Original Article

Dietary intakes of vitamin B_6, folate, vitamin B_{12} and erectile dysfunction: a national population-based study

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Background: While deficiencies in vitamin B_6, folate, and vitamin B_{12} are linked to various human diseases, including anemia, depression, peripheral neuropathy, and cardiovascular disease (CVD), literature regarding the association between vitamin B_6, folate, and vitamin B_{12} and erectile dysfunction (ED) is scarce. We aimed to determine the dietary intake of vitamin B_6, folate, and vitamin B_{12} and ED in the United States population.

Methods: We extracted data from the 2001–2004 cycles of the National Health and Nutrition Examination Survey (NHANES). Dietary intakes of B vitamins were collected based on one 24-hour dietary recall. The association between dietary intake of vitamin B_6, folate, vitamin B_{12} and ED was examined using multivariate logistic regression models.

Results: A total of 3,875 participants were included for analysis, with 1,201 reporting ED and 2,894 not experiencing ED. The multivariable odds ratios (ORs) for the highest *vs.* lowest quartiles of vitamin B_6 was 0.77 [95% confidence interval (CI): 0.60–0.99; P for trend =0.03] for the prevalence of ED. Subgroup analyses demonstrated a significant inverse association between dietary intake of vitamin B_6, folate, vitamin B_{12} and the prevalence of ED among men aged ≤60 years, individuals of Mexican American and non-Hispanic White ethnicity, and those without a history of CVD, diabetes, hypertension, and high cholesterol.

Conclusions: The consumption of dietary vitamin B_6, folate, and vitamin B_{12} was significantly linked to decreased risks of ED among younger healthier men, suggesting a potential protective role of these nutrients against ED in United States adults.

Keywords: Erectile dysfunction (ED); B vitamins; National Health and Nutrition Examination Survey (NHANES); cross-sectional study

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Introduction

Erectile dysfunction (ED) is one of the most common clinical entities that is defined as the inability to achieve or maintain a satisfactory erection for sexual performance (1). This condition is a significant health concern that can profoundly impact the psychosocial well-being of men. Recent research indicates a trend of ED occurring in increasingly younger age cohorts (2). It is reported that the prevalence of ED among young males may be as high as 30%, with its incidence increasing markedly as age advances (3). ED not only impacts overall quality of life of patients significantly but also serves as a pivotal indicator of

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subclinical cardiovascular disease (CVD) (4). Accumulating evidence indicates a strong correlation between the severity of ED and cardiovascular mortality and morbidity, and the effective management of ED has the potential to facilitate the mitigation of future CVD events (4). Thus, it is imperative to explore modifying factors and explore therapeutic strategies aiming at preventing or ameliorating ED.

B group vitamins, specifically vitamin B_6, folate (vitamin B_9), and vitamin B_{12}, display essential roles in various metabolic and regulatory processes, including cell replication, DNA synthesis, and immune response regulation (5). Deficiencies in vitamin B_6, folate, and vitamin B_{12} are linked to various human diseases, including anemia, depression, peripheral neuropathy, and CVD (6). Furthermore, a well-established study has suggested that vitamin B_6, folate, and vitamin B_{12} reduce serum homocysteine levels, which are presumed to be independently associated with an elevated risk of ED (7). Therefore, it is reasonable to hypothesize the protective effects of B vitamins on erectile function. Several studies with small sample sizes have investigated the association between vitamin B_6, folate, vitamin B_{12} and erectile function with controversial results. Xu *et al.* analyzed 134 patients with ED and 50 healthy controls (8). They found that elevated folate levels were correlated with a decreased risk of developing ED, while vitamin B_{12} had no effect on erectile function (8). In addition, Chen *et al.* did not observe an association between folate and erectile function, however, high levels of vitamin B_{12} were positively correlated with ED (9). Accordingly, in this study, we analyzed 3,875 samples from the 2001–2004 cycles of the National Health and Nutrition Examination Survey (NHANES), to investigate the independent association between dietary intake of B vitamins and ED. Our results showed that the consumption of dietary vitamin B_6, folate, and vitamin B_{12} was significantly associated with decreased risks of ED among younger healthier men in United States adults. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-161/rc).

Highlight box

Key findings

- Dietary intake of vitamin B_6, folate, and vitamin B_{12} is significantly associated with reduced risk of erectile dysfunction (ED) among younger healthier men.

What is known and what is new?

- ED is a multifactorial disease affected by dietary interventions.
- This study investigated the association between dietary intake of vitamin B_6, folate, and vitamin B_{12} and ED.

What is the implication, and what should change now?

- We suggest that men incorporate foods rich in B group vitamins into their diets, as this may help prevent and alleviate ED.

Methods

Data source and study population

NHANES is an ongoing research program conducted annually in the United States (available at https://www.cdc.gov/nchs/nhanes). These surveys systematically collect information from representative population, using a meticulously designed stratified, multistage, probability-based sampling methodology. For this investigation, we obtained data from two cycles covering the years 2001 to 2004, extracted from NHANES. Specifically, the 2001–2002 and 2003–2004 cycles are the only years containing an interview survey related to ED. Participants with incomplete assessments of erectile function or missing information on dietary vitamin B_6, folate, and vitamin B_{12} were excluded from our analysis. We utilized publicly accessible data from NHANES, and ethical approval was not required for the present study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The data of participants were obtained from the public dataset NHANES in an anonymous form. Thus, additional consents were waived in the present study.

Assessment of dietary folate, vitamin B6, and vitamin B12 intake

Dietary intake data regarding folate, vitamin B_6 and vitamin B_{12} were gathered via a standardized questionnaire, employing a retrospective dietary assessment approach that yielded data regarding food and total nutrient intakes over a 24-hour period. During the survey cycles spanning from 2001 to 2002, a single dietary recall was obtained from each person at the Mobile Examination Center (MEC). However, starting from 2003, the protocol shifted to conducting two dietary assessments. The initial assessment continued to take place at the MEC, while the second assessment was taken via telephone 3 to 10 days following the initial review. This study utilized the first 24-hour dietary review between 2001 and 2004 to analyze the dietary B vitamins intake (10,11).

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Assessment of erectile function

The outcome of our study was the presence of ED. Assessment of erectile function was performed based on responses to a validated survey question (12-15): "*How would you rate your ability to achieve and maintain an erection sufficient for satisfactory intercourse?*" Response choices included "*always or almost always able*", "*usually able*", "*sometimes able*", and "*never able*". In the current study, individuals who indicated being "*sometimes able*" or "*never able*" were classified as experiencing ED, while those who reported being "*almost always able*" or "*usually able*" were classified as having no history of ED (12-15).

Covariates

Potential covariates were identified in the current study based on previous reports (12-17): age, race/ethnicity, household income, educational attainment, marital status, body mass index (BMI) status, alcohol use, smoking status, physical activity levels, and the presence of CVD, diabetes mellitus, hypertension, and hypercholesterolemia. Alcohol use was specifically evaluated in terms of daily consumption, with categories delineated as none (0 g/d), light (<27.9 g/d), and heavy (≥28 g/d) (12). For smoking status determination, individuals who had smoked less than 100 cigarettes were classified as nonsmokers (12,14). Former smokers were identified as individuals who had ceased smoking at the time of the interview (12,14). Current smokers were those who displayed an ongoing smoking behavior during the interview (12,14). Physical activity status was assessed through participants' responses to a questionnaire regarding daily moderate or vigorous activities (12). Those who self-reported a medical history of angina pectoris or a coronary heart disease diagnosis were categorized as CVD patients. Men with a documented history of diabetes mellitus or a high fasting plasma glucose level (>126 mg/dL) were classified as diabetic (13). Participants with an elevated blood pressure (>140/90 mmHg), of being on antihypertensive drugs were regarded as hypertension patients (13). Individuals were classified as having hypercholesterolemia if they had elevated plasma total cholesterol (>240 mg/dL), a history of hypercholesterolemia, or self-reported the use of lipid-lowering drugs (13).

Statistical analysis

Participant characteristics were summarized using mean values with standard deviations (or median with quartile 1 to quartile 3) for continuous variables, and frequencies with percentages for categorical variables. The association between dietary intake of B vitamins and ED was examined using multivariate logistic regression models. Dietary B vitamins were categorized into four quartiles, with the first quartile serving as the reference category. Three models were employed: (I) an unadjusted model; (II) Model I, adjusting for age, race/ethnicity, and BMI; and (III) Model II, which further adjusted for household income, educational attainment, marital status, drinking, smoking habits, physical activity status, CVD, diabetes mellitus, hypertension, and hypercholesterolemia.

Subsequently, we conducted subgroup analyses to determine the association between dietary B vitamins and ED, stratified by age (≤60 or >60 years), race, history of CVD, diabetes mellitus, hypertension, and hypercholesterolemia. A two-tailed P value of <0.05 was considered statistically significant. All statistical analyses were performed utilizing EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc.) and the R statistical software packages (http://www.R-project.org; The R Foundation) (18).

Results

Figure 1 illustrates that the final analysis comprised 3,875 participants aged 20 years or older, with 1,201 reporting ED and 2,894 not experiencing ED. *Table 1* displays participant characteristics stratified by ED history. Participants with ED, compared to those with normal erectile function, exhibited characteristics including older age, non-Hispanic White ethnicity, lower annual household income, lower educational attainment, married or living with partner, higher BMI, non-drinking habits, former smoking status, physical inactivity, and a medical history comprising CVD, diabetes mellitus, hypertension, and hypercholesterolemia (all P<0.001; *Table 1*). Moreover, those with ED exhibited reduced dietary intake of vitamin B_6, folate, and vitamin B_{12} (all P<0.001; *Table 1*).

Table 2 displays the association between dietary intake of B vitamins and ED. In the unadjusted model, dietary intake of vitamin B_6 was negatively related to the prevalence of ED. The odds ratio (OR) and 95% confidence interval (95% CI) decreased from the lowest to the highest quartile of vitamin B_6, reaching 0.72 (0.60–0.87), 0.59 (0.49–0.71), and 0.40 (0.33–0.49), respectively (*Table 2*). The association was also significant in the adjusted model I (Q4 *vs.* Q1: OR

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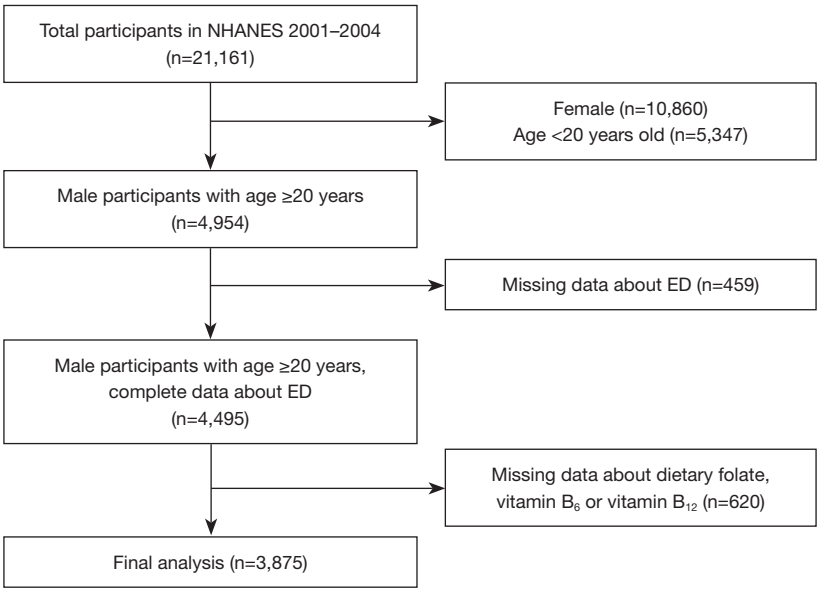

Figure 1 The flowchart showing the selection of study population. NHANES, National Health and Nutrition Examination Survey; ED, erectile dysfunction.

0.68; 95% CI: 0.53–0.87; P for trend <0.001) and model II (Q4 *vs.* Q1: OR 0.77; 95% CI: 0.60–0.99; P for trend =0.03). These findings suggest a protective effect of dietary vitamin B_6 against the development of ED. Additionally, an inverse relationship between folate, vitamin B_{12} and ED was observed in the crude model (*Table 2*). However, the correlation between dietary intake of folate, vitamin B_{12} and ED were no longer statistically significant after full adjustment in model II (*Table 2*).

We further conducted subgroup analyses to explore the relationship between dietary intake of B vitamins and ED among various subpopulations. Following full adjustment, individuals aged ≤60 years (OR 0.56; 95% CI: 0.39–0.80), Mexican American ethnicity (OR 0.41; 95% CI: 0.24–0.73), and individuals without CVD (OR 0.69; 95% CI: 0.53–0.92), diabetes (OR 0.70; 95% CI: 0.53–0.93), and hypertension (OR 0.59; 95% CI: 0.41–0.85) who consumed the highest quartile of dietary vitamin B_6 exhibited a negative correlation with the prevalence of ED compared with those in the lowest quartile (*Figure 2A*). Additionally, participants aged ≤60 years (OR 0.50; 95% CI: 0.35–0.71) who were in the quartile 4 of dietary folate intake demonstrated an inverse association with the prevalence of ED in contrast to those in the quartile 1 (*Figure 2B*). Furthermore, individuals aged ≤60 years (OR 0.67; 95% CI: 0.47–0.95), of Mexican American ethnicity (OR 0.50; 95% CI: 0.29–0.85), non-Hispanic White ethnicity (OR 0.69; 95% CI: 0.51–0.93), and those without a history of CVD (OR 0.66; 95% CI: 0.52–0.83), diabetes (OR 0.63; 95% CI: 0.49–0.80), hypertension (OR 0.53; 95% CI: 0.39–0.74), and high cholesterol (OR 0.61; 95% CI: 0.45–0.82) who were in the quartile 4 of dietary vitamin B_{12} intake demonstrated a negative association with the prevalence of ED in comparison with those in the quartile 1 (*Figure 2C*).

Discussion

This is the first study with large sample size to determine the correlation between dietary intakes of vitamin B_6, folate, vitamin B_{12} and ED. After full adjustment, we observed that dietary intake of vitamin B_6 was negatively correlated with the prevalence of ED, especially among men aged ≤60 years, Mexican American ethnicity, and those without a history of CVD, diabetes, and hypertension. In addition, folate levels were related to a decreased prevalence of ED among participants aged ≤60 years. Moreover, vitamin B_{12} levels were related to a reduced risk of ED among participants aged ≤60 years, Mexican American ethnicity, non-Hispanic White ethnicity, and those without CVD, diabetes mellitus, hypertension, and hypercholesterolemia.

Several mechanisms may account for the negative association between B vitamin levels and ED. First,

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Table 1 Baseline characteristics of participants with or without a history of erectile dysfunction in NHANES 2001–2004

Characteristics	History of erectile dysfunction		P value
	No (n=2,894)	Yes (n=1,201)	
Age, years	43.4±15.7	66.0±15.5	<0.001
Race			<0.001
Mexican American	588 (20.3)	245 (20.4)	
Other Hispanic	97 (3.4)	41 (3.4)	
Non-Hispanic White	1,511 (52.2)	705 (58.7)	
Non-Hispanic Black	599 (20.7)	184 (15.3)	
Other race	99 (3.4)	26 (2.2)	
Ratio of family income to poverty			<0.001
Less than 1.5	754 (26.1)	380 (31.6)	
1.5–3.5	902 (31.2)	430 (35.8)	
Over 3.5	1,088 (37.6)	319 (26.6)	
Missing	150 (5.2)	72 (6.0)	
Education level			<0.001
Less than high school	675 (23.3)	486 (40.5)	
High school	767 (26.5)	246 (20.5)	
Above high school	1,452 (50.2)	469 (39.1)	
Marital status			<0.001
Married or living with partner	1,910 (66.0)	876 (72.9)	
Living alone	984 (34.0)	325 (27.1)	
BMI, kg/m^2			<0.001
<20	109 (3.8)	40 (3.3)	
20≤ BMI <25	790 (27.3)	264 (22.0)	
25 ≤ BMI <30	1,182 (40.8)	484 (40.3)	
≥30	773 (26.7)	341 (28.4)	
Missing	40 (1.4)	72 (6.0)	
Alcohol intake			<0.001
Nondrinker	1,998 (69.0)	931 (77.5)	
Light drinker	370 (12.8)	107 (8.9)	
Heavy drinker	320 (11.1)	72 (6.0)	
Missing	206 (7.1)	91 (7.6)	
Smoking			<0.001
Nonsmoker	1,287 (44.5)	367 (30.6)	
Former smoker	740 (25.6)	589 (49.0)	
Current smoker	867 (29.9)	245 (20.4)	

Table 1 (*continued*)

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Table 1 (*continued*)

Characteristics	History of erectile dysfunction		P value
	No (n=2,894)	Yes (n=1,201)	
Physical activity status			
Moderate			<0.001
Yes	1,498 (51.8)	497 (41.4)	
No	1,396 (48.2)	704 (58.6)	
Vigorous			<0.001
Yes	1,172 (40.5)	195 (16.2)	
No	1,722 (59.5)	1,006 (83.8)	
History of cardiovascular disease			<0.001
Yes	158 (5.5)	271 (22.6)	
No	2,736 (94.5)	930 (77.4)	
History of diabetes			<0.001
Yes	154 (5.3)	273 (22.7)	
No	2,740 (94.7)	928 (77.3)	
History of hypertension			<0.001
Yes	855 (29.5)	719 (59.9)	
No	2,039 (70.5)	482 (40.2)	
History of high cholesterol			<0.001
Yes	928 (32.1)	548 (45.6)	
No	1,966 (67.9)	653 (54.3)	
Vitamin B_6 intake, mg/day	2.0 (1.4–2.8)	1.6 (1.1–2.3)	<0.001
Folate intake, mcg/day	528.0 (359.0–770.0)	452.0 (313.0–659.0)	<0.001
Vitamin B_{12} intake, mcg/day	4.8 (2.7–7.6)	4.0 (2.3–6.7)	<0.001

Data are presented as mean ± standard deviation, median (quartile 1 – quartile 3) or n (%). BMI, body mass index.

vitamin B_6, folate, and vitamin B_{12} play essential roles in homocysteine metabolism. Vitamin B_6 participates in trans-sulfuration, facilitating the conversion of homocysteine into sulfate (19-22). Additionally, both folate and vitamin B_{12} are necessary for remethylating homocysteine into methionine (19). Inadequate consumption of vitamin B_6, folate, and vitamin B_{12} can raise homocysteine levels (23). Further, elevated homocysteine levels can adversely affect erectile function by compromising endothelium homeostasis (24). Cui *et al.* reported that high hyperhomocysteinemia induced the downregulation of endothelial cell tight junction-associated proteins, such as VE-cadherin, occludin, and claudin-5, in rats (25). Similarly, Jiang *et al.* demonstrated impaired cavernosal endothelial nitric oxide synthase (eNOS) activity in a rat model of hyperhomocysteinemia (26). The expression of eNOS and phospho-eNOS was significantly reduced in the hyperhomocysteinemia group, whereas supplementation with B vitamins upregulated these proteins and ameliorated ED (26). Second, the dorsal nerve of the penis is responsible for normal erection and neurogenic damage is closely related to the development of ED (27-29). Recent studies revealed that vitamin B_6 contributed to the regulation of nerve metabolism, and vitamin B_{12} supported the survival of nerve cells and facilitated remyelination (30). Insufficiency of these vitamins may cause irreversible nerve degeneration,

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Table 2 Association between dietary B vitamins intake and erectile dysfunction among U.S. male in NHANES 2001–2004

Characteristics	Q1	Q2	Q3	Q4	P for trend
Vitamin B_6 intake, mg/day					
Crude model	1.00 (reference)	0.72 (0.60, 0.87)	0.59 (0.49, 0.71)	0.40 (0.33, 0.49)	<0.001
Model 1	1.00 (reference)	0.82 (0.65, 1.03)	0.73 (0.58, 0.93)	0.68 (0.53, 0.87)	<0.001
Model 2	1.00 (reference)	0.87 (0.69, 1.10)	0.80 (0.63, 1.02)	0.77 (0.60, 0.99)	0.03
Folate intake, mcg/day					
Crude model	1.00 (reference)	0.85 (0.71, 1.03)	0.68 (0.56, 0.82)	0.52 (0.43, 0.64)	<0.001
Model 1	1.00 (reference)	0.88 (0.70, 1.16)	0.85 (0.67, 1.07)	0.82 (0.64, 1.05)	0.11
Model 2	1.00 (reference)	0.92 (0.73, 1.17)	0.96 (0.75, 1.22)	0.90 (0.70, 1.16)	0.53
Vitamin B_{12} intake, mcg/day					
Crude model	1.00 (reference)	0.86 (0.71, 1.03)	0.68 (0.56, 0.82)	0.60 (0.50, 0.73)	<0.001
Model 1	1.00 (reference)	0.91 (0.73, 1.15)	0.76 (0.60, 0.96)	0.86 (0.67, 1.09)	0.10
Model 2	1.00 (reference)	0.92 (0.72, 1.16)	0.78 (0.61, 1.00)	0.92 (0.71, 1.18)	0.28

Data are presented as OR (95% CI). Crude model: non-adjusted model; Model 1: adjust for age, race and BMI; Model 2: adjust for age, race, ratio of family income to poverty, education level, marital status, BMI, alcohol intake, smoking, physical activity, diabetes, cardiovascular disease, hypertension and high cholesterol. NHANES, National Health and Nutrition Examination Survey; Q, quartile; BMI, body mass index; OR, odds ratio; CI, confidence interval.

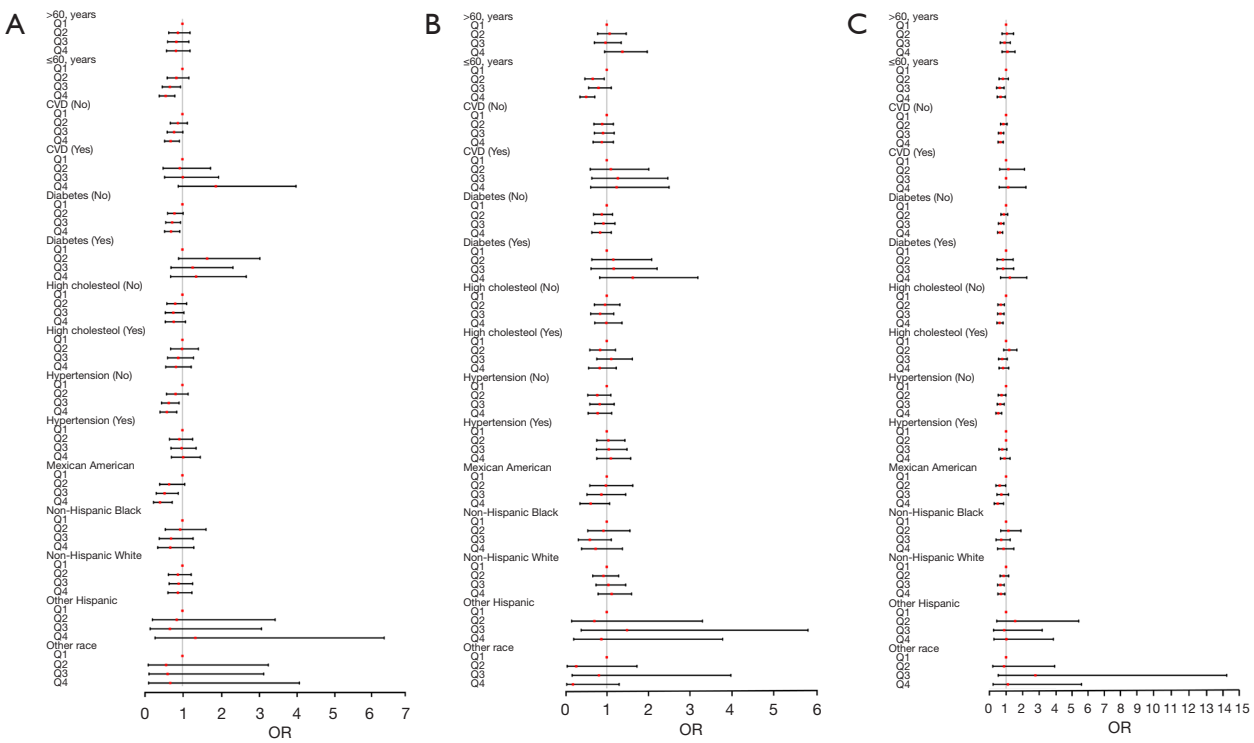

Figure 2 The association between dietary intake of vitamin vitamin B_6 (A), folate (B), B_{12} (C) and ED among various subpopulations. CVD, cardiovascular disease; OR, odds ratio; ED, erectile dysfunction.

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ultimately resulting in peripheral neuropathy and ED (30). Third, B group vitamins exhibit powerful antioxidant properties that could efficiently mitigate oxidative stress and inflammation (31). The downregulation of oxidative and inflammatory parameters is related to an improvement of erectile function (32). Therefore, we suggest that men consume foods rich in B group vitamins into their diets, such as beef, organ meats, leafy greens, peanuts, and bananas, as this may aid in the prevention and alleviation of ED (30).

Interestingly, our subgroup analyses demonstrated a significant inverse association between dietary B vitamins intake and the prevalence of ED among men aged ≤60 years, and those without a history of CVD, diabetes, and hypertension. This might be explained by that increasing oxidative stress exists in conditions including aging, CVD, diabetes and hypertension (33-35). Extensive oxidative stress response compromises the protective effects of B vitamins, thus contributing to the development of ED in this subpopulation.

Our study has several strengths. Firstly, it is the first to provide evidence of the association between B vitamin intake and the prevalence of ED. Subgroup analyses were conducted to identify which subpopulation could benefit most from increased B vitamin intake. Additionally, we categorized dietary B vitamins into four quartiles, demonstrating a dose-response effect of B vitamins on ED. Furthermore, we utilized data from NHANES, which has large sample sizes, providing insights representative of the broader United States adult population, thereby enhancing the generalizability of our findings. However, our study also has limitations that should be noted. Firstly, the baseline data on B vitamin intake were based on one 24-hour dietary recall and did not capture long-term fluctuations, and the self-reported nature of dietary B vitamin intake in the population increases susceptibility to recall bias. Secondly, there are still unmeasured variables that could influence both dietary intake and ED risk, such as genetic predispositions or detailed lifestyle factors. Thirdly, due to the cross-sectional design of NHANES, establishing causality is not feasible, and residual confounding variables remain a possibility that cannot be entirely eliminated. Fourth, the data regarding whether the patient was on any ED medication therapy was not collected.

Conclusions

In conclusion, our study demonstrated an inverse association between dietary B vitamin intake and the prevalence of ED, particularly notable among men aged ≤60 years, individuals of Mexican American and non-Hispanic White ethnicity, and those without a history of CVD, diabetes, hypertension, and high cholesterol. Thus, our results suggest that men incorporate B vitamin-rich foods into their diets to mitigate the risk of developing ED within this subpopulation.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-161/rc

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-24-161/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-161/coif). J.Y. reports fundings from the Natural Science Foundation of China (No. 82071639) and the Sichuan Science and Technology Program (Nos. 2022YFS0028 and 2022YFS0134). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The data of participants were obtained from the public dataset NHANES in an anonymous form. Thus, additional consents were waived in the present study.

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