Reproductive Health

RESEARCH

Open Access

The association between vitamin intake and endometriosis: a cross-sectional study of the NHANES 1999–2006

Ting Xu[1], Yuan Zhuang[1] and Huabin Cao[1*]

Abstract

Background Endometriosis is a common cause of female reproductive problems, and vitamin intake may affect its incidence. Therefore, we further explored the association between multivitamin intake and endometriosis in a large population-based study.

Methods This study included 3351 participants from the National Health and Nutrition Examination Survey (NHANES) 1999–2006. The dietary intake of eight vitamins was calculated as the average of two 24-h recall interviews, and information on endometriosis was obtained through questionnaires that included gynecological history. Multiple logistic regression analysis was used to explore the relationship between multivitamin intake and endometriosis. Smoothed curve fitting analysis was employed to assess the dose–response relationship between vitamins and endometriosis. Finally, subgroup analysis and interaction tests were conducted to determine the association of covariates between vitamins and endometriosis.

Results In this large-scale cross-sectional study, multiple logistic regression analysis showed that the intake of vitamins A, B1, B2, B6, C and folate was negatively associated with the occurrence of endometriosis. The odds ratios associated with a per-SD increase were 0.836 (95%CI: 0.702, 0.997), 0.817 (95%CI: 0.702, 0.951), 0.860 (95%CI: 0.746, 0.991), 0.784 (95%CI: 0.669, 0.919), 0.845 (95%CI: 0.718, 0.994), and 0.772 (95%CI: 0.660, 0.903), respectively. Smoothed curve fitting analysis revealed that the intake of vitamins A, B1, B2, B6, C, and folate was negatively associated with the risk of endometriosis ($P < 0.05$). Vitamin E showed a saturating effect, with an optimal cutoff point at 13.18. Below this cutoff, the intake of vitamin E was negatively correlated with the risk of endometriosis (OR = 0.947, 95% CI: 0.906, 0.989), whereas above the cutoff, there was no significant correlation between vitamin E intake and the risk of endometriosis (OR = 1.001, 95% CI: 0.997, 1.005).

Conclusions The results of this study indicate a significant linear negative correlation between the intake of vitamins A, B1, B2, B6, C, and folate, and the risk of endometriosis, and reveal a threshold effect for vitamin E intake on the risk of endometriosis. These findings could inform clinical dietary interventions and may support the development of preventive strategies for endometriosis, potentially aiding in its reduction.

Keywords Vitamin, Intake, Endometriosis, Multiple logistic regression

Introduction

Endometriosis is an estrogen-dependent, chronic inflammatory disease characterized by the appearance of endometrial tissue in sites other than the uterus [1]. It affects approximately 10‰ of the female population in the reproductive age group, with a higher prevalence in

*Correspondence:
Huabin Cao
chb2019@189.cn
[1] Department of Ambulatory Surgical Center, Jiangxi Maternal and Child Health Hospital, Maternal and Child Health Hospital of Nanchang Medical College, Nanchang, China

patients with infertility or chronic pelvic pain [2]. The etiology of endometriosis is multifactorial and not fully understood [3], with inflammatory responses, oxidative stress, angiogenesis, apoptosis resistance, and immune regulation implicated in its pathologic process [4–6].

Diets with anti-inflammatory, antioxidant, antiproliferative, estrogenic effects, immunomodulatory, and smooth muscle contraction properties may significantly influence the risk of endometriosis [7]. While dietary intake of red meat, soy and alcohol has been strongly associated with the development of endometriosis [8], the relationship between vitamin intake and endometriosis remains a topic of debate. For patients with endometriosis, a well-balanced diet may alleviate pain through interactions with visceral sensory inputs [9, 10]. Thus, an anti-inflammatory diet could potentially improve the inflammatory state of endometriosis. Some studies suggest a protective role for antioxidant vitamins such as vitamins C and E in mitigating oxidative stress and associated inflammation [11–13], while others, like the case–control study by Trabert et al. [14], found no significant correlation between vitamin intake and endometriosis risk. This discrepancy may highlight gaps in previous research regarding the role of vitamins in the pathogenesis of endometriosis and the need for more robust study designs to determine their relationship.

The study aims to examine the association between vitamin intake and endometriosis using data from the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2006. Eight vitamins were analyzed, including vitamin A, B1, B2, B6, B12, C, E, and folic acid. This analysis may help in the development of targeted dietary interventions, providing a clinical rationale for the prevention of endometriosis.

Materials and methods

Study population in NHANES

The NHANES is a program of studies designed to assess the health and nutritional status of adults and children in the United States. Conducted by the National Center for Health Statistics (NCHS), which is part of the Centers for Disease Control and Prevention (CDC), NHANES combines interviews and physical examinations to provide a comprehensive view of the nation's health [15].

For this study, we utilized data from four consecutive two-year cycles of NHANES (1999–2006). The data collection methods employed in NHANES are designed to ensure a representative sample of the U.S. population, and all procedures are approved by the NCHS Research Ethics Review Board. Informed consent is obtained from all participants, ensuring ethical compliance with research standards [16]. We excluded the following individuals: (1) males; (2) those lacking vitamin intake data; (3) those lacking endometriosis data; (4) pregnant women; and (5) women lacking important covariates, including age, body mass index (BMI), race, education, poverty-income ratio (PIR), smoking, drinking, hypertension, diabetes, marital status, age at menarche, number of pregnancies and oral contraceptive. Finally, 3351 participants were enrolled in the study and the flow chart is shown in Fig. 1.

Study variables

Vitamin intakes were obtained from the total nutrient intakes recorded in the dietary data of NHANES 1999–2006. The study included vitamin A, B1, B2, B6, B12, C, E and folic acid. Notably, the dietary interview questionnaire was administered twice during the two cycles of NHANES 2003–2006. For participants who completed both dietary interviews, we utilized the average of the two vitamin intakes.

In the NHANES study, data on endometriosis were collected from health questionnaires completed by participants. Participants were categorized as having endometriosis based on their response to the question, "Has a doctor or health professional ever told you that you have endometriosis?" with an affirmative response leading to classification as affected. Although relying on questionnaire answers to determine the primary study outcome may introduce a degree of uncertainty, the absence of direct diagnostic evidence such as laparoscopy or ultrasound examinations in the NHANES dataset poses challenges in accurately identifying cases of endometriosis. Nonetheless, previous studies have validated the feasibility and acceptability of using survey data to ascertain the status of endometriosis among NHANES participants [17, 18].

Other variables

With reference to recent relevant studies [19, 20], covariates in our study included the following variables: age, BMI, race, education, Poverty-income ratio (PIR), smoking, drinking, hypertension, diabetes, marital status, age at menarche, number of pregnancies and oral contraceptive. Race was self-reported and categorized as Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black and Others. Education levels were classified as less than high school, high school or equivalent, and college or above. The PIR was divided into three categories: low (<1), middle (≥ 1 to <3) and high (≥ 3). Marital status was categorized as married, never married and Other. Age at menarche, defined as the age at which participants first began menstruating, was divided into two groups: less than 13 and 13 or older. The number of pregnancies was categorized as up to 3 and more than 3. Oral contraceptives use was categorized as "Yes" or "No" based on participant responses.

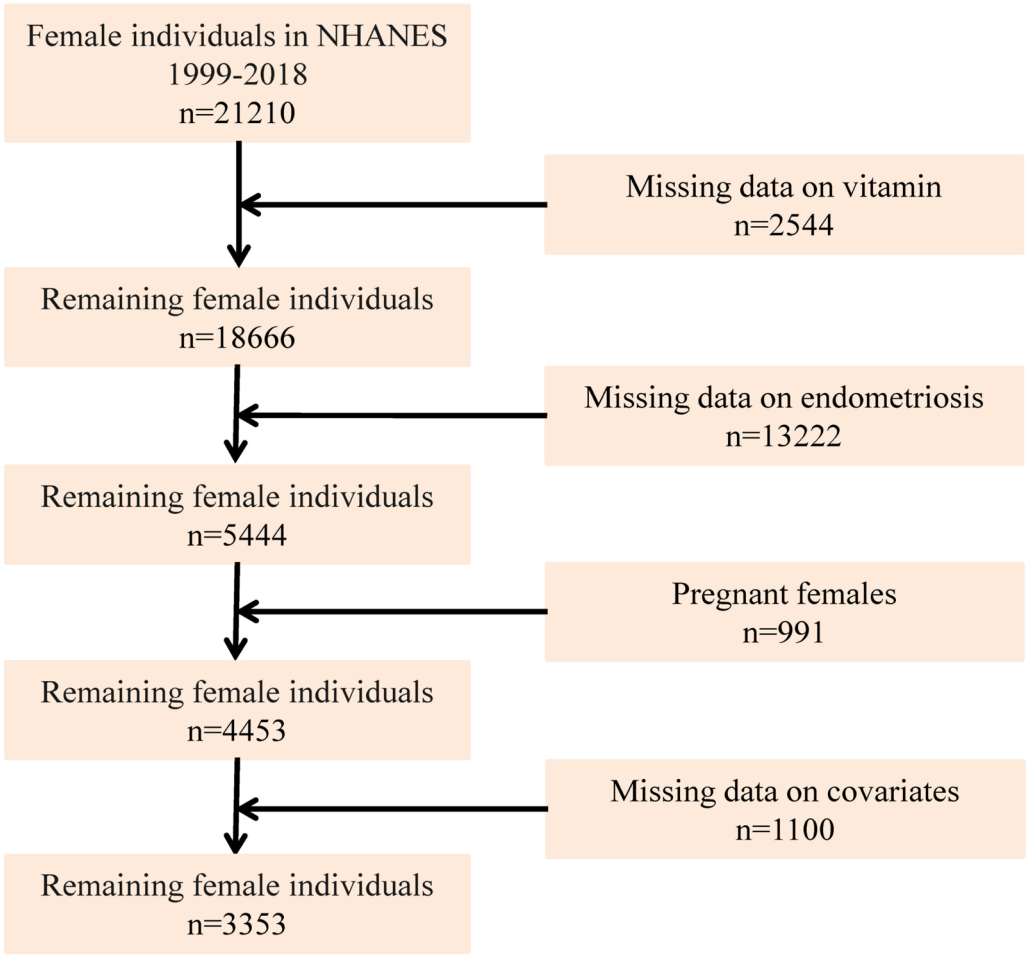

Fig. 1 Flowchart of participants selection in the National Health and Nutrition Examination Survey

Statistical analysis

Data from NHANES 1999–2006 were extracted, combined, processed and analyzed using R software (vision 4.3.0, http://www.R-project.org) and Empower software (vision 4.1, http://www.empowerstats.net/analysis/). The weighted t-test or Kruskal–Wallis test was employed to analyze the relationship between continuous variables, and the weighted chi-square test was used for categorical variables.

Considering potential collinearity among covariates, variance inflation factors for all covariates were calculated, with a value > 5 indicating multicollinearity [21]. Moreover, the presence of heteroscedasticity was assessed using the Breusch-Pagan statistical test, a robust method for evaluating non-constant variance in regression models [22]. Detailed collinearity screening and heteroscedasticity analysis information are presented in Supplementary Tables 1 and 2. To analyze the association between vitamin intake and endometriosis, vitamin intake was divided into quartiles from the lowest (Q1) to the highest (Q4) group. Multivariate logistic regression analysis was used to construct three regression models: Model A was unadjusted for any covariates, Model B was adjusted for age, BMI, and race, and Model C was adjusted for all covariates, including age, BMI, race, education, PIR, hypertension, diabetes, smoking, drinking, marital status, number of pregnancies, age at menarche, and use of oral contraceptives. Based on the fully adjusted model, we further fitted the relationship between different vitamin intakes and the risk of endometriosis by smoothed curve (penalized spline) analysis. Finally, subgroup analysis and interaction tests were performed to determine the role of covariates between different levels of vitamin intake and endometriosis. The P-value < 0.05 was considered statistically significant difference.

Results

General characteristics of the study population

According to the exclusion criteria, a total of 3351 participants from NHANES 1999–2006 were included in

our study (Fig. 1). Table 1 illustrates the demographic characteristics of participants. Participants with endometriosis were older, had a higher percentage of non-Hispanic Whites, higher levels of education, were more likely to smoke, had an age at menarche less than 13, used oral contraceptives, and were less likely to have had multiple pregnancies ($P < 0.05$). More importantly, individuals with endometriosis had lower intakes of Vitamin B1, Vitamin B6, Vitamin C, and folate (Table 1).

Association between vitamin intake and endometriosis

Table 2 demonstrates the results of the multivariate regression models between different vitamin intakes and endometriosis. After adjusting for all confounding factors, it was observed that the intaking of vitamin A, B1, B2, B6, C and folate was negatively associated with the occurrence of endometriosis. The odds ratios (OR) associated with a per- standard deviation (SD) increase were 0.836 (95%CI: 0.702, 0.997), 0.817 (95%CI: 0.702, 0.951), 0.860 (95%CI: 0.746, 0.991), 0.784 (95%CI: 0.669, 0.919), 0.845 (95%CI: 0.718, 0.994), and 0.772 (95%CI: 0.660, 0.903), respectively. In addition, when the vitamin intakes were divided into quartiles, the ORs for endometriosis with the intakes of vitamin A, B2, B6, C, E, and folate in the Q4 group were 0.689 (95%CI: 0.474, 1.000), 0.641 (95%CI: 0.440, 0.936), 0.629 (95%CI: 0.435, 0.910), 0.523 (95%CI: 0.347, 0.787), 0.630 (95%CI: 0.435, 0.912) and 0.834 (95%CI: 0.741, 0.938), respectively, compared to those in Q1 group. The P-value for trend was statistically significant.

Dose–response curves for vitamin intake and risk of endometriosis

The effect sizes of the ORs at quartile intervals suggest a potential linear dose–response relationship between vitamin intake and endometriosis. After adjusting for all covariates, analysis using a smooth curve model revealed that the intake of vitamins A, B1, B6, B12, C, and folate was negatively associated with the risk of endometriosis ($P < 0.05$, Fig. 2A-F). In contrast, vitamin E showed a saturating effect on the risk of endometriosis (Fig. 2G), with an optimal cutoff point at 13.18. Below this cutoff, the intake of vitamin E was negatively correlated with the risk of endometriosis (OR = 0.947, 95% CI: 0.906, 0.989), whereas above the cutoff, there was no significant correlation between vitamin E intake and the risk of endometriosis (OR = 1.001, 95% CI: 0.997, 1.005). Additionally, only the intake of vitamin B12 showed no significant association with endometriosis ($P > 0.05$, Fig. 2H).

Subgroup analysis

After establishing the relationship between eight vitamins and endometriosis, we further investigated how this association might differ in various subgroups. Figure 3 presents the results of stratified subgroup analyses based on factors such as age, BMI, race, education level, PIR, hypertension, diabetes, smoking status, number of pregnancies, marital status, age at menarche, and oral contraceptive use. The results indicate that, with the exception of the diabetes subgroup, where a significant interaction between vitamin B12 intake and endometriosis risk was observed (P for interaction < 0.05, Fig. 3), there were no significant interactions between the eight vitamins and these stratifying variables in all other assessed subgroups (all P for interaction > 0.05, Fig. 3).

Discussion

Endometriosis, a condition with an unknown etiology, presents a medically intractable problem. Despite this, clinical treatments including medications and surgery, can manage its symptoms [1, 23]. The aim of our cross-sectional study was to investigate the association between vitamin and endometriosis, as both vitamins and endometriosis have significant impacts on human fertility. In a large general population study in the United States, we found that the intake of vitamins A, B1, B2, B6, C, and folate were negatively correlated with the risk of endometriosis, while vitamin E showed a saturating effect, with its intake also negatively correlated with the risk of endometriosis before reaching a saturation point. In addition, subgroup analyses revealed no significant interactions between the intake of these seven vitamins and the risk of endometriosis across different subgroups (P for interaction > 0.05). These findings may aid in the development of targeted treatment strategies or personalized dietary interventions that could potentially provide preventive or therapeutic benefits for patients with endometriosis.

We conducted a multifactorial logistic regression analysis and curve fitting to examine the association between the intake of eight different vitamins and the risk of endometriosis. Our findings indicated that, of these vitamins, only vitamin B12 was not significantly associated with the risk of endometriosis. In contrast, the intake of the other seven vitamins showed a negative correlation with the risk of endometriosis, suggesting that a higher intake of these vitamins may be associated with a reduced risk of developing the condition. This finding challenges the previous conclusion from another study that reported no significant relationship between vitamins and endometriosis [14]. The conflicting results may be attributed to differences in study populations, interventions, outcome definitions, and analytical methods. Roshanzadeh et al. found that intake of appropriate amounts of vitamin B6 and vitamin C can reduce the risk of endometriosis, and they noted that folic acid intake was significantly lower in the endometriosis group [24]. In a prospective cohort

Table 1 Baseline characteristics of the participants with and without endometriosis

	Non-endometriosis	Endometriosis	P-value
Age (years)	39.390 (38.949, 39.831)	41.515 (40.656, 42.374)	< 0.001
BMI (kg/m^2)	28.398 (28.013, 28.784)	28.137 (27.214, 29.060)	0.589
Race (%)			< 0.001
Mexican American	8.601 (7.095, 10.390)	2.528 (1.522, 4.171)	
Other Hispanic	6.104 (4.346, 8.511)	2.263 (0.873, 5.740)	
Non-Hispanic White	66.768 (62.903, 70.421)	84.132 (79.397, 87.944)	
Non-Hispanic Black	14.194 (11.870, 16.886)	7.205 (5.457, 9.457)	
Others	4.333 (3.501, 5.351)	3.871 (1.901, 7.722)	
Education (%)			< 0.001
Less than high school	18.661 (16.849, 20.620)	10.472 (7.577, 14.303)	
High school or equivalent	25.089 (22.814, 27.510)	34.499 (28.888, 40.579)	
College or above	56.250 (53.095, 59.355)	55.028 (48.525, 61.365)	
PIR (%)			0.243
< 1	15.286 (13.549, 17.201)	11.802 (8.012, 17.052)	
≥ 1, < 3	33.746 (31.531, 36.034)	31.260 (24.287, 39.199)	
≥ 3	50.968 (47.880, 54.050)	56.938 (49.699, 63.892)	
Smoking (%)			0.032
Yes	45.121 (42.466, 47.805)	52.752 (46.477, 58.941)	
No	54.879 (52.195, 57.534)	47.248 (41.059, 53.523)	
Drinking (%)			0.438
Yes	66.749 (63.950, 69.436)	69.756 (61.959, 76.559)	
No	33.251 (30.564, 36.050)	30.244 (23.441, 38.041)	
Hypertension (%)			0.429
Yes	20.334 (18.593, 22.193)	22.708 (16.946, 29.729)	
No	79.666 (77.807, 81.407)	77.292 (70.271, 83.054)	
Diabetes (%)			0.219
Yes	4.440 (3.725, 5.284)	2.847 (1.368, 5.832)	
No	95.560 (94.716, 96.275)	97.153 (94.168, 98.632)	
Marital status (%)			0.158
Married	64.144 (61.560, 66.648)	65.663 (57.387, 73.086)	
Never married	25.908 (23.942, 27.977)	28.725 (21.619, 37.063)	
Others	9.948 (8.424, 11.713)	5.611 (3.428, 9.056)	
Age at menarche			0.047
< 13	48.043 (45.906, 50.187)	55.599 (48.502, 62.475)	
≥ 13	51.957 (49.813, 54.094)	44.401 (37.525, 51.498)	
Number of pregnancies			0.040
≤ 3	70.493 (68.449, 72.458)	76.583 (70.840, 81.491)	
> 3	29.507 (27.542, 31.551)	23.417 (18.509, 29.160)	
Oral contraceptive use (%)			0.007
Yes	84.236 (82.663, 85.691)	90.256 (86.040, 93.298)	
No	15.764 (14.309, 17.337)	9.744 (6.702, 13.960)	
Vitamin A	495.825 (472.247, 519.403)	456.518 (395.491, 517.545)	0.844
Vitamin B1	1.393 (1.353, 1.433)	1.290 (1.195, 1.384)	0.010
Vitamin B12	4.254 (4.067, 4.440)	3.810 (3.321, 4.300)	0.416
Vitamin B2	1.859 (1.816, 1.902)	1.804 (1.651, 1.958)	0.467
Vitamin B6	1.595 (1.549, 1.640)	1.443 (1.329, 1.556)	0.006
Vitamin C	80.746 (75.779, 85.713)	67.275 (57.528, 77.022)	0.005
Vitamin E	6.864 (6.658, 7.071)	6.797 (5.835, 7.758)	0.168
Folate	347.879 (337.106, 358.652)	311.096 (287.475, 334.717)	0.009

Data was presented as median (95%CI). *BMI* body mass index, *PIR* poverty income ratio

Table 2 Association between vitamins intake and the risks of endometriosis in logistic regression analysis

Vitamins (As continuous, per SD)	Model A OR (95% CI) P-value	Model B OR (95% CI) P-value	Model C OR (95% CI) P-value
Vitamin A	0.942 (0.815, 1.088) 0.415	0.845 (0.713, 1.001) 0.051	0.836 (0.702, 0.997) 0.046
Q1 (– 0.937–0.570)	Reference	Reference	Reference
Q2 (– 0.570–0.228)	0.833 (0.581, 1.195) 0.321	0.785 (0.544, 1.133) 0.196	0.743 (0.511, 1.080) 0.120
Q3 (– 0.228–0.299)	1.125 (0.802, 1.577) 0.496	0.960 (0.679, 1.357) 0.817	0.910 (0.637, 1.299) 0.603
Q4 (0.300–18.735)	0.938 (0.660, 1.332) 0.721	0.713 (0.497, 1.023) 0.066	0.689 (0.474, 1.000) 0.049
P for trend	1.011 (0.905, 1.129) 0.849	0.922 (0.823, 1.032) 0.159	0.913 (0.811, 1.027) 0.130
Vitamin B1	0.833 (0.721, 0.962) 0.013	0.815 (0.703, 0.945) 0.007	0.817 (0.702, 0.951) 0.009
Q1 (– 1.903–0.644)	Reference	Reference	Reference
Q2 (– 0.644–0.147)	1.090 (0.784, 1.516) 0.609	1.043 (0.745, 1.459) 0.806	1.018 (0.723, 1.432) 0.919
Q3 (– 0.147–0.470)	0.815 (0.574, 1.158) 0.253	0.815 (0.570, 1.164) 0.261	0.803 (0.559, 1.155) 0.237
Q4 (0.471–19.889)	0.713 (0.496, 1.024) 0.067	0.675 (0.467, 0.975) 0.036	0.690 (0.474, 1.005) 0.053
P for trend	0.025	0.017	0.025
Vitamin B2	0.961 (0.846, 1.091) 0.536	0.863 (0.752, 0.990) 0.036	0.860 (0.746, 0.991) 0.037
Q1 (– 1.975–0.670)	Reference	Reference	Reference
Q2 (– 0.669–0.165)	1.081 (0.767, 1.523) 0.657	1.014 (0.714, 1.439) 0.939	0.978 (0.686, 1.395) 0.903
Q3 (– 0.165–0.497)	1.003 (0.708, 1.420) 0.988	0.858 (0.600, 1.227) 0.402	0.828 (0.576, 1.192) 0.311
Q4 (0.497–10.741)	0.873 (0.610, 1.249) 0.457	0.645 (0.445, 0.936) 0.020	0.641 (0.440, 0.936) 0.021
P for trend	0.954 (0.854, 1.066) 0.407	0.864 (0.771, 0.969) 0.012	0.862 (0.766, 0.969) 0.013
Vitamin B6	0.791 (0.680, 0.921) 0.003	0.788 (0.675, 0.920) 0.003	0.784 (0.669, 0.919) 0.003
Q1 (– 1.735–0.636)	Reference	Reference	Reference
Q2 (– 0.636–0.179)	0.804 (0.575, 1.126) 0.204	0.793 (0.563, 1.116) 0.183	0.760 (0.536, 1.076) 0.122
Q3 (– 0.179–0.416)	0.792 (0.565, 1.109) 0.174	0.762 (0.540, 1.075) 0.121	0.753 (0.531, 1.069) 0.113
Q4 (0.417–16.354)	0.638 (0.447, 0.910) 0.013	0.633 (0.441, 0.909) 0.013	0.629 (0.435, 0.910) 0.014
P for trend	0.016	0.014	0.017
Vitamin B12	0.887 (0.739, 1.066) 0.201	0.866 (0.714, 1.049) 0.141	0.869 (0.713, 1.058) 0.161
Q1 (– 0.833–0.445)	Reference	Reference	Reference
Q2 (– 0.445–0.187)	1.244 (0.881, 1.758) 0.215	1.252 (0.881, 1.779) 0.210	1.269 (0.889, 1.812) 0.190
Q3 (– 0.187–0.195)	1.137 (0.800, 1.615) 0.474	1.080 (0.755, 1.544) 0.674	1.071 (0.746, 1.538) 0.711
Q4 (0.196–24.270)	0.915 (0.633, 1.321) 0.634	0.868 (0.597, 1.261) 0.458	0.883 (0.605, 1.290) 0.521
P for trend	0.966 (0.865, 1.080) 0.546	0.946 (0.845, 1.059) 0.333	0.948 (0.846, 1.063) 0.363
Vitamin C	0.796 (0.679, 0.932) 0.005	0.842 (0.716, 0.989) 0.036	0.845 (0.718, 0.994) 0.043
Q1 (– 0.949–0.660)	Reference	Reference	Reference
Q2 (– 0.660–0.305)	0.903 (0.647, 1.259) 0.548	0.866 (0.618, 1.216) 0.406	0.847 (0.600, 1.196) 0.346
Q3 (– 0.305–0.323)	1.000 (0.722, 1.385) 1.000	1.009 (0.723, 1.407) 0.960	1.037 (0.736, 1.461) 0.835
Q4 (0.324–14.575)	0.474 (0.320, 0.701) < 0.001	0.522 (0.350, 0.779) 0.001	0.523 (0.347, 0.787) 0.002
P for trend	0.001	0.010	0.016
Vitamin E	0.981 (0.864, 1.114) 0.765	0.938 (0.822, 1.069) 0.335	0.935 (0.818, 1.068) 0.321
Q1 (– 1.395–0.612)	Reference	Reference	Reference
Q2 (– 0.610–0.216)	0.768 (0.542, 1.086) 0.135	0.747 (0.524, 1.064) 0.106	0.743 (0.519, 1.064) 0.105
Q3 (– 0.215–0.294)	0.953 (0.685, 1.327) 0.776	0.866 (0.618, 1.214) 0.404	0.848 (0.600, 1.198) 0.351
Q4 (0.296–10.709)	0.685 (0.480, 0.979) 0.038	0.633 (0.441, 0.910) 0.014	0.630 (0.435, 0.912) 0.015
P for trend	0.914 (0.818, 1.022) 0.114	0.886 (0.791, 0.993) 0.037	0.883 (0.786, 0.992) 0.036
Folate	0.805 (0.695, 0.932) 0.004	0.774 (0.665, 0.900) < 0.001	0.772 (0.660, 0.903) 0.001
Q1 (– 1.786–0.652)	Reference	Reference	Reference
Q2 (– 0.651–0.179)	1.130 (0.813, 1.572) 0.467	1.115 (0.796, 1.560) 0.527	1.112 (0.789, 1.566) 0.545
Q3 (– 0.179–0.399)	0.948 (0.675, 1.333) 0.760	0.916 (0.647, 1.296) 0.619	0.905 (0.634, 1.291) 0.582
Q4 (0.401–13.294)	0.600 (0.410, 0.878) 0.009	0.547 (0.371, 0.807) 0.002	0.554 (0.372, 0.825) 0.004
P for trend	0.857 (0.767, 0.958) 0.007	0.833 (0.743, 0.934) 0.002	0.834 (0.741, 0.938) 0.002

Table 2 (continued)

Model A adjust for: None

Model B adjust for: Age; BMI; Race

Model C adjust for: Age; BMI; Race; Education; Poverty-to-income ratio; Hypertension; Diabetes; Smoking; Number of pregnancies; Marital status; Age at Menarche; Oral contraceptive use

95% CI 95% confidence interval, *OR* odds ratio

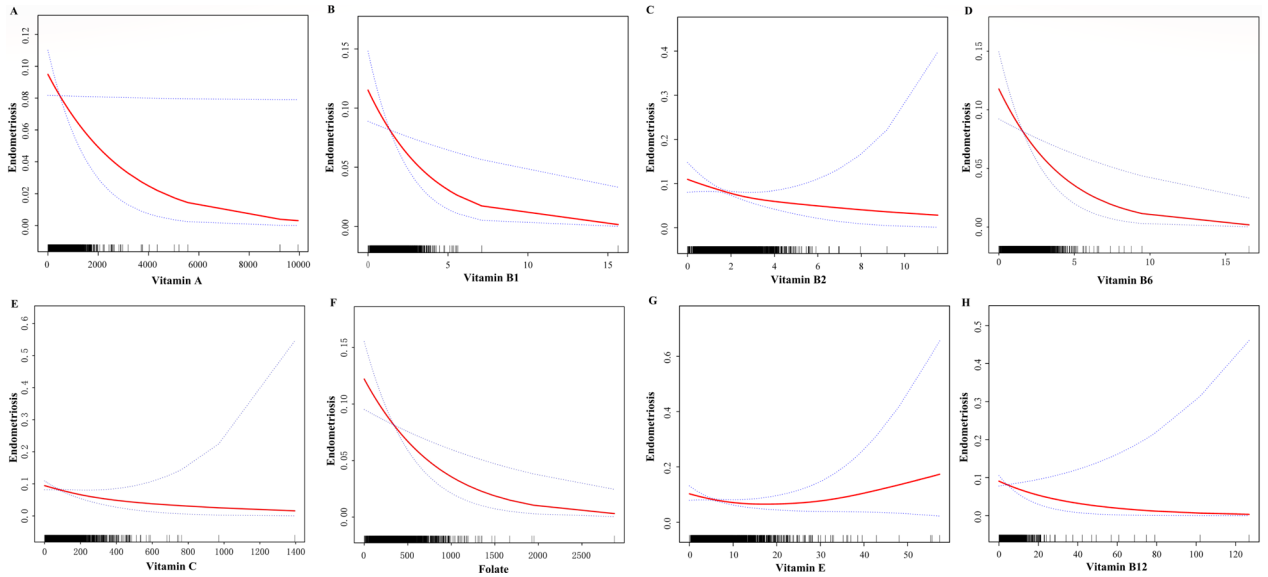

Fig. 2 Smoothed curve fitting (penalized spline) analysis between the intake of Vitamin A (**A**), Vitamin B1 (**B**), Vitamin B2 (**C**), Vitamin B6 (**D**), Vitamin C (**E**), Folate (**F**), Vitamin E (**G**), and Vitamin B12 (**H**) and endometriosis. Adjusted for age, BMI, race, education, poverty-to-income ratio, hypertension, diabetes, smoking, number of pregnancies, marital status, age at Menarche, oral contraceptive use

Fig. 3 Forest plots of subgroup analysis between the intake of Vitamin A (**A**), Vitamin B1 (**B**), Vitamin B2 (**C**), Vitamin B6 (**D**), Vitamin C (**E**), Folate (**F**), Vitamin E (**G**) and Vitamin B12 (**H**), and endometriosis

study, dietary sources of vitamin B1, folic acid, and vitamin C were found to be negatively associated with the risk of endometriosis [25]. These results are consistent with our study.

Decreased levels of vitamin A may affect the proliferation of endometrial cells and the balance of immune responses, leading to the occurrence of endometriosis [26]. The metabolite of vitamin A, retinoic acid, can significantly prevent the proliferation of endometrial tissue cysts and reduce the production of local estradiol [27]. Impaired biosynthesis of retinoic acid in endometriosis lesions may disrupt the regulation of local inflammatory and cell signaling processes [27]. This also suggests that the reduction of vitamin A and its metabolites may be an important factor in the pathophysiology of endometriosis. Research into the relationship between B vitamins (B1, B2, B6, B12 and folic acid) and endometriosis has focused on vitamin B6 and folic acid. Vitamin B1 is recognized for its antioxidant properties, including the scavenging of reactive oxygen species (ROS), which are implicated in the pathogenic mechanisms of endometriosis [28]. However, there is a paucity of research on the relationship between vitamin B2 and endometriosis, and this study provides new insights into their association. Vitamin B6 facilitates the metabolism of estrogen into its inactive form and converts linoleic acid to gamma-linoleic acid, a crucial component in the synthesis of anti-inflammatory prostaglandins [29]. These prostaglandins have been shown to inhibit the proliferation of endometrial tissue. In addition, vitamin B6, as a lipophilic nutrient, has the capacity to modify gene expression and potentially DNA methylation in humans, thus potentially decreasing the risk of endometriosis [30]. Folic acid has been the subject of previous studies that have suggested it may reduce the risk associated with endometriosis [25]. Interestingly, in a recent case–control study, Gersekowski et al. found that higher folic acid intake was correlated with an increased risk of ovarian cancer in patients with endometriosis, but the correlation was not observed in women without the condition [31]. Further research into the benefits of folic acid in endometriosis is necessary. With regard to vitamin B12, existing research has suggested that it may improve dysmenorrhea symptoms in individuals with endometriosis. However, combined with the findings of this study, it appears that vitamin B12 intake does not reduce the risk of endometriosis. Vitamin C, an essential water-soluble vitamin, is known for its ability to reduce oxidative stress [32]. It has been suggested that intravenous vitamin C helps to prevent the induction of endometriotic implants and reduce the size of endometriotic implants, potentially due to its anti-inflammatory and antiangiogenic effects [33]. Studies have shown that endometriotic implants treated with vitamin C were significantly smaller compared to those in the control group [7, 33]. These findings indicate that vitamin C has potential as a complementary treatment for endometriosis. Vitamin E, a lipid-soluble antioxidant, plays a crucial role in neutralizing oxidative stress in endometriosis by scavenging free radicals and reactive oxygen species [34]. In conjunction with vitamin C, it can have synergistic effects, enhancing the body's defense against oxidative damage and potentially reducing the cellular harm induced by endometriosis [35]. The combined use of vitamin E and vitamin C may serve as a therapeutic strategy to mitigate the oxidative stress associated with endometriosis.

Few studies have investigated the relationship between vitamins and endometriosis, and the mechanisms underlying the association remain unclear. However, diet is a potentially modifiable risk factor for endometriosis. The beneficial effects of dietary antioxidants on endometriosis have been widely discussed [36, 37]. Oxidative stress (OS), characterized by an imbalance between ROS and antioxidants, is a major factor in the pathophysiology of endometriosis, leading to cellular damage [38, 39]. In the state of OS, the overproduction of pro-oxidants can lead to systemic damage when the expression of pro-oxidants exceeds the ability of biological systems to rapidly detoxify or repair them [40]. Excessive formation of ROS in women may disrupt antioxidant defense mechanisms, potentially damaging oocytes and follicles, affecting implantation, altering endocrine function, and contributing to the development of endometriosis [41]. Antioxidants neutralize reactive free radicals, mitigate the formation of ROS, and facilitate the repair of oxidative cellular damage [42]. Dietary vitamins, which are natural antioxidants predominantly obtained from food, help stabilize and counteract the harmful effects of ROS by neutralizing free radicals [37]. Therefore, dietary vitamin supplementation is essential for maintaining women's reproductive health.

Notably, although our study did not alter existing prevention or treatment strategies for endometriosis, it highlights the potential of dietary therapies to enhance them. However, we acknowledge several inherent in our research. Firstly, the cross-sectional design of our study precludes the determination of causality, limiting our ability to generalize these findings and establish a causal relationship between vitamin intake and endometriosis. Secondly, the dietary data were obtained from two 24-h dietary recall interviews, which may not accurately reflect an individual's habitual dietary patterns. Nonetheless, some studies suggest that two 24-h recalls may be sufficient to assess daily dietary intake (43). Furthermore, the reliance on self-reported endometriosis diagnoses through questionnaires may lead to

an underestimation of the disease's prevalence. Additionally, since the NHANES data is derived from a U.S. population, the findings may not be readily generalizable to other racial or ethnic groups, reflecting a constraint in the study's external validity.

Conclusions

This research indicates a significant inverse correlation between the intake of vitamins A, B1, B6, B12, C, and folic acid and the reduced risk of endometriosis. Vitamin E intake exhibited a threshold effect on endometriosis risk, with an optimal cut-off point; below this point, there was a negative association, and above it, no significant further reduction in risk was observed. These findings suggest that these micronutrients may exert a protective role in the development of endometriosis, and they also provide guidance for clinical dietary therapies that may be more effective in preventing endometriosis.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12978-024-01895-x.

Supplementary Material 1.

Acknowledgements
We acknowledge and thank all participants for their cooperation.

Author contributions
Conceptualization, Ting Xu; Data curation, Ting Xu and Yuan Zhuang; Funding acquisition, Ting Xu; Investigation, Yuan Zhuang and Huabin Cao; Methodology, Ting Xu and and Huabin Cao; Supervision, Huabin Cao; Validation, Yuan Zhuang and Huabin Cao; Writing–original draft, Ting Xu and Yuan Zhuang; Writing–review & editing, Huabin Cao.

Funding
The authors' research was supported by Health and Family Planning Commission of Jiangxi Province (Grant Number: 202211101).

Availability of data and materials
Publicly available datasets were analyzed in this study. The data of NHANES can be downloaded from the website: https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate
The data of NHANES is public database. The patients involved in the database received ethical approval. Users can download relevant data for free for research and publication purposes.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 19 November 2023 Accepted: 21 October 2024
Published online: 04 November 2024

References

1. Smolarz B, Szyłło K, Romanowicz H. Endometriosis: epidemiology, classification, pathogenesis, treatment and genetics (review of literature). Int J Mol Sci. 2021;22(19):10554. https://doi.org/10.3390/ijms221910554.
2. Eisenberg VH, Weil C, Chodick G, Shalev V. Epidemiology of endometriosis: a large population-based database study from a healthcare provider with 2 million members. BJOG. 2018;125(1):55–62.
3. Zubrzycka A, Zubrzycki M, Perdas E, Zubrzycka M. Genetic, epigenetic, and steroidogenic modulation mechanisms in endometriosis. J Clin Med. 2020. https://doi.org/10.3390/jcm9051309.
4. Koninckx PR, Ussia A, Adamyan L, Tahlak M, Keckstein J, Wattiez A, et al. The epidemiology of endometriosis is poorly known as the pathophysiology and diagnosis are unclear. Best Pract Res Clin Obstet Gynaecol. 2021;71:14–26.
5. Okten SB, Cetin C, Tok OE, Guler EM, Taha SH, Ozcan P, et al. Cannabidiol as a potential novel treatment for endometriosis by its anti-inflammatory, antioxidative and antiangiogenic effects in an experimental rat model. Reprod Biomed Online. 2023;46(5):865–75.
6. Shin S, Chung YJ, Moon SW, Choi EJ, Kim MR, Chung YJ, et al. Single-cell profiling identifies distinct hormonal, immunologic, and inflammatory signatures of endometriosis-constituting cells. J Pathol. 2023;261(3):323–34.
7. Yalçın Bahat P, Ayhan I, Üreyen Özdemir E, İnceboz Ü, Oral E. Dietary supplements for treatment of endometriosis: a review. Acta Biomed. 2022;93(1): e2022159.
8. Nowakowska A, Kwas K, Fornalczyk A, Wilczyński J, Szubert M. Correlation between endometriosis and selected allergic and autoimmune diseases and eating habits. Medicina (Kaunas). 2022. https://doi.org/10.3390/medicina58081038.
9. Sverrisdóttir U, Hansen S, Rudnicki M. Impact of diet on pain perception in women with endometriosis: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2022;271:245–9.
10. Cirillo M, Argento FR, Becatti M, Fiorillo C, Coccia ME, Fatini C. Mediterranean diet and oxidative stress: a relationship with pain perception in endometriosis. Int J Mol Sci. 2023. https://doi.org/10.3390/ijms241914601.
11. Rizzo G, Laganà AS, Rapisarda AM, La Ferrera GM, Buscema M, Rossetti P, et al. Vitamin B12 among vegetarians: status, assessment and supplementation. Nutrients. 2016. https://doi.org/10.3390/nu8120767.
12. Giampaolino P, Della Corte L, Foreste V, Bifulco G. Is there a relationship between vitamin D and endometriosis? An overview of the literature. Curr Pharm Des. 2019;25(22):2421–7.
13. Cirillo M, Argento FR, Attanasio M, Becatti M, Ladisa I, Fiorillo C, et al. Atherosclerosis and endometriosis: the role of diet and oxidative stress in a gender-specific disorder. Biomedicines. 2023. https://doi.org/10.3390/biomedicines11020450.
14. Trabert B, Peters U, De Roos AJ, Scholes D, Holt VL. Diet and risk of endometriosis in a population-based case-control study. Br J Nutr. 2011;105(3):459–67.
15. Resnick B. National Health and Nutrition Examination Survey (NHANES). In: Gellman MD, editor. Encyclopedia of behavioral medicine. Cham: Springer International Publishing; 2020. p. 1451.
16. Paulose-Ram R, Graber JE, Woodwell D, Ahluwalia N. The National Health and Nutrition Examination Survey (NHANES), 2021–2022: adapting data collection in a COVID-19 environment. Am J Public Health. 2021;111(12):2149–56.
17. Pan G, Zhang P, Li S, Cao L, Yang C. Association of endometriosis with asthma: a study of the NHANES database in 1999–2006. J Health Popul Nutr. 2024;43(1):50.
18. Li K, Zhang W. The association between daily intake of dietary supplements and self-reported endometriosis: a NHANES-based study. Reprod Sci. 2024;31(7):1936–47.
19. Hall MS, Talge NM, Upson K. Urinary cadmium and endometriosis prevalence in a US nationally representative sample: results from NHANES 1999–2006. Hum Reprod. 2023;38(9):1835–42.

20. Sasamoto N, Yland J, Vitonis AF, Cramer DW, Titus LJ, De Vivo I, et al. Peripheral blood leukocyte telomere length and endometriosis. Reprod Sci. 2020;27(10):1951–9.
21. Kim JH. Multicollinearity and misleading statistical results. Korean J Anesthesiol. 2019;72(6):558–69.
22. Cook RD, Weisberg S. Diagnostics for heteroscedasticity in regression. Biometrika. 1983;70(1):1–10.
23. Pašalić E, Tambuwala MM, Hromić-Jahjefendić A. Endometriosis: classification, pathophisiology, and treatment options. Pathol Res Pract. 2023;251:154847.
24. Roshanzadeh G, Jahanian Sadatmahalleh S, Moini A, Mottaghi A, Rostami F. The relationship between dietary micronutrients and endometriosis: a case-control study. Int J Reprod Biomed. 2023;21(4):333–42.
25. Darling AM, Chavarro JE, Malspeis S, Harris HR, Missmer SA. A prospective cohort study of Vitamins B, C, E, and multivitamin intake and endometriosis. J Endometr. 2013;5(1):17–26.
26. Anderson G. Endometriosis pathoetiology and pathophysiology: roles of vitamin A, estrogen, immunity, adipocytes, gut microbiome and melatonergic pathway on mitochondria regulation. Biomol Concepts. 2019;10(1):133–49.
27. Yamagata Y, Takaki E, Shinagawa M, Okada M, Jozaki K, Lee L, et al. Retinoic acid has the potential to suppress endometriosis development. J Ovarian Res. 2015;8:49.
28. Mrowicka M, Mrowicki J, Dragan G, Majsterek I. The importance of thiamine (vitamin B1) in humans. 2023. Biosci Rep. https://doi.org/10.1042/BSR20230374.
29. Jin L, Lorkiewicz P, Malovichko MV, Bhatnagar A, Srivastava S, Conklin DJ. Acetaldehyde induces an endothelium-dependent relaxation of superior mesenteric artery: potential role in postprandial hyperemia. Front Physiol. 2019;10:1315.
30. Mikkelsen K, Apostolopoulos V. Vitamin B1, B2, B3, B5, and B6 and the immune system. In: Mahmoudi M, Rezaei N, editors. Nutrition and immunity. Cham: Springer International Publishing; 2019. p. 115–25. https://doi.org/10.1007/978-3-030-16073-9_7.
31. Gersekowski K, Ibiebele TI, Doherty JA, Harris HR, Goodman MT, Terry KL, et al. Folate intake and ovarian cancer risk among women with endometriosis: a case-control study from the ovarian cancer association consortium. Cancer Epidemiol Biomarkers Prev. 2023;32(8):1087–96.
32. Liu F, Zhu Y, Zhang J, Li Y, Peng Z. Intravenous high-dose vitamin C for the treatment of severe COVID-19: study protocol for a multicentre randomised controlled trial. BMJ Open. 2020;10(7): e039519.
33. Erten OU, Ensari TA, Dilbaz B, Cakiroglu H, Altinbas SK, Çaydere M, et al. Vitamin C is effective for the prevention and regression of endometriotic implants in an experimentally induced rat model of endometriosis. Taiwan J Obstet Gynecol. 2016;55(2):251–7.
34. Vitale SG, Capriglione S, Peterlunger I, La Rosa VL, Vitagliano A, Noventa M, et al. The role of oxidative stress and membrane transport systems during endometriosis: a fresh look at a busy corner. Oxid Med Cell Longev. 2018;2018:7924021.
35. Ansariniya H, Hadinedoushan H, Javaheri A, Zare F. Vitamin C and E supplementation effects on secretory and molecular aspects of vascular endothelial growth factor derived from peritoneal fluids of patients with endometriosis. J Obstet Gynaecol. 2019;39(8):1137–42.
36. Brouns F, Van Haaps A, Keszthelyi D, Venema K, Bongers M, Maas J, et al. Diet associations in endometriosis: a critical narrative assessment with special reference to gluten. Front Nutr. 2023;10:1166929.
37. Zheng SH, Chen XX, Chen Y, Wu ZC, Chen XQ, Li XL. Antioxidant vitamins supplementation reduce endometriosis related pelvic pain in humans: a systematic review and meta-analysis. Reprod Biol Endocrinol. 2023;21(1):79.
38. Didziokaite G, Biliute G, Gudaite J, Kvedariene V. Oxidative stress as a potential underlying cause of minimal and mild endometriosis-related infertility. Int J Mol Sci. 2023. https://doi.org/10.3390/ijms24043809.
39. D'Amico R, Impellizzeri D, Cordaro M, Siracusa R, Interdonato L, Marino Y, et al. Complex interplay between autophagy and oxidative stress in the development of endometriosis. Antioxidants (Basel). 2022. https://doi.org/10.3390/antiox11122484.
40. Di Meo S, Reed TT, Venditti P, Victor VM. Role of ROS and RNS sources in physiological and pathological conditions. Oxid Med Cell Longev. 2016;2016:1245049.
41. Kaltsas A, Zikopoulos A, Moustakli E, Zachariou A, Tsirka G, Tsiampali C, et al. The silent threat to women's fertility: uncovering the devastating effects of oxidative stress. Antioxidants (Basel). 2023. https://doi.org/10.3390/antiox12081490.
42. Joó JG, Sulyok E, Bódis J, Kornya L. disrupted balance of the oxidant-antioxidant system in the pathophysiology of female reproduction: oxidative stress and adverse pregnancy outcomes. Curr Issues Mol Biol. 2023;45(10):8091–111.
43. Knüppel S, Norman K, Boeing H. Is a single 24-hour dietary recall per person sufficient to estimate the population distribution of usual dietary intake? J Nutr. 2019;149(9):1491–2.

Publisher's Note