Original Article

Association of folate, vitamin B-12 and vitamin B-6 intake with diabetes and prediabetes in adults aged 20 years and older

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Background and Objectives: This study aimed to assess the association of folate, vitamin B-12 and vitamin B-6 from diet and supplements with diabetes and prediabetes in U.S. adults. **Methods and Study Design:** We used data from the National Health and Nutrition Examination Survey (NHANES) 2007–2016 to conduct this cross-sectional study. Diabetes and prediabetes status were based on self-report, medication use, fasting plasma glucose levels (FPG), haemoglobin A1c (HbA1c) levels and the two hours plasma glucose (PG) value during a 75-g oral glucose tolerance test (OGTT). Logistic regression models and restricted cubic spline models were used to evaluate the associations between dietary folate, vitamin B-12, vitamin B-6 and diabetes. **Results:** After adjustment for the potential confounders, compared with the lowest quartile, the ORs (odds ratios) with 95%CIs (confidence intervals) of diabetes for the highest quartile intakes of folate and vitamin B-6 were 0.65 (0.47–0.90) and 0.61 (0.42–0.89), the OR with 95% CI of diabetes for the third quartile of dietary vitamin B-12 was 0.76 (0.60–0.97). Further excluded participants with diabetes history, the ORs with 95% CI of newly diagnosed diabetes were 0.60 (0.39–0.94), 0.84 (0.58–1.23), and 0.65 (0.43–0.98) for the third quartile of dietary folate, vitamin B-12 and vitamin B-6, respectively. A linear inverse relationship was found between vitamin B12 and diabetes, and a non-linear inverse relationship was found between dietary folate, dietary vitamin B6 and diabetes. **Conclusions:** Our study suggested that folate, vitamin B-12 and vitamin B-6 intake were inversely associated with the risk of diabetes in US adults.

Key Words: diabetes, dietary folate, dietary vitamin B-12, dietary vitamin B-6, dose-response

INTRODUCTION

Type 2 diabetes (T2DM), defined as a group of metabolic disorders characterized by high blood glucose levels, is a worldwide public health problem.[1] The data from the International Diabetes Federation showed that 1 in every 11 adults (451 million) had diabetes in 2017, and 1 in 10 (693 million) will have diabetes by 2045.[2] Recently, the World Health Organization (WHO) stated in World Health Statistics 2020[3] that approximately 1.6 million people worldwide died of diabetes in 2016, and premature mortality caused by diabetes increased by 5%. People with diabetes may have more serious complications such as diabetic retinopathy, diabetic nephropathy, skin infections, osteoporosis and so on,[4] which would increase medical costs, reduce quality of life and increase mortality. Thus, it is indispensable to pay attention to the prevention and control of diabetes.

Epidemiological evidence has revealed improving diet quality should be targeted for diabetes's prevention.[5-8] So far, many studies have been conducted to evaluate the association of macronutrient intake especially carbohydrates and fats with the risk of diabetes,[5] but few are known about the role of micronutrients, including B group vitamins, in influencing diabetes. Some studies[9-11] have reported that B group vitamins, especially folic acid, vitamins B-6 and B-12, may be involved in the pathogenesis of glucose intolerance. Folic acid, vitamin B-12 and vitamin B-6 may reduce the risk of diabetes by regulating homocysteine synthesis to alleviate insulin resistance[12,13] and oxidative stress. However other studies reported that daily supplementation with folate, vitamins B-6 and B-12 did not reduce the risk of developing diabetes.[14,15] Therefore, the finding of studies on the association between folate, vitamin B-12, vitamin B-6 and diabetes is completely inconsistent. As far as we know, the previous observations were either the folate, vitamin B-12 and vitamin B-6 serum levels[15-17] or supplemental[18] rather than dietary intake.[19] Moreover, epidemiological studies which investigated the association of folate, vitamin B-12 and vitamin B-6 intake with diabetes in the general population

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are scarce. Additionally, few studies have investigated the dose-response relationship between folate, vitamin B-12 and vitamin B-6 intake with diabetes. As a result, we conducted this study to evaluate the association of folate, vitamin B-12 and vitamin B-6 intake with type 2 diabetes in Americans aged 20 years or older.

METHODS

Study population

The cross-sectional National Health and Nutrition Examination Survey (NHANES) is a 2-year-cycle nationally representative survey of the non-institutionalized U.S. population and is intended to assess the health and nutritional status of the U.S. population. Representative samples of NHANES are selected by using a complex, stratified and multistage sample design. The study protocol is approved by the National Centers for Health Statics (NCHS), and all participants gave informed consent.

The present article used publicly available data from NHANES 2007-2008, 2009-2010, 2011-2012, 2013-2014 and 2015-2016. In NHANES 2007–2016, there were a total of 50,588 individuals and our analyses were restricted to 29,201 individuals aged 20 years and older. Among them, 5,290 participants with incomplete or unreliable 24-h recall dietary data were excluded. Then 401 pregnant or lactating women were further removed. Moreover, 32 participants were omitted who had extreme total energy intakes (men with daily energy intake less than 500kcal/day or more than 8,000kcal/day and women with daily energy intake less than 500kcal/day or more than 5,000kcal/day). Ultimately, a total of 22,041 participants (10,672 men and 11,369 women) were included in the present study (Figure 1).

Diabetes and its component conditions

To improve the accuracy of results, five diagnostic criteria were used to definite diabetes. Three of these definitions are based on laboratory data and two are based on diabetes questionnaires. First, participants with self-reported taking diabetes medications or being told doctors that they had diabetes were considered as diabetes. Second, following the guidelines of the American Diabetes Association20, participants with FPG $\geq$126 mg/dL or HbA1c $\geq$6.5% or 2-h PG $\geq$200 mg/dL were defined as diabetics. After excluding diabetics, participants with 125$\geq$FPG$\geq$100 mg/dL or 6.4%$\geq$HbA1c$\geq$5.7% or 199$\geq$PG$\geq$140 mg/dL were defined as persons with prediabetes.

Dietary folate, vitamin B-12 and vitamin B-6 intake

The data of dietary folate (DFE), vitamin B-12 and vitamin B-6 were assessed using two 24-hour recall interviews. The primary dietary data was collected in the mobile examination center (MEC) and a follow-up interview was collected by telephone 3 to 10 days later. The average daily dietary folate, vitamin B-12 and vitamin B-6 intake were calculated according to the U.S. Department of Agriculture's Dietary Study Food and Nutrition Data-

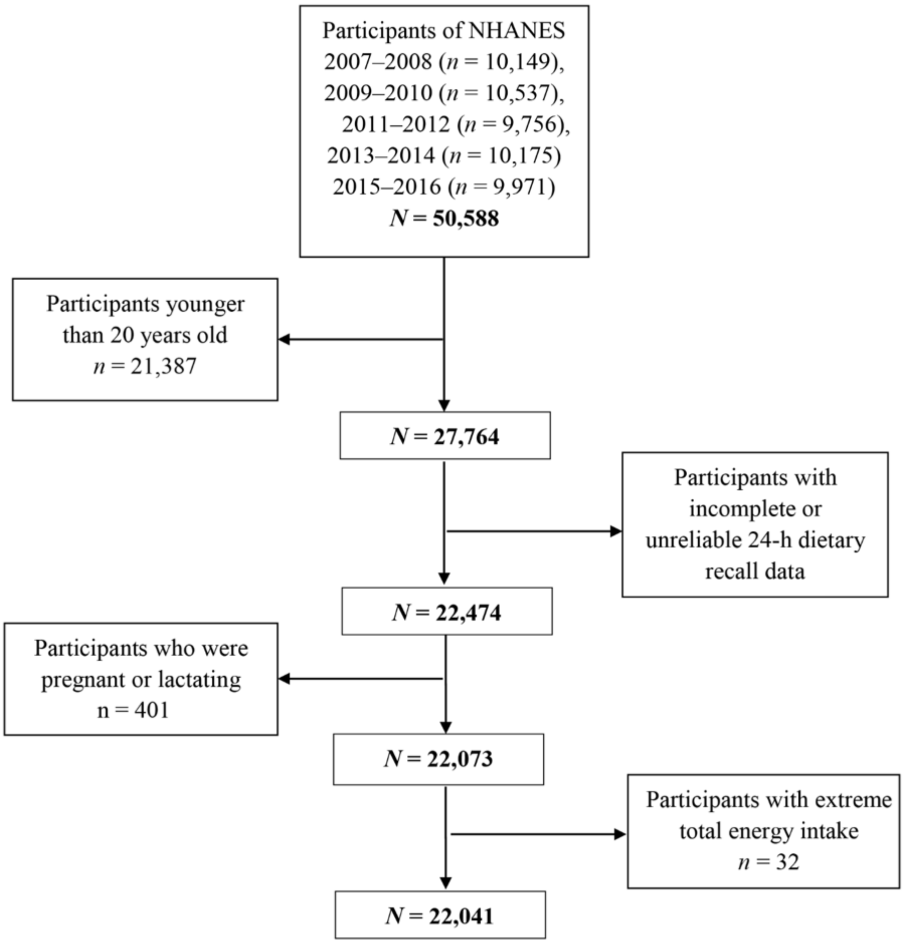

Figure 1. Flow chart of the screening process for the selection of eligible participants.

base for Dietary Studies.[21] Evidence based on biomarkers suggests that the 24-hour dietary recall interview bias from dietary intake is less than the food frequency questionnaire.[22] Intakes of folate, vitamin B-12 and vitamin B-6 were the average of two 24-hour dietary intake plus supplement intake. They were categorized based on quartiles and the Recommended Dietary Allowance (RDA), where the lowest quartile of dietary intake and below the RDA were used as the reference group.

Covariates

The following covariates were used in the adjusted analyses: age (20–39 years, 40–59 years, and ≥60 years), gender (men and women), race (Mexican American, other Hispanic, Non-Hispanic White, Non-Hispanic Black and other races), exercise (Vigorous activity, Moderate activity, and Other), smoking status (never, never smoked or smoked <100 cigarettes in life; current, smoked ≥100 cigarettes in life and currently smoking; former, smoked ≥100 cigarettes in life and currently no longer smoking), drinking (Having at least 12 alcohol drinks per year or not), body mass index (BMI) (normal: <25 kg/m^2; overweight: 25 to <30 kg/m^2; obese: ≥30 kg/m^2), hypertension (Yes/No), hypercholesteremia (Yes/No), total daily energy and vitamin B-1 intake. Hypertension and hypercholesteremia were defined according to self-reported disease history. Total daily energy and vitamin B-1 intake were calculated by aggregating daily dietary and dietary supplements.

Statistical analysis

The normality of continuous variables was tested by Kolmogorov–Smirnov normality tests. If the variables were normally distributed, the mean±standard deviation was used to describe them; if the variables were non-normally distributed, the median (interquartile range) was used to describe them. Student's t-tests or chi-square tests were used to compare the differences between the diabetes group and the non-diabetes group. Folate, vitamin B-12 and vitamin B-6 intakes were categorized based on quartiles (Q1: <25th percentile, Q2: ≥25 to 50th percentile, Q3: ≥50 to 75th percentile, Q4: ≥75th percentile) and the RDA, Q1 and below the RDA were the referent category. We conducted logistic regression analyses to explore the associations between dietary folate, vitamin B-12, vitamin B-6 and the risk of diabetes and prediabetes. In multivariate logistic regressions, model 1 adjusted for age and gender, and model 2 adjusted for race, exercise, BMI, drinking status, smoking status, hypertension, hypercholesteremia, total energy and vitamin B-1 intake. Considering that the participants who had a history of diabetes might change their dietary pattern, we further excluded these participants and conducted logistic regression analyses to examine the association of dietary folate, vitamin B-12 and vitamin B-6 intake with newly diagnosed diabetes. Moreover, we conducted the stratified analysis based on age (20–39 years, 40–59 years, and ≥60 years), gender (men and women) to assess the association between dietary folate, vitamin B-12 and vitamin B-6 intakes with diabetes in adults. To further assess the dose–response relationships we used restricted cubic spline with three knots at the 5th, 50th, and 95th percentiles of the exposure distribution in the multivariate-adjusted model 2. The *p*-value for non-linearity was calculated by testing the value of the coefficient of the second spline of zero. In the present study, we combined five 2-year survey cycles of the continuous NHANES (2007–2008, 2009–2010, 2011–2012, 2013-2014 and 2015-2016). New special 10-year dietary weights were created by taking one-fifth of the 2-year dietary weights following the NHANES analytical guidelines provided on its website.23 All statistical analyses were conducted using Stata 15.0. A two-sided *p*-value less than 0.05 was considered statistically significant.

RESULTS

Characteristics of the 22,041 participants included in the analysis are presented in Table 1. The prevalence of diabetes was 18.3%, and the patients were mostly over 60 years old in the diabetic group. Diabetes was more likely to occur in Mexican American and Non-Hispanic Black participants. Compared with non-diabetes participants, those with diabetes tended to be men, obese, smokers, lower exercise, not drink alcohol. The prevalence of diabetes was high in the subjects with hypertension and hypercholesteremia. Furthermore, those without diabetes consistently consumed more dietary folate, vitamin B-1, vitamin B-6, vitamin B-12 and energy than those with diabetes (Table 1).

Weighted ORs and 95%CIs for diabetes, prediabetes and newly diagnosed diabetes according to quartiles of daily dietary folate, vitamin B-12 and vitamin B-6 intakes are shown in Table 2. In the crude model of binary logistic regression analyses, dietary folate and vitamin B-6 were associated with a decreased risk of diabetes. For the highest group versus the reference group, the ORs (95% CIs) of diabetes for dietary folate and vitamin B-6 intakes were 0.84 (0.70-0.99) and 0.82 (0.69-0.97), respectively. After adjustment for age and gender (model 1), the results indicated that dietary folate, vitamin B-12 and vitamin B-6 were inversely associated with diabetes. Adjusted for additional covariates in Model 2, the results remained statistically significant, compared with the reference group, the ORs of the highest group of dietary folate and vitamin B-6 were 0.65 (0.47-0.90) and 0.61 (0.42-0.89), and the ORs of the third group of dietary vitamin B-12 was 0.76 (0.60-0.97). Taking the possibility that participants with a history of diabetes might change their dietary pattern into account, we further excluded 2864 participants who had diabetes history or taking diabetes medications for analysis. The results showed that dietary folate and vitamin B-6 were negatively associated with newly diagnosed diabetes, and the ORs of third group of dietary folate and vitamin B-6 were 0.60 (0.39-0.94) and 0.65 (0.43-0.98), respectively. Then non-diabetic patients were further divided into pre-diabetic patients and normal people, and the results showed that vitamin B-12 and vitamin B-6 were inversely associated with prediabetes. For the highest group versus the reference group, the ORs of prediabetes for the intakes of vitamin B-12 and vitamin B-6 were 0.78 (0.65-0.93) and 0.72 (0.58-0.89), respectively.

Weighted ORs and 95% CIs for diabetes according to quartiles of daily dietary folate, vitamin B-12 and vitamin B-6 intakes, stratified by age and gender are shown in

Table 1. Characteristics of participants by diabetes status, NHANES 2007-2016

	Non-diabetes	Diabetes	*p* value
Number of subjects (%)	17998 (81.7)	4043 (18.3)	
Age (%)[1]			<0.001
20-39	6703 (95.8)	297 (4.2)	
40-59	6213 (82.8)	1295 (17.2)	
≥60	5082 (67.5)	2451 (32.5)	
Gender (%)[†]			<0.001
Men	8609 (80.7)	2063 (19.3)	
Women	9389 (82.6)	1980 (17.4)	
Race (%)[†]			<0.001
Mexican American	2534 (78.3)	703 (21.7)	
Other Hispanic	1858 (80.5)	450 (19.5)	
Non-Hispanic White	8191 (84.2)	1533 (15.8)	
Non-Hispanic Black	3601 (77.6)	1042 (22.4)	
Other Race	1814 (85.2)	315 (14.8)	
Smoking status (%)[†]			<0.001
Never	10183 (83.5)	2011 (16.5)	
Currently	3716 (84.9)	660 (15.1)	
Former	4089 (74.9)	1370 (25.1)	
Drinking status (%)[†]			<0.001
Yes	12490 (83.2)	2518 (16.8)	
No	4432 (76.4)	1367 (23.6)	
Exercise (%)[†]			<0.001
Vigorous activity	1508 (93.0)	113 (7.0)	
Moderate activity	7697 (85.8)	1270 (14.2)	
Other	8793 (76.8)	2660 (23.2)	
Body mass index (%)[†]			<0.001
<25 kg/m^2	5660 (91.3)	540 (8.7)	
25 to <30 kg/m^2	6154 (84.6)	1121 (15.4)	
≥30 kg/m^2	6184 (72.2)	2382 (27.8)	
Hypertension (%)[†]			<0.001
Yes	5449 (66.9)	2692 (33.1)	
No	12536 (90.3)	1345 (9.7)	
Hypercholesteremia (%)[†]			<0.001
Yes	5332 (69.6)	2324 (30.4)	
No	10152 (87.2)	1495 (12.8)	
Total folate intake (mcg/day)[‡]	580 (612)	529 (616)	<0.001
Total vitamin B-12 intake (mcg/day)[‡]	6.3 (10.5)	6.0 (11.8)	<0.001
Total vitamin B-6 intake (mg/day)[‡]	2.3 (2.3)	2.1 (2.3)	<0.001
Total vitamin B-1 intake (mg/day)[‡]	1.7 (1.5)	1.6 (1.4)	<0.001
Total energy intake (kcal/day)[‡]	1941 (994)	1720 (885)	<0.001

DEF: dietary folate equivalent.
Data are the number of subjects (percentage) or medians (interquartile ranges).
[†]Chi-square test was used to compare the percentage between participants with and without diabetes.
[‡]Student's t-test was used to compare the mean value (standard deviation) between participants with and without diabetes.

Table 3 and Table 4. In stratified analyses by age, the highest levels of dietary folate, vitamin B-12 and vitamin B-6 intake were associated with a decreased risk of diabetes in three models for participants over 60 years old. The corresponding ORs (95% CIs) in multivariate adjustment model 2 were 0.46 (0.28–0.76), 0.65 (0.47–0.89) and 0.45 (0.27–0.76), respectively. Among women, all levels of dietary folate intakes were inversely associated with the risk of diabetes in the three models; the OR (95% CI) of diabetes in the highest quartile of dietary folate was 0.59 (0.38-0.92) in model 2, and the vitamin B-6 intake was negatively correlated with the risk of diabetes only among men; the OR (95%CI) was 0.53 (0.41-0.70) in model 2. However, vitamin B-12 was negatively associated with diabetes in both men and women only in model 1, but not significantly in model 2.

Weighted odds ratios (95% CIs) for being below the RDA or meeting or being above the RDA for daily dietary folate, vitamin B-12 and vitamin B-6 intakes are shown in Table 5. Compared with participants with dietary folate and vitamin B-6 intakes below the RDA, participants with dietary folate and vitamin B-6 intakes met the RDA had a lower risk of T2DM. In model 2, people who met the RDA for dietary folate and vitamin B-6 intakes had a significantly lower prevalence of diabetes. The adjusted ORs (95% CIs) were 0.69 (0.56-0.86) and 0.76 (0.62-0.94), respectively. However, the association was not statistically significant for vitamin B-12 intake (OR: 1.01; 95% CI: 0.81-1.26).

Figures 2–4 depict the dose-response relationship between dietary folate, vitamin B-12 and vitamin B-6 intakes with the risk of diabetes. There was a nonlinear negative and U-shaped association between dietary folate intake and diabetes ($p_{\text{for nonlinearity}}$=0.003), and no significant association was found with an intake beyond 1098 mcg/day (OR: 0.70; 95% CI: 0.49–1.00). Meanwhile, a linear inverse relationship between vitamin B-12 intake and the risk of diabetes was also found ($p_{\text{for nonlinearity}}$ = 0.051). With an increase of vitamin B-12 intake, there was no significant association in diabetes risk beyond 22

Table 2. Weighted ORs and 95% CIs for diabetes, prediabetes and newly diagnosed diabetes according to quartiles of daily dietary folate, vitamin B-12 and vitamin B-6 intakes

	Diabetes			Prediabetes		
	Crude† OR (95% CI)	Model 1† OR (95% CI)	Model 2† OR (95% CI)	Crude† OR (95% CI)	Model 1† OR (95% CI)	Model 2† OR (95% CI)
Daily DFE intake (mcg/day)						
<363.50	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
363.50 to <570.50	0.74 (0.61-0.90)*	0.74 (0.60-0.92)*	0.80 (0.61-1.05)	0.94 (0.83-1.06)	0.93 (0.82-1.07)	0.94 (0.79-1.11)
570.50 to <976.50	0.66 (0.57-0.77)**	0.65 (0.54-0.78)**	0.62 (0.48-0.79)**	0.97 (0.85-1.11)	0.95 (0.82-1.10)	0.99 (0.80-1.23)
≥976.50	0.84 (0.70-0.99)*	0.59 (0.48-0.72)*	0.65 (0.47-0.90)*	1.03 (0.90-1.19)	0.82 (0.71-0.95)*	0.92 (0.73-1.15)
Daily dietary vitamin B-12 intake (mcg/day)						
<4.59	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
4.59 to <9.17	0.87 (0.74-1.01)	0.82 (0.70-0.97)*	0.88 (0.73-1.06)	0.92 (0.81-1.04)	0.87 (0.77-0.98)*	0.89 (0.75-1.05)
9.17 to <20.77	0.77 (0.65-0.91)*	0.68 (0.56-0.82)**	0.76 (0.60-0.97)*	0.99 (0.86-1.13)	0.89 (0.77-1.03)	0.94 (0.78-1.13)
≥20.77	1.26 (1.06-1.48)*	0.71 (0.58-0.87)*	0.84 (0.64-1.10)	1.12 (0.97-1.29)	0.75 (0.65-0.86)**	0.78 (0.65-0.93)*
Daily dietary vitamin B-6 intake (mg/day)						
<1.54	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
1.54 to <2.60	0.79 (0.69-0.91)*	0.75 (0.64-0.87)*	0.79 (0.66-0.95)*	0.92 (0.83-1.02)	0.88 (0.79-0.98)*	0.91 (0.78-1.05)
2.60 to <4.55	0.73 (0.63-0.84)**	0.61 (0.52-0.73)**	0.61 (0.46-0.82)*	0.90 (0.79-1.03)	0.79 (0.69-0.91)*	0.80 (0.66-0.98)*
≥4.55	0.82 (0.69-0.97)*	0.52 (0.43-0.64)**	0.61 (0.42-0.89)*	0.94 (0.81-1.09)	0.70 (0.60-0.81)**	0.72 (0.58-0.89)*

	Newly Diagnosed Diabetes		
	Crude† OR (95% CI)	Model 1† OR (95% CI)	Model 2† OR (95% CI)
Daily DFE intake (mcg/day)			
<363.50	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
363.50 to <570.50	0.73 (0.55-0.97)*	0.73 (0.55-0.97)*	0.77 (0.53-1.13)
570.50 to <976.50	0.60 (0.47-0.76)**	0.59 (0.45-0.77)**	0.60 (0.39-0.94)**
≥976.50	0.80 (0.59-1.08)	0.57 (0.41-0.77)*	0.71 (0.38-1.31)
Daily dietary vitamin B-12 intake (mcg/day)			
<4.59	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
4.59 to <9.17	0.86 (0.66-1.12)	0.81 (0.62-1.06)	0.95 (0.68-1.32)
9.17 to <20.77	0.77 (0.58-1.04)	0.67 (0.49-0.93)*	0.84 (0.58-1.23)
≥20.77	1.23 (0.95-1.59)	0.69 (0.53-0.91)*	0.97 (0.68-1.38)
Daily dietary vitamin B-6 intake (mg/day)			
<1.54	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
1.54 to <2.60	0.90 (0.74-1.09)	0.86 (0.70-1.07)	0.94 (0.69-1.27)
2.60 to <4.55	0.74 (0.59-0.94)*	0.63 (0.48-0.81)*	0.65 (0.43-0.98)*
≥4.55	0.80 (0.61-1.05)	0.52 (0.39-0.69)*	0.64 (0.39-1.07)

OR: odd ratio; CI: confidence interval; DFE: dietary folate equivalent.
†Calculated using binary logistic regression; Model 1 adjusted for age and gender. Model 2 adjusted for age, gender, race, smoking status, drinking status, body mass index (BMI), exercise, hypertension, hypercholesteremia, daily dietary vitamin B-1 and daily energy intake.
*p<0.05; **p<0.01.

Table 3. Weighted ORs and 95% CIs for diabetes according to quartiles of daily dietary folate, vitamin B-12 and vitamin B-6 intakes, stratified by age

	20≤age<40 years			40≤age <60 years		
	Crude†	Model 1†	Model 2†	Crude†	Model 1†	Model 2†
Daily DFE intake (mcg/day)						
<363.50	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
363.50 to <570.50	0.66 (0.42-1.02)	0.64 (0.42-0.99)*	0.64 (0.30-1.39)	0.77 (0.57-1.04)	0.74 (0.55-1.00)	0.83 (0.57-1.21)
570.50 to <976.50	0.61 (0.37-0.98)*	0.58 (0.35-0.95)*	0.48 (0.17-1.31)	0.67 (0.49-0.90)**	0.64 (0.48-0.86)*	0.69 (0.48-0.99)*
≥976.50	0.55 (0.33-0.91)*	0.53 (0.31-0.89)*	0.31 (0.12-0.83)*	0.83 (0.62-1.11)	0.79 (0.59-1.06)	1.19 (0.66-2.15)
Daily dietary vitamin B-12 intake (mcg/day)						
<4.59	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
4.59 to <9.17	0.94 (0.63-1.42)	0.96 (0.63-1.44)	0.94 (0.63-1.42)	0.82 (0.47-1.41)	0.91 (0.70-1.19)	0.90 (0.69-1.17)
9.17 to <20.77	0.74 (0.43-1.29)	0.76 (0.44-1.30)	0.74 (0.43-1.29)	0.66 (0.32-1.37)	0.76 (0.58-1.01)	0.75 (0.56-0.99)*
≥20.77	0.87 (0.50-1.50)	0.91 (0.54-1.53)	0.87 (0.50-1.50)	0.64 (0.30-1.35)	1.01 (0.74-1.36)	0.99 (0.73-1.34)
Daily dietary vitamin B-6 intake (mg/day)						
<1.54	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
1.54 to <2.60	0.86 (0.54-1.37)	0.83 (0.52-1.35)	0.62 (0.32-1.20)	0.74 (0.58-0.94)**	0.71 (0.56-0.90)*	0.74 (0.52-1.03)
2.60 to <4.55	0.78 (0.47-1.31)	0.75 (0.44-1.27)	0.45 (0.19-1.09)	0.68 (0.52-0.87)**	0.64 (0.49-0.84)*	0.70 (0.48-1.04)
≥4.55	0.62 (0.37-1.04)	0.58 (0.34-1.01)	0.36 (0.15-0.86)*	0.72 (0.54-0.96)**	0.68 (0.52-0.90)*	0.96 (0.55-1.69)

	Age ≥60 years		
	Crude†	Model 1†	Model 2†
Daily DFE intake (mcg/day)			
< 363.50	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
363.50 to < 570.50	0.85 (0.61-1.16)	0.79 (0.57-1.09)	0.84 (0.57-1.24)
570.50 to < 976.50	0.77 (0.58-1.04)	0.70 (0.52-0.95)*	0.58 (0.38-0.90)*
≥976.50	0.52 (0.40-0.67)**	0.47 (0.36-0.62)**	0.46 (0.28-0.76)*
Daily dietary vitamin B-12 intake (mcg/day)			
< 4.59	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
4.59 to < 9.17	0.70 (0.54-0.91)*	0.68 (0.52-0.88)*	0.73 (0.54-0.99)*
9.17 to < 20.77	0.58 (0.43-0.79)**	0.56 (0.41-0.76)**	0.63 (0.42-0.96)*
≥20.77	0.52 (0.42-0.65)**	0.50 (0.40-0.62)**	0.65 (0.47-0.89)*
Daily dietary vitamin B-6 intake (mg/day)			
< 1.54	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
1.54 to < 2.60	0.83 (0.64-1.08)	0.77 (0.59-1.00)	0.95 (0.72-1.26)
2.60 to < 4.55	0.60 (0.46-0.78)**	0.55 (0.42-0.71)**	0.53 (0.33-0.86)*
≥4.55	0.45 (0.34-0.58)**	0.40 (0.30-0.52)**	0.45 (0.27-0.76)*

DFE: dietary folate equivalent.
†Calculated using binary logistic regression; Model 1 adjusted for age and gender. Model 2 adjusted for age, gender, race, smoking status, drinking status, body mass index (BMI), exercise, hypertension, hypercholesteremia, daily dietary vitamin B-1 and daily energy intake.
*p<0.05; **p<0.01.

Table 4. Weighted ORs and 95% CIs for diabetes according to quartiles of daily dietary folate, vitamin B-12 and vitamin B-6 intakes, stratified by gender

	Male			Female		
	Crude†	Model 1†	Model 2†	Crude†	Model 1†	Model 2†
Daily DFE intake (mcg/day)						
<363.50	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
363.50 to <570.50	0.80 (0.60-1.07)	0.78 (0.58-1.05)	0.95 (0.65-1.38)	0.66 (0.52-0.84)*	0.72 (0.54-0.95)*	0.73 (0.52-1.03)
570.50 to <976.50	0.64 (0.51-0.80)**	0.63 (0.49-0.83)*	0.76 (0.50-1.15)	0.66 (0.51-0.84)*	0.68 (0.51-0.91)*	0.51 (0.35-0.75)*
≥976.50	0.88 (0.68-1.13)	0.62 (0.47-0.83)*	0.74 (0.45-1.22)	0.76 (0.59-0.97)*	0.56 (0.43-0.74)**	0.59 (0.38-0.92)*
Daily dietary vitamin B-12 intake (mcg/day)						
<4.59	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
4.59 to <9.17	0.89 (0.73-1.09)	0.87 (0.70-1.10)	0.88 (0.65-1.19)	0.81 (0.65-1.01)	0.78 (0.62-0.99)*	0.89 (0.69-1.14)
9.17 to <20.77	0.73 (0.55-0.96)*	0.67 (0.49-0.93)*	0.73 (0.49-1.08)	0.79 (0.63-0.98)*	0.69 (0.54-0.89)*	0.81 (0.60-1.09)
≥20.77	1.20 (0.98-1.48)	0.74 (0.57-0.96)*	0.81 (0.59-1.11)	1.26 (0.99-1.62)	0.68 (0.51-0.92)*	0.93 (0.60-1.45)
Daily dietary vitamin B-6 intake (mg/day)						
<1.54	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
1.54 to <2.60	0.81 (0.67-0.99)*	0.77 (0.61-0.97)*	0.88 (0.64-1.20)	0.73 (0.61-0.87)*	0.73 (0.60-0.89)*	0.74 (0.58-0.93)*
2.60 to <4.55	0.66 (0.53-0.81)**	0.58 (0.44-0.75)**	0.61 (0.41-0.91)*	0.76 (0.60-0.95)*	0.66 (0.51-0.86)*	0.63 (0.41-0.97)*
≥4.55	0.79 (0.62-1.00)	0.53 (0.41-0.70)**	0.63 (0.41-0.96)*	0.76 (0.58-1.01)	0.51 (0.37-0.70)**	0.61 (0.34-1.10)

DFE: dietary folate equivalent.
†Calculated using binary logistic regression; Model 1 adjusted for age and gender. Model 2 adjusted for age, gender, race, smoking status, drinking status, body mass index (BMI), exercise, hypertension, hypercholesteremia, daily dietary vitamin B-1 and daily energy intake.
*$p<0.05$; **$p<0.01$.

Table 5. Weighted odds ratios (95% confidence intervals) for being below the RDA or meeting or being above the RDA for daily dietary folate, vitamin B-12 and vitamin B-6 intakes

	Diabetes			Prediabetes		
	Crude† OR (95% CI)	Model 1† OR (95% CI)	Model 2† OR (95% CI)	Crude† OR (95% CI)	Model 1† OR (95% CI)	Model 2† OR (95% CI)
Daily DFE intake (mcg/day)						
Below the RDA	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Met the RDA	0.75(0.66-0.85)**	0.66 (0.58-0.77)**	0.69 (0.56-0.86)*	0.94 (0.84-1.05)	0.87 (0.77-0.98)*	0.89 (0.76-1.04)
Daily dietary vitamin B-12 intake (mcg/day)						
Below the RDA	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Met the RDA	0.94(0.80-1.11)	0.80 (0.67-0.97)*	1.01 (0.81-1.26)	1.04 (0.90-1.19)	0.91 (0.79-1.05)	0.98 (0.80-1.19)
Daily dietary vitamin B-6 intake (mg/day)						
Below the RDA	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Met the RDA	0.94(0.80-1.11)	0.80 (0.67-0.97)*	1.01 (0.81-1.26)	1.04 (0.90-1.19)	0.91 (0.79-1.05)	0.98 (0.80-1.19)

	Newly diagnosed diabetes		
	Crude† OR (95% CI)	Model 1† OR (95% CI)	Model 2† OR (95% CI)
Daily DFE intake (mcg/day)			
Below the RDA	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Met the RDA	0.73 (0.58-0.91)*	0.64 (0.51-0.81)*	0.72 (0.49-1.05)
Daily dietary vitamin B-12 intake (mcg/day)			
Below the RDA	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Met the RDA	0.98 (0.74-1.30)	0.86 (0.63-1.17)	1.13 (0.80-1.59)
Daily dietary vitamin B-6 intake (mg/day)			
Below the RDA	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Met the RDA	0.76 (0.62-0.94)*	0.63 (0.50-0.80)*	0.79 (0.57-1.10)

OR: odd ratio; CI: confidence interval; DFE: dietary folate equivalent.

†Model 1 adjusted for age and gender. Model 2 adjusted for age, gender, race, smoking status, drinking status, body mass index (BMI), exercise, hypertension, hypercholesteremia, daily dietary vitamin B-1 and daily energy intake.

*$p<0.05$; **$p<0.01$.

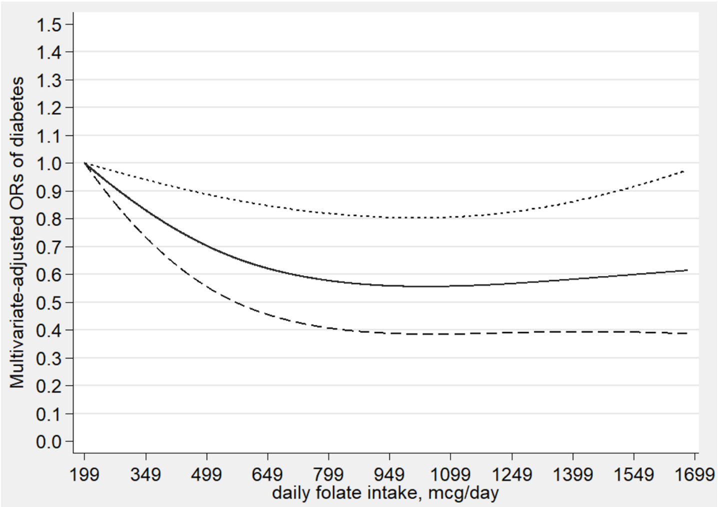

Figure 2. Dose–response relationship between folate intake and the risk of diabetes. The solid line represents the OR values and dashed lines represent the 95% confidence intervals.

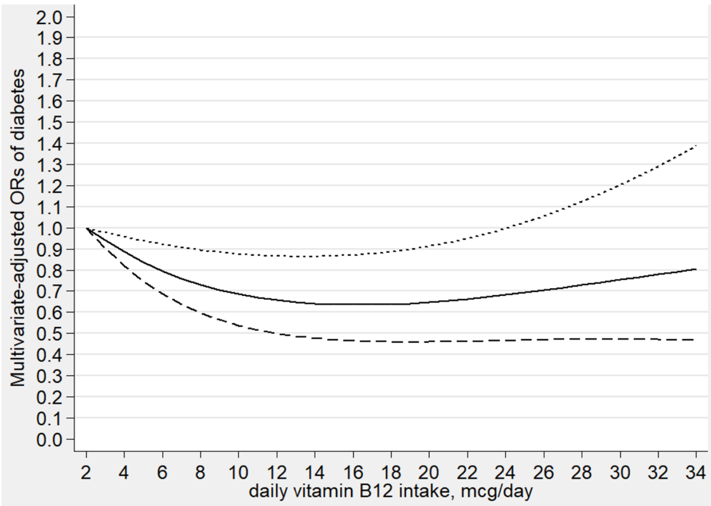

Figure 3. Dose–response relationship between vitamin B-12 intake and the risk of diabetes. The solid line represents the OR values and dashed lines represent the 95% confidence intervals.

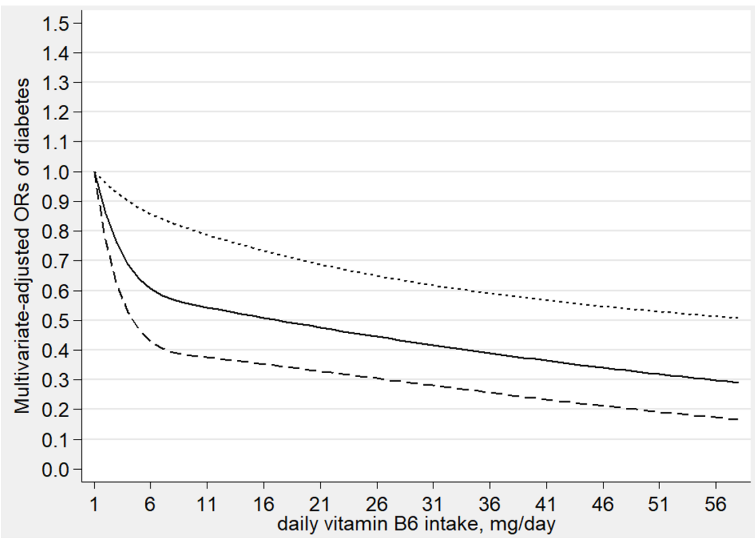

Figure 4. Dose–response relationship between vitamin B-6 intake and the risk of diabetes. The solid line represents the OR values and dashed lines represent the 95% confidence intervals.

mcg/day (OR: 0.74; 95% CI: 0.55–1.00). In addition, there also existed a nonlinear negative and L-shaped association between vitamin B-6 intake and the risk of diabetes ($p_{\text{for nonlinearity}}$=0.041), and the prevalence of diabetes decreased with increasing vitamin B-6 intake and reached a plateau when vitamin B-6 intake above 6 mg/day (OR: 0.70; 95% CIs: 0.53-0.92).

DISCUSSION

Our study indicated that the intakes of dietary folate, vitamin B-12 and vitamin B-6 were inversely associated with the risk of diabetes, particularly in the people over the age of 60. Similar significantly negative associations were found between dietary folate, vitamin B-6 intakes and diabetes based on RDA in all models, whereas the association was not statistically significant for vitamin B-12 in model 2. Moreover, the results of the restricted cubic spline dose-response relationship analysis found the dietary folate and vitamin B-6 intake had nonlinear and inverse associations with the risk of diabetes, which indicates that the relationship between quantities is not proportional and not linear while vitamin B-12 was linear inverse associated with the risk of diabetes.

Several previous epidemiological studies have reported the association between dietary folate intake and diabetes. Our study found that dietary folate intake was inversely associated with diabetes, which is consistent with these studies.[24-28] Eshak ES et al[24] suggested that higher dietary intakes of folate, but not other water-soluble vitamins, were associated with reduced risk of type 2 diabetes. Two prospective cohort studies performed by Hong SM et al[25] and Mengying Li SL et al[26] also indicated higher dietary intake of folate was prospectively associated with lower risk of diabetes. Moreover, the results from a meta-analysis[27] indicated that folic acid supplementation in patient with type 2 diabetes mellitus may reduce total homocysteine levels and have a trend to associate with better glycemic control compared with placebo. The negatively association between dietary folate intake and diabetes may be explained by the following mechanisms. Firstly, DNA damage as measured by the presence of micronuclei can be reverted by folic acid supplementation, thus reducing the effect of oxidative stress.[29] Auto-oxidation and metabolic stress of glucose can lead to dysfunction and cell damage, so folic acid supplementation will reduce the incidence of diabetic damage and complications.[30] Secondly, folate supplementation has also been shown to improve glycemic control by reducing glycosylated hemoglobin fasting blood glucose, serum insulin and insulin resistance in type 2 diabetes patients.[18] Thirdly, hyperhomocysteinaemia is linked with many other diseases such as cardiovascular diseases and inflammation along with T2DM,[31] hyperhomocysteinaemia is negatively proportional to the folate,[32] so increasing folic acid intake may reduce the risk of diabetes.

In our study, moderate vitamin B-12 intake was inversely associated with diabetes. Similar to our results, Jun S Lai et al[33] found that higher vitamin B-12 levels were associated with lower fasting and 2-hour glucose, and lower odds of diabetes. Furthermore, a meta-analysis[34] and a cross-sectional study[35] also shows that vitamin B-12 insufficiency is associated with increased risk of diabetes. However, the mechanisms between vitamin B-12 intake and the decreased diabetes risk are not fully cleared, but several possible mechanisms have been explained. Firstly, vitamin B-12 deficiency inhibits the conversion of 5-methyltetrahydrofolic acid to tetrahydrofolate. This disrupts the production of purines and thymine for DNA/RNA synthesis, and impaired DNA synthesis, particularly mitochondrial DNA, has been observed to be associated with the development of insulin resistance.[36] Secondly, with vitamin B-12 and folic acid supplementation, plasma homocysteine level is reduced and the risk of diabetes is reduced.[10]

Few studies have assessed the relationship between vitamin B-6 intake and diabetes. Our findings suggest that vitamin B-6 was inversely associated with diabetes, which is consistent with several previous studies.[9,37,38] Bennink HJ et al[37] suggested that vitamin B-6 supplementation reduced postprandial glucose concentrations in pregnant women. In addition, Polizzi FC et al also found that the combination of vitamin B-6 with Vitamin B-1 has been shown to decrease DNA glycation in leukocytes of diabetic patients.[39] The role of vitamin B-6 in diabetes may be a deficiency of vitamin B-6, B-12, and folate can lead to hyperhomocysteinaemia,[40] and elevated homocysteine level is causally associated with increased risk of type 2 diabetes mellitus (T2DM).[41] And, further research is required to explore more specific physiological mechanisms.

There are several advantages in this study. First, in order to be more objective, we further excluded subjects with a history of diabetes or taking diabetes medications, given the possibility that subjects with a history of diabetes may change their eating patterns. Second, we investigated the dose-response relationship between dietary folate, vitamin B-12 and vitamin B-6 intake with diabetes. Third, we explored age and gender differences in the association between dietary folate and diabetes, respectively. Finally, we used a large nationally representative sample, which provides a more reliable and accurate result.

However, this study has some limitations. First, as a cross-sectional study, it was difficult to ascertain causality. Second, we controlled some confounding factors as much as possible, but we still didn't control all confounding factors. Third, dietary data were obtained through two 24-h dietary recall interviews, which could not accurately reflect individuals' dietary intake because of false memories and under-reporting.

Conclusion

Our study indicates that dietary folate, vitamin B-12 and vitamin B-6 intake might be inversely associated with the risk of diabetes. Further large-scale prospective studies research is needed to verify whether these relationships are consistent.

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AUTHOR DISCLOSURES
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