

# Vitamin D3 Level And Risk of Diabetes In Patients With Hyperuricemia

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## Research Article

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# Abstract

## Background

Previous studies have shown that hyperuricemia is involved in diabetes, obesity, hypertension, chronic kidney disease, and other diseases. At the same time, studies have shown that vitamin D3 levels in the body are linked to the onset of diabetes. However, there is currently no sufficient evidence to prove whether this connection is affected by uric acid levels. Therefore, we attempted to investigate the relationship between vitamin D3 content and the occurrence of diabetes in the hyperuricemia population by using the data of the NHANES database from 2009 to 2018.

## Method

We conducted a cross-sectional study using the NHANES database. According to strict inclusion and exclusion criteria, we finally selected 3543 representative data. Multivariate logistic regression analysis was used to explore the relationship between vitamin D3 and diabetes in the hyperuricemia population after complete adjustment. We found a linear relationship between vitamin D3 content and the incidence of diabetes.

## Result

The results of this study showed that there was a correlation between the content of vitamin D3 and the incidence of diabetes in people with hyperuricemia, and the effect values (OR and 95% confidence interval) were 0.95 and (0.92-0.98), respectively, and the difference was statistically significant.

## Conclusion

Our study shows that vitamin D3 content is associated with the incidence of diabetes in people with high uric acid. This study provides a new idea for exploring the factors affecting the pathogenesis of diabetes in patients with hyperuricemia.

## Background

In the past, the prevalence rate of hyperuricemia remained stable [1]. However, in recent years, with the improvement of living standards and lifestyle changes, hyperuricemia increased year by year. Now, hyperuricemia has become a significant public health problem [2]. Studies have shown that the prevalence of hyperuricemia in American adult males is 20.2% and that in adult females is 20.0% [1]. Hyperuricemia is a potential risk factor for various diseases[3]. Epidemiological and experimental studies have shown that hyperuricemia is closely related to diabetes[4] [5], cardiovascular disease[6] [7], metabolic syndrome[8] [9], hypercholesterolemia[10], hypertriglyceridemia[11], obesity[12], and chronic nephropathy[13] and other diseases. Diabetes is a common chronic disease[14]. With the development of the economy, people's living standards are gradually improving, and the number of patients with diabetes is also increasing [15]. Diabetes is the leading cause of death in the United States. According to the Global Burden of Disease report 2015, the number of people with diabetes increased by 30.6% from 2005 to 2015. Diabetes has become a significant killer that seriously endangers people's health and affects their daily work and life. Studies have shown that hyperuricemia is related to diabetes, and serum uric acid is an independent risk factor for diabetes [16].

Vitamin D is the precursor of hormones [17], including vitamin D2 and vitamin D3. The phenomenon of vitamin D deficiency is widespread [18]. Vitamin D deficiency has been found in all regions, races, and age groups [19], and this phenomenon has been on the rise in recent years. Vitamin D3, also known as bile calcified alcohol, is metabolized to produce 25-hydroxyvitamin D3 [20]. There are two main ways for the human body to obtain vitamin D3: 1. Vitamin D3 was obtained by photolysis of 7-dehydrocholesterol caused by sunlight or ultraviolet B (UVB) irradiation on the skin. Supplement vitamin D3 through foods such as oily fish, milk, fruit juices, grains, and oral supplements. Therefore, vitamin D3 deficiency may be caused by insufficient light, limited oral intake, or impaired intestinal absorption. [21]. Vitamin D3 can promote the absorption of calcium and phosphorus in the body [22] and bone calcification and tooth growth [23].

Studies have shown that vitamin D3 levels are associated with the occurrence of diabetes [19] [24]. However, it has not been confirmed whether vitamin D3 is related to the occurrence of diabetes in patients with hyperuricemia. We analyzed samples from the NHANES database from 2009 to 2018 to explore whether vitamin D3 levels are associated with diabetes in people with hyperuricemia.

## Method

### Data sources

The data in this study are all from the NHANES database. The full name of NHANES is the National Health and Nutrition Inspection Survey. NHANES is a cross-sectional population-based survey that collects information about household health and nutrition in the United States. The data mainly consists of five parts, including demographic data, diet data, examination data, laboratory data, and questionnaire data, including American adults and children from various states across the country. The NHANES project was approved by the (NCHS) Research Ethics Review Committee of the National Center for Health Statistics, and NCHS collected the data in NHANES. All participants are aware of and agree to the data collection activity. More details can be found on the official NHANES website.

### Participant selection

We analyzed data from five consecutive survey cycles from 2009 to 2018 in the NHANES database. We collected survey data from a total of 49696 participants. We have established strict inclusion and exclusion criteria. First, a total of 43880 participants without hyperuricemia and without data on uric acid were excluded, and a total of 5816 participants with hyperuricemia were screened out. We further excluded 2273 participants who lacked vitamin D3 data. In the end, we included 3543 participants who met the inclusion criteria.

### Data Collection

Trained investigators collected all the information. The data we collected include Demographics (age, gender, race/nationality, educational attainment, and so on.), Anthropometric Measurements (height, waistline, weight, BMI, etc.), Health-related Behavior (smoking and drinking), Biochemistry Tests (TC, TG, GLU, UA, etc.). The height, weight, and waistline of the subjects were measured according to the standard scheme and technique. BMI formula is:  $BMI = \text{weight (kg)} / \text{height (M)}^2$  [25]. According to the criteria of WHO, the normal range of body mass index ( $18.5 \sim 24.9 \text{ kg/m}^2$ ) [26], the range of overweight ( $25.0 \sim 29.9 \text{ kg/m}^2$ ), and the range of obesity ( $BMI \geq 30.0 \text{ kg/m}^2$ ) [27]. Fasting blood glucose data were measured in the Minnesota lab. The fasting blood glucose of all participants was measured in the morning, and the data was measured in mg/dL. All blood pressure data (systolic blood pressure and diastolic blood pressure) are measured by professionals certified for blood pressure measurement in the Mobile Examination Center (MEC). The blood pressure was measured after the participants remained at rest for 5 minutes

and measured three times in a row. Uric acid results were provided by the National Center for Environmental Health in mg/dL.

## **Evaluation Criterion**

### **Hyperuricemia**

By multiplying the measured value by 59.48, the unit is converted from mg/dL to  $\mu\text{mol/L}$ . Through consulting the literature, we know that the diagnostic criteria of hyperuricemia are as follows: the level of uric acid in men is higher than  $420\ \mu\text{mol/L}$ , and that in women is higher than  $360\ \mu\text{mol/L}$  [28].

### **Diabetes**

Multiply the measured blood glucose by 0.05551 (rounded to three decimal places) to convert the unit from mg/dL to mmol/L. The diagnostic criteria of diabetes are fasting blood glucose  $\geq 7\text{mmol/L}$  [29] or have been diagnosed with diabetes.

### **Hypertension**

Take the average of the three blood pressure measurements, and use the average blood pressure to evaluate whether the participants are patients with hypertension. The diagnostic criteria of hypertension are systolic blood pressure  $\geq 140\text{mmHg}$  and diastolic blood pressure  $\geq 90\text{mmHg}$  [30].

### **Drinking**

We looked at the classification of alcohol consumption in previous studies and finally divided drinking into two levels. Drinker: a person who drinks more than 12 drinks a year. Non-drinker: a person who drinks no more than 12 drinks a year [31] [32].

### **Smoking**

In this study, we divided smoking into two levels. Smoker: refers to a person who smokes more than 100 cigarettes in his life and is still smoking. Non-smoker: refers to a person who smokes no more than 100 cigarettes in his lifetime or does not smoke now [33].

### **Covariable Selection**

By reviewing the literature, we screened out the potential confounding factors related to the content of vitamin D3 and the occurrence of diabetes in people with hyperuricemia. The demographic variables involved in this study include age, sex, race (black and non-black). Biochemical indexes include glycosylated hemoglobin (HbA1c), total cholesterol (TC), triglyceride (TG), glutamic pyruvic transaminase (ALT), and blood urea nitrogen (BUN).

Other covariates include height, weight, BMI, blood pressure, and so on. Height and weight are measured by rangefinder and electronic scale [34]. Blood pressure was obtained through a standard medical procedure repeated several times, with each participant measuring systolic and diastolic blood pressure three times. Blood pressure is measured in millimeters of mercury (mmHg). BMI and blood pressure as described earlier.

### **Statistical Approach**

NHANES selects 5000 people each year from a sampling framework of 15 different locations in all counties in the United States. Its data are extensive and universal. The unique multi-stage probability sampling technique used by NHANES allows us to estimate the incidence and trends of diabetes in the United States over the past few years. To make our research more convincing, we collected five consecutive cycles of samples from the NHANES database. We selected the data that meet our requirements through strict overall screening to obtain more representative

samples. Version R3.4.3 is used for statistical analysis, and multiple interpolations are carried out for the missing data. Multivariate Logistic regression was used to analyze the relationship between vitamin D3 and diabetes in patients with hyperuricemia. Continuous variables are represented by detailed sample descriptions, with an average confidence interval of 95%. Classification variables are represented by counts and weighted percentages, using problematic sample frequencies. The skewness distribution is based on median and Q1-Q3. The normal distribution is described by median and standard deviation.

We established three multivariate Logistic regression models to analyze the relationship between vitamin D3 and diabetes in patients with hyperuricemia and drew a smooth fitting curve.

## Result

In this study, 3543 participants from the NHANES database (2009–2018) were enrolled. In this study population, the number of male diabetic patients (304, 39.5%) was less than that of female diabetic patients (466, 60.5%). The level of vitamin D3 in the diabetic group was 54.6 (35.7, 78.1), which was lower than that in the non-diabetic group (56.0, 38.5). Among people with diabetes, there were more drinkers (483, 62%) than non-drinkers (268, 38%). The average age of diabetic patients was higher than that of non-diabetic groups. The average age and standard deviation of diabetic patients and non-diabetic patients were (62.5 ± 14.7) years and (42.7 ± 20.6) years, respectively (Table 1).

Table 1. Baseline Characteristics of the Participants				
Variables	Total (n = 3542)	Non-diabetes (n = 2772)	Diabetes (n = 770)	p-value
<b>Sex, n (%)</b>				< 0.001
male	1798 (50.8)	1494 (53.9)	304 (39.5)	
female	1744 (49.2)	1278 (46.1)	466 (60.5)	
<b>Age, Mean ± SD</b>	50.6 ± 20.5	47.2 ± 20.6	62.5 ± 14.7	< 0.001
<b>Race, n (%)</b>				< 0.001
Non-black	2660 (75.1)	2122 (76.6)	538 (69.9)	
Black	882 (24.9)	650 (23.4)	232 (30.1)	
<b>BMI, Mean ± SD</b>	32.2 ± 7.9	31.8 ± 7.8	34.0 ± 8.1	< 0.001
<b>Waist, Mean ± SD</b>	106.6 ± 17.0	105.3 ± 17.0	111.6 ± 16.0	< 0.001
<b>Smoking, n (%)</b>				0.001
NO	2046 (57.8)	1641 (59.2)	405 (52.6)	
YES	1496 (42.2)	1131 (40.8)	365 (47.4)	
<b>Drink, n (%)</b>				< 0.001
NO	896 (29.8)	628 (27.3)	268 (38)	
YES	2106 (70.1)	1668 (72.5)	438 (62)	
<b>Education, n (%)</b>				< 0.001
Less Than 9th Grade	337 (10.5)	210 (8.6)	127 (16.6)	
9-11th Grade (Includes 12th grade with no diploma)	481 (15.0)	346 (14.1)	135 (17.7)	
High School Grad/GED or Equivalent	733 (22.8)	562 (23)	171 (22.4)	
Some College or AA degree	1029 (32.0)	797 (32.6)	232 (30.4)	
College Graduate or above	628 (19.6)	533 (21.8)	95 (12.5)	
<b>Hypercholesteremia, n (%)</b>				< 0.001
NO	596 (24.7)	509 (28.7)	87 (13.7)	
YES	1813 (75.3)	1267 (71.3)	546 (86.3)	
<b>Hypertension, n (%)</b>				< 0.001

NO	1557 (44.0)	1394 (50.3)	163 (21.2)	
YES	1985 (56.0)	1378 (49.7)	607 (78.8)	
FBG(mmol / L), Median (IQR)	5.4 (4.9, 6.2)	5.2 (4.8, 5.7)	7.4 (6.1, 8.7)	< 0.001
VitD3(nmol/L), Median (IQR)	55.8 (38.0, 76.0)	56.0 (38.5, 75.2)	54.6 (35.7, 78.1)	0.521
Hb-A1c(n%), Median (IQR)	5.6 (5.3, 6.1)	5.5 (5.2, 5.8)	6.6 (6.0, 7.5)	< 0.001
TC(mmol / L), Median (IQR)	4.9 (4.2, 5.7)	5.0 (4.3, 5.7)	4.7 (3.9, 5.5)	< 0.001
ALT(IU/L), Median (IQR)	22.0 (17.0, 32.0)	23.0 (17.0, 32.0)	21.0 (16.0, 29.0)	< 0.001
BUN(mmol/L), Median (IQR)	5.0 (3.9, 6.4)	4.6 (3.6, 6.1)	6.1 (4.3, 8.5)	< 0.001
TG(mmol / L), Median (IQR)	1.6 (1.1, 2.4)	1.6 (1.0, 2.3)	1.8 (1.3, 2.8)	< 0.001
Abbreviations: BMI, body mass index; FBG, fasting blood-glucose; Vit D3, vitamin D3; Hb-A1c, glycosylated hemoglobin; TC, total cholesterol; ALT, Alanine aminotransferase; BUN, blood urea nitrogen; TG, Triglyceride				

This study analyzed the influence of age, gender, race, BMI, waist circumference, drinking, and smoking on the incidence of diabetes in the hyperuricemia population. We found that women have a higher incidence of diabetes than men. The effect size OR and 95% confidence interval of gender were 1.79 (1.52 ~ 2.11). Compared with non-blacks, blacks have a higher incidence of diabetes, and the effect size OR and 95% confidence interval are 1.41 and (1.18 ~ 1.68), respectively. The effect OR and 95% confidence interval of age are 1.04 and (1.04 ~ 1.05), respectively, the effect OR and 95% confidence interval of BMI are 1.03 and (1.02 ~ 1.04), respectively, and the effect OR of waist circumference and 95% The confidence intervals for are 1.02 and (1.02 ~ 1.03) respectively (Table 2).

Table2. Univariate analysis for diabetes		
Variables	OR(95%CI)	P(Wald's test)
<b>Sex</b>	1.79 (1.52,2.11)	< 0.001
<b>Age</b>	1.04 (1.04,1.05)	< 0.001
<b>Race</b>		
Non-black	1	
Black	1.41 (1.18,1.68)	< 0.001
<b>Education</b>		
Less Than 9th Grade	1	
9-11th Grade (Includes 12th grade with no diploma)	0.65 (0.48,0.87)	0.004
High School Grad/GED or Equivalent	0.5 (0.38,0.67)	< 0.001
Some College or AA degree	0.48 (0.37,0.63)	< 0.001
College Graduate or above	0.29 (0.22,0.4)	< 0.001
<b>BMI</b>	1.03 (1.02,1.04)	< 0.001
<b>W.C(cm)</b>	1.02 (1.02,1.03)	< 0.001
<b>Smoking</b>		
NO	1	
YES	1.31 (1.11,1.54)	0.001
<b>Drinking</b>		
NO	1	
YES	1.63 (1.36,1.94)	< 0.001
TC(mmol/L)	0.8 (0.74,0.86)	< 0.001
ALT(IU/L)	0.9989 (0.9956,1.0021)	0.501
BUN (mmol/L)	1.22 (1.18,1.25)	< 0.001
TG(mmol/L)	1.15 (1.09,1.21)	< 0.001
VitD3(nmol/L)	0.9992 (0.9964,1.0021)	0.606
Abbreviations: BMI, body mass index; W.C, waist; TC, total cholesterol; ALT, Alanine aminotransferase; BUN, blood urea nitrogen; TG, Triglyceride; Vit D3, vitamin D3		

Table 3 shows the relationship between vitamin D3 content and the probability of diabetes after adjusting for potential confounding factors. We established four regression models. Model 1 did not make any adjustments, while Model 2 was adjusted according to age, gender, race, education, smoking, and drinking. Model 3 adds serum cholesterol, HTC, and urea nitrogen based on model 2, and model 4 adds waist circumference and BMI based on model 3. The results show that the adjusted model 2, model 3, and model 4 suggest that vitamin D3 is related to the occurrence of diabetes. The OR and 95% confidence interval adjusted according to Model 2 were 0.94 and (0.91 ~



0.97), respectively,  $P < 0.001$ ; the difference was statistically significant. The effect OR and 95% confidence interval adjusted according to Model 3 were 0.93 and (0.90 ~ 0.97), respectively,  $P < 0.001$ , and the difference was statistically significant. According to Model 4, the adjusted OR and 95% confidence interval were 0.95 and (0.92 ~ 0.98), respectively,  $P = 0.0027$ , and the difference was statistically significant. The results of the three adjusted models all show that the content of vitamin D3 in people with high uric acid is correlated with the occurrence of diabetes. The unadjusted model effect OR and 95% confidence interval were 0.99 and (0.96 ~ 1.02) respectively,  $P = 0.61$ , and the correlation lost statistical significance.

Table 3.The association between vitaminD3 and diabetes in a multiple model								
Outcome	Model1		Model2		Model3		Model4	
	OR(95%CI)	P-value	OR(95%CI)	P-value	OR(95%CI)	P-value	OR(95%CI)	P-value
vitaminD3	0.99 (0.96,1.02)	0.61	0.94 (0.91,0.97)	< 0.001	0.93 (0.90,0.97)	< 0.001	0.95(0.92,0.98)	0.002706
Non-adjusted model adjust for: None. Adjust I model adjust for: Gender; age; race; education; smoking; drink. Adjust II model adjust for: Adjust model I + TC; HTC; BUN. Adjust III model adjust for: Adjust model I +Waist; BMI								

We also drew a smooth curve fitting graph, and the results showed a linear relationship between vitamin D3 and the occurrence of diabetes in the hyperuricemia population.

## Discussion

Our results show that vitamin D3 is associated with diabetes in people with hyperuricemia after adjusting for potential confounding factors. In people with hyperuricemia, age, sex, race, smoking, and drinking are all related to the occurrence of diabetes. For example, women are more likely to develop diabetes than men, and blacks are more likely to develop diabetes than non-blacks. Smokers have a higher prevalence of diabetes than non-smokers. People who drink alcohol have a higher incidence of diabetes than those who do not drink alcohol. The effect values of the unadjusted model OR and 95% confidence interval were 0.99 and (0.96–1.02),  $P > 0.05$ , respectively). The results were not statistically significant, caused by the older participants in the diabetes group. Previous studies have also shown that vitamin D3 is associated with diabetes in the general population. Some studies have identified the reason why vitamin D3 reduces glycosuria by inhibiting inflammation [24]. Insulin resistance can cause diabetes. One of the causes of insulin resistance is inflammatory cytokines, such as interleukin-6 and tumor necrosis factor- $\alpha$ , phosphorylate insulin receptor-1 and attenuate insulin signal by activating Jun N-terminal kinase 1 (JNK1) and IKK- $\beta$ /NF- $\kappa$ B pathway. Vitamin D3 can reduce the incidence of diabetes by reducing the release of chemokines and cytokines to reduce insulin resistance. Our study is consistent with previous studies in the general population. Our study further proves that this relationship still applies to people with hyperuricemia.

Previous studies have shown that vitamin D has a beneficial effect on glucose homeostasis [15]. Vitamin D3 can improve many indexes of patients with diabetes. Studies have shown that vitamin D3 can effectively control blood glucose and blood lipids in patients with type 2 diabetes and may also help to improve complications caused by low blood glucose control, such as cardiovascular disease [15]. This study confirmed the link between vitamin D3 and diabetes in people with hyperuricemia, which may indicate that vitamin D3 on diabetes is still applicable to people with hyperuricemia.

After developing insulin resistance, islet  $\beta$  cells release more insulin to keep blood sugar within the normal range [35]. It is worth mentioning that the vitamin D3 response element was found in the promoter region of the human insulin receptor gene [15]. Many diabetes-related genes are inactivated due to hypermethylation. Vitamin D3 can prevent this hypermethylation by increasing the expression of DNA demethylase. Therefore, it can regulate blood glucose by regulating the expression of insulin receptors [35]. Animal experimental studies have also shown that 1-hydroxy-25-dihydroxy vitamin D3 (1 (OH) 2D3) can stimulate pancreatic  $\beta$ -cells to secrete insulin [36]. This study confirmed a link between vitamin D3 and diabetes in patients with hyperuricemia, which may indicate that the regulation of vitamin D3 on the expression of the insulin receptor is not significantly affected by the increase of uric acid.

When vitamin D3 is deficient, the various responses it regulates begin to decline, and people may suffer from various diseases as a result. A study shows that vitamin D3 supplementation has beneficial effects on blood glucose control, metabolic regulation, and gene regulation in patients with type 2 diabetes [15]. Therefore, vitamin D3 may be an excellent choice to regulate the health status of patients with diabetes. However, more prospective studies are needed to prove whether this effect still applies to diabetes with hyperuricemia. There are some limitations to this study. Although the results show that vitamin D3 is associated with diabetes in people with hyperuricemia, this study is a cross-sectional study. Further cohort studies or cross-sectional studies are needed on the relationship and mechanism of vitamin D3 and diabetes in people with hyperuricemia. The second limitation: the incidence of diabetes is closely related to genetic factors, and there is no discussion related to genetic factors in our study.

Although this study has some limitations, it also has the following advantages. The first one, This study used the data of five consecutive survey cycles from 2009 to 2018 in the NHANES database for analysis. The NHANES database is based on data from every state in the United States, and its data is universal. The Second one, we've used a decade's worth of data, including the last few years. We also subjected the data to rigorous screening and complex analysis. Therefore, our data are more representative and time-sensitive among the general population in the United States. The last advantage, we are specifically concerned about the relationship between vitamin D3 and diabetes in patients with hyperuricemia.

## Conclusion

In summary, the results of this cross-sectional study of NHANE database data from 2009 to 2018 show an association between vitamin D3 levels and diabetes in hyperuricemia patients in the United States. However, whether the specific mechanism between vitamin D3 and diabetes in the population with high uric acid is the same as that in the general population remains to be further studied. This study provides a new idea for exploring the factors affecting the pathogenesis of diabetes in patients with hyperuricemia. It is expected that in the near future, more factors related to diabetes will be found in people with hyperuricemia, which will provide effective help for the prevention and treatment of diabetes.

## Abbreviations

BMI, body mass index; FBG, fasting blood-glucose; VitD3, vitamin D3; Hb-A1c, glycosylated hemoglobin; TC, total cholesterol; ALT, Alanine aminotransferase; BUN, blood urea nitrogen; W.C, waist; TG, Triglyceride; CI—confidence interval; OR—odds ratio; HUA: hyperuricemia

## Declarations

## Compliance with Ethical Standards

### Authors' contributions

Rongpeng Gong and Xiaoxing Wei conceived the idea; Rongpeng Gong and Zixin Xu wrote the manuscript; Zixin Xu and Rongpeng Gong collected and read the literature and revised the article; Xiaoxing Wei read through and corrected the manuscript. All authors read and approved the final manuscript. Rongpeng Gong is the first author. Zixin Xu is the co-first author. Xiaoxing Wei is the corresponding author of this paper.

### Competing interests

The authors declare that they have no competing interests.

### Availability of data and materials

Not applicable.

### Consent for publication

Not applicable

### Ethics approval and consent to participate

All participants provided written informed consent, and the study was approved by the NCHS Research Ethics Review Board(<https://wwwn.cdc.gov/nchs/nhanes/default.aspx>).

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Not applicable

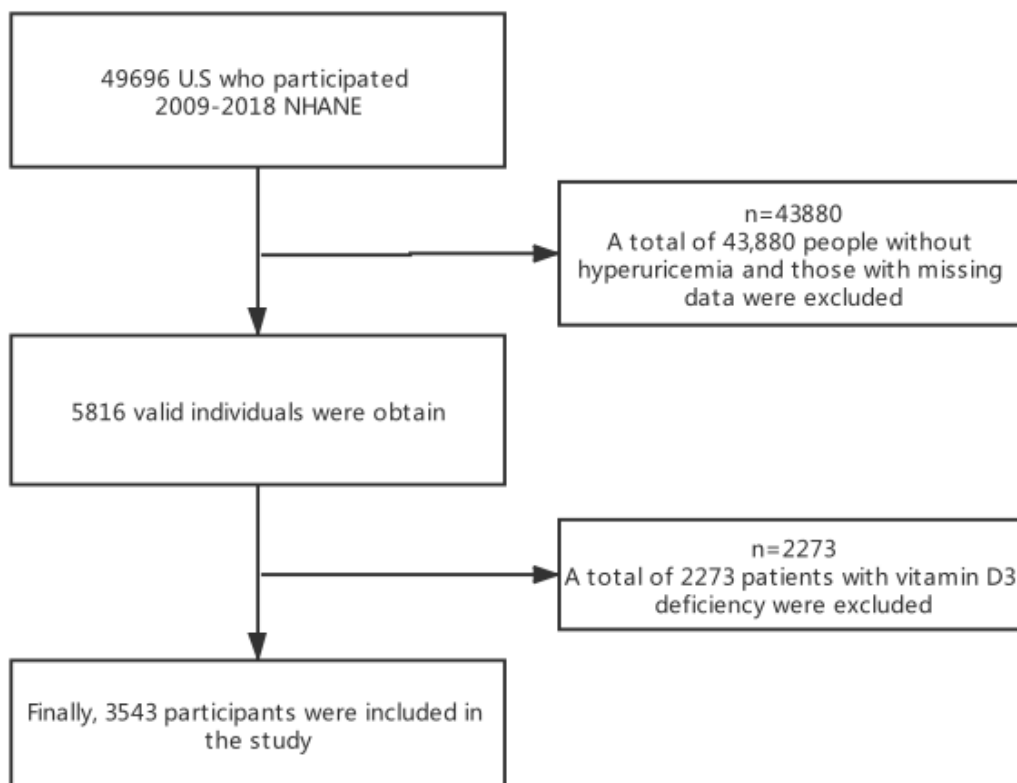
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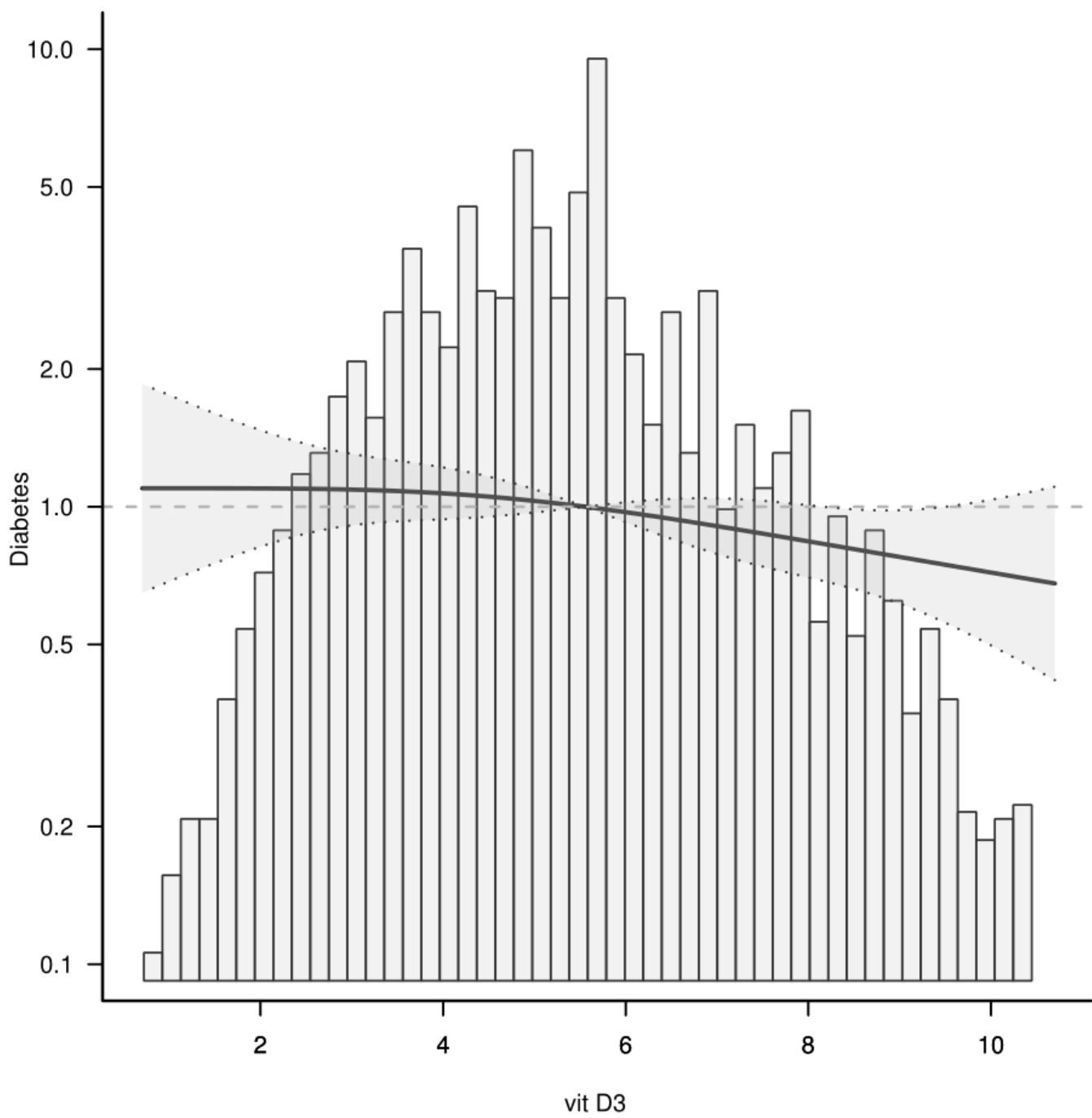
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## Figures



**Figure 1**

Flowchart of patient selection.



**Figure 2**

Association between Vitamin D3 and Diabetes.