthcare: 2021: MDPI; 2021:35. https://doi.org/10.3390/healthcare9010035

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