

Association Between Serum 25-Hydroxyvitamin D Levels and Glucose Status in US Adults: A Multinomial Logistic NHANES Analysis

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Abstract. The increasing diabetes prevalence in the U.S. highlighted the importance of adequate vitamin D intake in reducing diabetes risk. However, confounders and non-linear relationship between vitamin D concentration and glucose level still remain unclear. This study aims to analyze the impact of age, sex, physical activity, season type, and BMI on diabetes prevention. We used the normal blood sugar as the reference and performed multinomial logistic regression models on the diabetes and the impaired fasting glucose group. The RRR for the IFP group was 0.89, showed no clear linear relationship; and 0.57 for the diabetes group, showed a negative correlation. The RCS plot indicate that the diabetes' risk decreases with increasing vitamin levels, then, after the vitamin D concentration reaches a certain level, the risk will rise rapidly. Furthermore, we conducted the sensitivity analysis on the high, medium and insufficient vitamin D levels using terciles and considered the other confounding factors. Results indicate that higher vitamin D was associated with a lower risk of diabetes and abnormal glucose metabolism. However, its protective effect on abnormal glucose metabolism is more dependent on specific metabolic backgrounds such as body weight, age, and exercise intensity. This study confirmed that higher serum vitamin D acts as independent protective factor against diabetes and IFG. Subgroup and sensitivity analyses indicated that this protective effect shows significant heterogeneity among different populations with different weights, ages, and exercise intensities.

Keywords: Vitamin D, Glucose Metabolism, Diabetes, Multinomial Logistic Regression

1. Introduction

Nearly 589 million adults worldwide, based on the IDF Diabetes Atlas (2025), were living with diabetes, with a global prevalence of 11.1%, and could reach 853 million by 2050 according to current estimates [1]. In the United States, a total of 40.1 million individuals had diabetes in 2023, with an addition of 115.2 million American adults living with prediabetes [2]. However, Fasting

plasma glucose (FPG), as a core indicator for the diagnosis and screening of diabetes, has modifiable nutritional determinants that have not yet been fully elucidated. Identifying dietary and nutritional factors that influence FPG is of urgent public health significance for formulating diabetes prevention strategies at the population level [3].

This has prompted investigation into specific nutrients such as vitamin D that recently emerged as a nutrient of interest beyond its classic physiology role [4]. Vitamin D has transcended the traditional scope of bone health and is recognized as a steroid hormone that plays a role in regulating systemic metabolism. Pancreatic β cells, skeletal muscle, and liver all express vitamin D receptors (VDRs). 25-hydroxyvitamin D [25(OH)D] enhances gene transcription of insulin through genomic pathways and improves peripheral insulin sensitivity through non-genomic pathways. In addition, vitamin D plays an important role in regulating inflammation and immune function, that can alleviate local inflammation in the islets. These observations imply that vitamin D might involve in connecting nutritional status and glucose homeostasis [5].

Multiple observational studies conducted on European and American populations indicate that higher serum 25(OH)D levels are inversely associated with FPG [6-8]. A meta-analysis indicates that individuals with vitamin D deficiency (< 20 ng/mL) have a greater likelihood of developing diabetes, which is approximately 50% higher than that with adequate levels [9]. However, the existing evidence shows significant heterogeneity. For example, some research has shown that vitamin D and blood glucose level may be nonlinear, which suggest that both extremely low and extremely high concentrations may be harmful [10]. Also, data for minority ethnic groups such as African Americans and Hispanics are relatively scarce, while these groups are precisely the ones with higher incidences of vitamin D deficiency and diabetes [11, 12]. Furthermore, the residual confounding factors and reverse causation as inherent limitations of observational designs constrain the reliability of causal inference.

The results of an analytical cross-sectional study [13] and a cross-sectional observational study [14] failed to consistently validate the benefits of vitamin D. The cross-sectional analytical demonstrated a statistically significant but relatively weak association between diabetes and inverse correlations with FPG, whereas the cross-sectional observational study showed that 25(OH)D level were not significantly associated with glucose levels. The contradiction reflects that an optimal range of 25(OH)D concentration may exist. More critically, the observational association between vitamin D and FPG is susceptible to multiple confounding factors: BMI, age, sex, season and frequency of physical activity. However, most existing NHANES studies only make crude adjustments or do not fully consider these confounding factors with the nonlinear association of 25(OH)D with them, resulting in biased estimates. Moreover, the statistical processing of complex sampling design weights and non-linear modeling are often overlooked.

Data from the 2021-2023 NHANES were used in this study. We use complex sampling design weights and conduct multivariate adjustments with age, sex, body mass index (BMI), season and physical activity frequency as core covariates. Multinomial logistic regression models were constructed to estimate the relative risk ratios (RRRs) and 95% confidence intervals for IFG and diabetes, with the normal glucose group as the reference. Hypothesis: Elevated 25(OH)D levels are linked to a decreased risk of diabetes, and this correlation is modified by sex, obesity and age. This study will provide evidence for precision nutrition intervention in the diverse American population.

2. Method

2.1. Data source and sample selection

The analysis was conducted using data from the National Health and Nutrition Examination Survey (NHANES) 2021–2023 cycle. Five datasets (VID_L, GLU_L, BMX_L, PAQ_L, DEMO_L) were merged by SEQN. Figure 1 illustrates the sample selection procedure. After merging ($n = 3996$), participants lacking vitamin D or glucose were excluded from the study ($n = 442$), invalid sampling weights ($WTSAF2YR \leq 0$, $n = 299$), missing BMI ($n = 37$), and extreme BMI values (<12 or >70 kg/m^2 , $n = 1$). All individual has their season data. In that case, the final sample after disposed contains 3217 participants.

2.2. Exposure and outcome measurements

Serum 25 hydroxyvitamin D's concentration (25(OH)D) was the main exposure, measured in nmol/L (laboratory code LBXVIDMS) via ultra-high performance liquid chromatography tandem mass spectrometry [15]. All measured values were above the detection limit ($LBDVIDLC = 0$). In the primary analysis, vitamin D was treated as a continuous variable in the analysis (increase 1nmol/L per unit). For sensitivity analysis, it was also categorized into tertiles: <30 , 30-50, 50 nmol/L [16].

The outcome was fasting plasma glucose (FPG), measured in mmol/L (laboratory code LBDGLUSI) using an enzymatic hexokinase method. Glucose undergoes phosphorylated by hexokinase and then glucose-6-phosphate dehydrogenase catalyzed its oxidation, during which $NADP^+$ is reduced to NADPH. Change in absorbance increases proportionally to glucose concentration. Based on the American Diabetes Association criteria [17], participants were classified into three groups: Normal glucose group with $FPG < 5.6$ mmol/L, IFG group with $FPG 5.6$ - 6.9 mmol/L, and finally Diabetes group with $FPG \geq 7.0$ mmol/L. All analyses were performed using the normal group as the reference category.

2.3. Other factors

Other factors considered beyond the exposure are the age, sex, BMI, season and frequency of physical activity are included in the models because they can both influence the vitamin D levels and the diabetes risk. Age was modeled as a continuous variable (years), as older people tend to have lower vitamin D absorption and higher diabetes risk [18]. Sex was included as a categorical variable (male/female) because vitamin D status and diabetes risk differ between men and women due to different fat mass [19]. BMI was entered as a continuous variable (kg/m^2), giving that higher BMI is linked to decreasing vitamin D and increased diabetes risk [16]. Physical activity was included as a continuous variable (number of times/month) as active individuals generally have better glucose control and may spend more time outdoors, affecting vitamin D synthesis. Season was categorized as month into two groups: Winter/Spring and Summer/Autumn, given that vitamin D levels vary by sunlight exposure across seasons.

2.4. Sample selection

Participants with missing vitamin D, glucose, or BMI were excluded. Invalid sampling weights ($n = 299$) and extreme BMI values ($n = 1$) were removed. The sample selection process is shown in Figure 1. After processing, 3217 samples left.

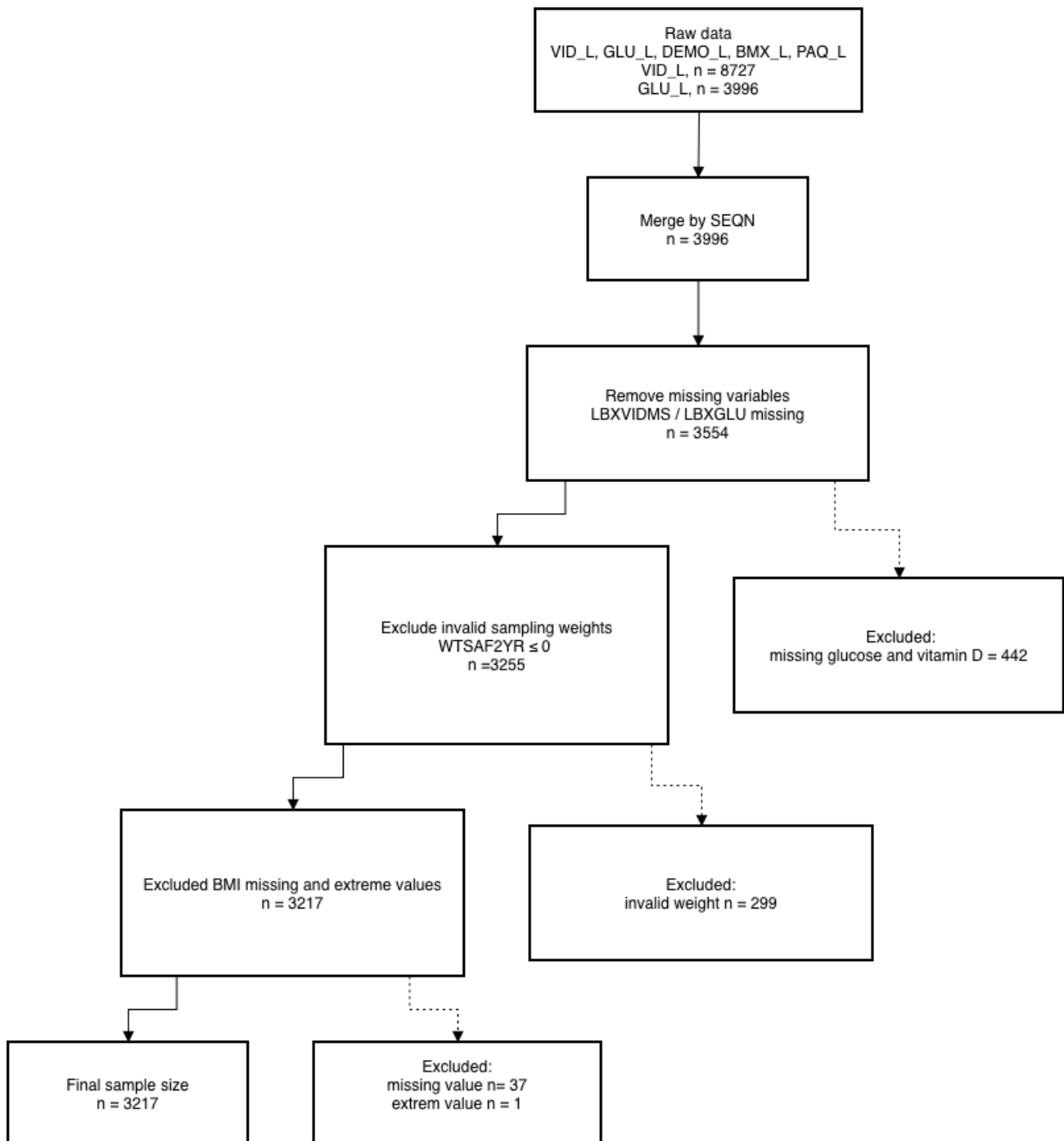


Figure 1. Flowchart of sample selection process from NHANES 2021–2023

2.5. Analysis

To analyze the potential relationship between Vitamin D concentration which is serum 25-hydroxyvitamin D (nmol/L) and fasting glucose categories (mmol/L), we performed multinomial logistic regression with the normal group (<5.6 mmol/L) as the reference category. This method was chosen because the outcome variable has three unordered categories (normal, IFG, and diabetes) and aimed to estimate the risk of IFG and diabetes separately relative to normal glucose levels.

Multinomial logistic regression was conducted to examine the relationship of log-transformed vitamin D concentrations in blood and glycemic categories (normal glucose as reference, impaired fasting glucose, and diabetes).

We used the relative risk ratio (RRR) to present the results, including the 95% confidence interval, which was calculated by exponentiating the regression coefficients. We used the group with normal blood sugar levels as the reference group, and compared the other two groups to this reference group. The RRR shows how the relative risk changes for each group contrasted with the reference normal group when log vitamin D levels increase by one unit.

2.6. Models

In the crude model, vitamin D is the only predictor included to assess the unadjusted association between vitamin D status and disease risk, using normal glucose level as the reference category. In the adjusted model, other factors, considered as covariates, were taken into consideration to control for potential confounding variables. In our research, we added age, gender, body mass index (BMI), season and average time of exercise per month to the model along with vitamin D. These variables were selected because they are commonly influencing both vitamin D concentration in blood and glucose metabolism. By adjusting for these factors, the model aims to help provide a clearer understanding of how vitamin D levels are independently related to glucose status.

3. Result

3.1. Baseline of participants

Our study consisted of 3217 participants. Participants were classified into three glycemic categories: normal glucose (n=1645), IFG (n=1199), and diabetes (n=345). Table 1 summarizes the baseline characteristics of each group.

Table 1. Participants' baseline characteristics

Characteristic	Total (n=3217)	Normal (<5.6) (n=1645)	Impaired (5.6–6.9) (n=1227)	Diabetes (≥7.0) (n=345)
Number of participants	3217	1645	1227	345
Age, weighted mean(SD) (years)	44.4(19.5)	38.4(18.4)	50.2(18.8)	58.0(14.4)
Vitamin D, weighted mean(SD) (nmol/L)	76.4(34.9)	75.7(34.6)	78.0(34.2)	74.6(39.5)
physical activity, weighted mean(SD) (times/month)	15.3(18.1)	16.1(17.8)	14.2(16.7)	14.5(24.0)
Sex				
Male	1449(49.7%)	613(43.2%)	647(57.7%)	189(58.1%)
Female	1768(50.3%)	1032(56.8%)	580(42.3%)	156(41.9%)
Race				
Mexican American	279(8.5%)	137(7.2%)	106(9.8%)	36(11.2%)
Other Hispanic	338(9.6%)	186(10.2%)	116(8.9%)	36(9.5%)
Non-Hispanic White	1887(58.6%)	940(58.1%)	761(60.8%)	186(52.9%)

Table 1. (continued)

Non-Hispanic Black	326(11.0%)	173(11.3%)	112(9.6%)	41(14.7%)
Non-Hispanic Asian	182(6.3%)	94(6.9%)	65(5.8%)	23(4.8%)
Other Race Including Multi-Racial	205(6.0%)	115(6.5%)	67(5.1%)	23(6.9%)
BMI category				
<18.5	75(2.7%)	63(3.9%)	12(1.4%)	0(0.0%)
18.5–24.9	934(30.0%)	644(39.1%)	251(20.3%)	39(12.2%)
25–29.9	981(29.8%)	470(28.7%)	412(32.4%)	99(26.1%)
≥30	1227(37.5%)	468(28.3%)	552(45.9%)	207(61.8%)
Season of examination				
November–April	1466(39.7%)	747(38.7%)	553(40.1%)	166(44.1%)
May–October	1751(60.3%)	898(61.3%)	674(59.9%)	179(55.9%)

Note: Values are n(%) for categorical variables; weighted mean(SD) for continuous variables.

3.2. RRR results and data analysis

Table 2. Association of glycemic status with outcomes risk in crude and adjusted analyses

	Outcome	Category	RRR(OR)	95% CI	p-value
Model 1 (Crude)	Normal	<5.6		Reference	
	Impaired	5.6-6.9	1.30	1.11-1.51	0.01
	Diabetes	≥7.0	1.05	0.83-1.33	0.70
Model 2 (Adjusted)	Normal	<5.6		Reference	
	Impaired	5.6-6.9	0.89	0.74-1.08	0.24
	Diabetes	≥7.0	0.57	0.43-0.76	0.00

From Table 2, for the unadjusted model, a one-unit increase in log vitamin D was related with a 30% higher risk of impaired fasting glucose (RRR=1.30, 95% CI is [1.11, 1.51]), however, no statistically significant relationship was observed with diabetes (RRR=1.05, 95% CI is [0.83, 1.33]).

After adjusting for covariates. For impaired fasting glucose (RRR = 0.89, 95% CI is [0.74, 1.08]) and p-value is 0.24. So, every unit increase in log-transformed vitamin D levels will cause 11% decrease in the relative risk ratio of a person getting impaired fasting glucose. However, as the RRR CI range contains 1. This association is not statistically significant.

For diabetes (RRR = 0.57, 95% CI is [0.43, 0.76]), and the p-value is lower than 0.001. So, every unit increase in log-transformed vitamin D levels and glycemia status will cause 43% decrease in the relative risk ratio of a person suffering diabetes. This association has a statistically significant result because the RRR CI range does not contain 1.

In summary, higher vitamin D status are associated with a modest decline in both impaired glucose status (weak) and diabetes (strong) after control all the confounders.

3.3. RCS analysis

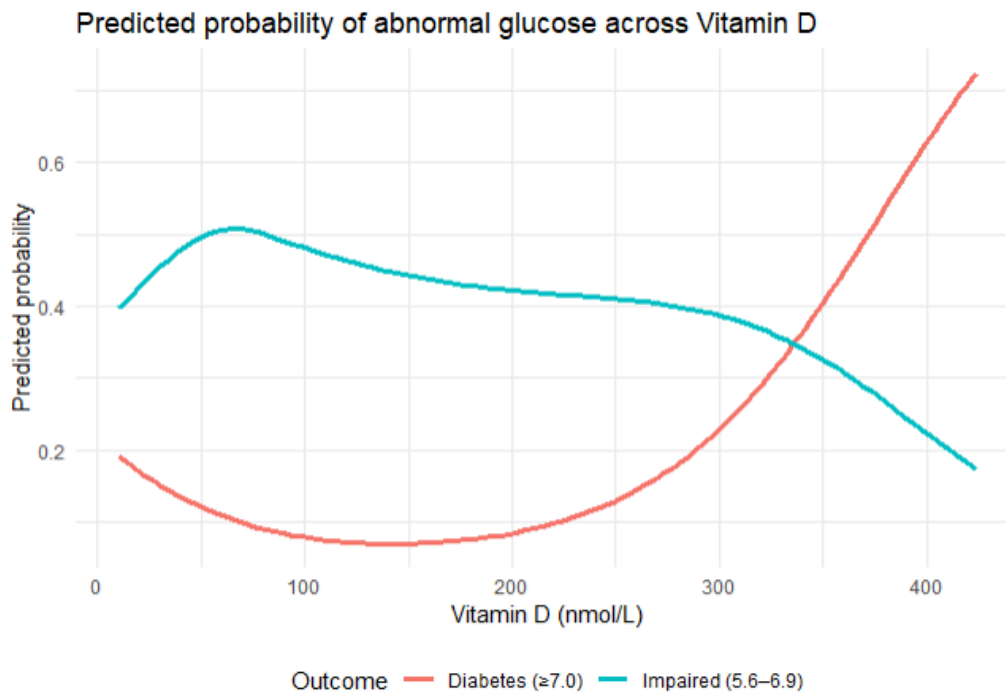


Figure 2. RCS plot which shows vitamin D and glycemic status' relationship. Two solid lines predict the probability of the two abnormal blood sugar level

Restricted cubic spline regression demonstrated the trend in glycemic outcomes according to Vitamin D concentration is non-linear in Figure 2.

For IFG, the overall trend is downward. In the low vitamin D level, the probability increases to a peak at about 70 nmol/L, after which the risk decreased continuously. For diabetes, a lower probability of diabetes was observed among participants with higher Vitamin D levels. The risk decreases first until vitamin D reach approximate 150 nmol/L, after which it increases continuously.

3.4. Forest plot analysis

The vertical dashed line represents a relative risk ratio of 1, which indicates no association. In that case, the points to the left of the confidence level suggest a protective effect, while the points to the right indicate increased risk. If the CI range includes 1, it indicates that there is no significant relationship between the two, and thus no proof of any connection (figure 3).

Starting with diabetes compared to the normal group, vitamin D and female gender are less likely to be associated with diabetes. By contrast, higher BMI along with older age are associated with an greater risk. While season as well as physical activity do not show statistically significant associations.

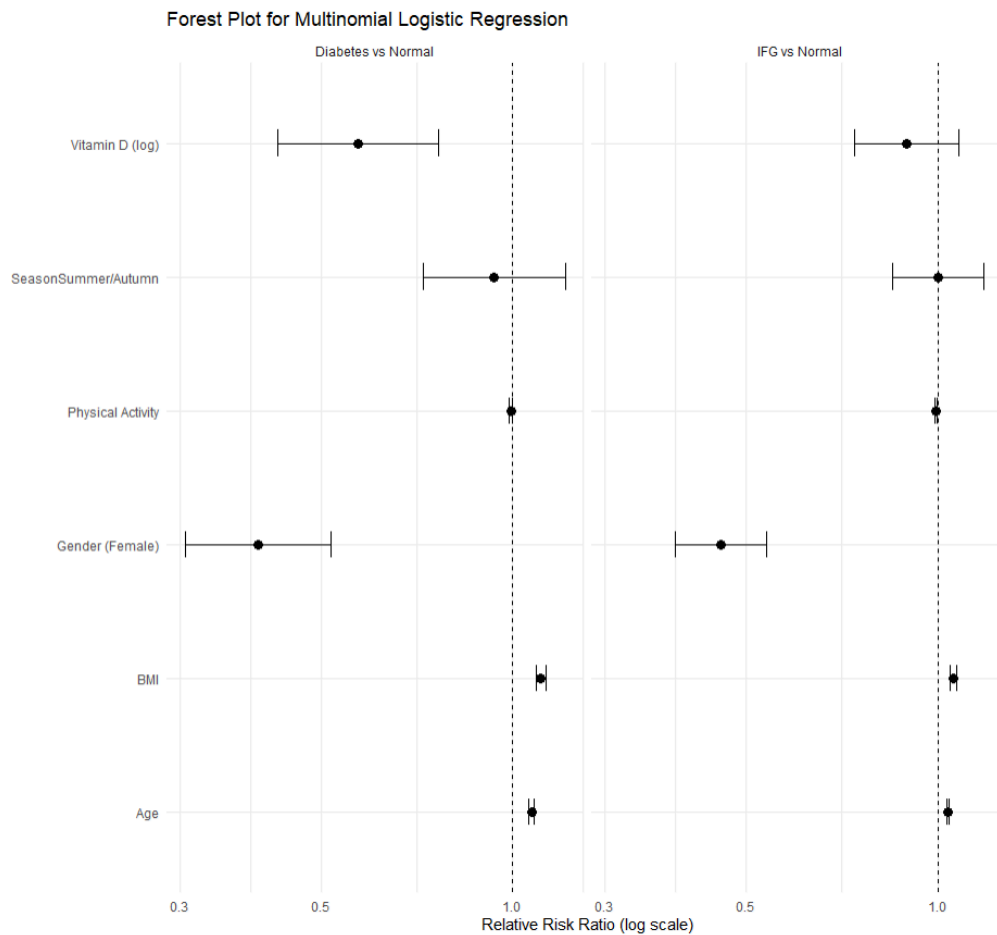


Figure 3. The forest plot of glucose level and all factors. The plot illustrates the connection between log-transformed vitamin D status and glucose levels, alongside selected factors, using multinomial logistic regression

For impaired fasting glucose compared to the normal group, gender still shows a protective trend, while BMI and age are associated with increased risk, they are the same as the previous diabetes result. However, except for season and physical activity, vitamin D showed no significant associations with IFG at this time.

In that case, individuals with higher vitamin D levels were significantly less likely to have diabetes, while no significant relationship was observed for impaired fasting glucose. In other words, vitamin D likely be more closely related to the progression to diabetes rather than in the early stage of glucose impairment.

Table 3. Association between vitamin D levels and the risk of impaired fasting glucose and diabetes

Exposure	Fasting plasma glucose status			
	Impaired fasting glucose(FPG 5.6-6.9 mmol/L)		Diabetes(FPG ≥ 7.0 mmol/L)	
	OR(95% CI)	p value	OR(95% CI)	p value
VitD level				
Vitamin D T1(lowest)	reference	reference	reference	reference
Vitamin D T2(Medium)	0.863(0.709,1.051)	0.1422	0.477(0.340,0.670)	<0.0001

Table 3. (continued)

Vitamin D T3(Highest)	0.678(0.540,0.851)	0.0008	0.318(0.218,0.465)	<0.0001
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The tertile sensitivity analysis of multinomial logistic regression indicated that high levels of vitamin D were an independent protective factor for abnormal blood sugar, and its preventive effect showed a clear dose-response relationship as the concentration increased. With the lowest level group (T1) as the reference, the middle level group (T2) could significantly reduce the risk of developing diabetes by 52.3%, but its protective effect on impaired fasting glucose (pre-diabetes) was not statistically significant. When vitamin D reached the highest level (T3), the protective effects on both of these outcomes were highly significant, reducing the risks of impaired fasting glucose and diabetes by 32.2% and 68.2% respectively.

Table 4. Subgroup analysis of vitamin D effects on diabetes and IFG risks

Factors	Fasting plasma glucose status			
	Impaired fasting glucose(FPG 5.6-6.9 mmol/L)		Diabetes(FPG ≥ 7.0 mmol/L)	
	OR(95% CI)	p value	OR(95% CI)	p value
BMI category				
<25	1.218(0.838,1.768)	0.3013	0.667(0.298,1.493)	0.3246
25~29.9	0.601(0.424,0.852)	0.0043	0.209(0.111,0.395)	<0.0001
≥ 30	0.784(0.586,1.048)	0.1006	0.415(0.279,0.618)	<0.0001
Age				
20~44	0.933(0.695,1.254)	0.6465	0.353(0.189,0.659)	0.0011
45~64	0.838(0.603,1.165)	0.2937	0.443(0.283,0.696)	0.0004
≥ 65	0.980(0.604,1.589)	0.9333	0.856(0.455,1.609)	0.6284
Sex				
Female	0.868(0.664,1.134)	0.2995	0.383(0.244,0.600)	<0.0001
Male	0.809(0.613,1.069)	0.1362	0.498(0.322,0.770)	0.0017
Season of blood sample				
May-Oct	0.735(0.568,0.950)	0.0189	0.395(0.261,0.600)	<0.0001
Nov-Apr	1.034(0.775,1.380)	0.8183	0.501(0.313,0.801)	0.0040
Physical activity				
High PA(T3)	0.604(0.434,0.841)	0.0028	0.612(0.333,1.125)	0.1139
Moderate(T2)	0.936(0.652,1.346)	0.7222	0.250(0.129,0.484)	<0.0001
Low PA(T1)	1.074(0.784,1.471)	0.6577	0.544(0.347,0.853)	0.0080

The subgroup analysis results indicate that the independent protective effect of vitamin D on abnormal blood sugar (especially diabetes) shows consistent robustness across different demographic groups and presents a significant pattern. In the BMI stratification, the protective effect is concentrated in the overweight and obese populations, among which the overweight group (25–29.9) benefits the most comprehensively, with the risks of diabetes and fasting blood sugar impairment significantly reduced by 79.1% and 39.9% respectively. In the age stratification, the protective effect of vitamin D weakens with age, mainly having a significant protective effect on diabetes in the young and middle-aged adult with the risk reduction being the greatest in the 20–44

age group, reaching 64.7%. In the gender stratification, the diabetes risk for both women and men have significantly decreased by more than 50%. In the collection season stratification, the protective benefit has a time window, and its significant protective effect on diabetes is mainly observed in the population in the summer and autumn (May–October) (risk reduction of 60.5%). In terms of physical activity, the analysis presents a unique pattern, with the potential protective role of vitamin D in diabetes perfectly concentrated in the moderate physical activity group (Moderate), resulting in an extremely significant reduction of the risk of 75%.

4. Discussion

4.1. Core findings

Our research has confirmed that the level of circulating 25-hydroxyvitamin D is negatively correlated with diabetes. By adjusting for age, gender, body mass index, blood collection season, and physical activity (PA), for every one-unit increase in log-transformed vitamin D level, the risk of developing diabetes decreased by 43%. This main finding indicates that serum vitamin D is a powerful protective factor for preventing the deterioration of blood sugar in diabetes [20].

4.2. Non-linear dose-response relationship

The RCS graph suggests that serum vitamin D level has a non-linear relationship with abnormal blood sugar. For the diabetes group, the serum vitamin D level and abnormal blood sugar present a U-shaped curve. When the serum vitamin D level is less than 150 nmol/L, abnormal blood sugar is inversely associated with the serum vitamin D level, and it reaches the highest protective effect at 150 nmol/L [21]. For the impaired fasting glucose group, the serum vitamin D level and abnormal blood sugar present an inverted U-shaped relationship. At a concentration of 75 nmol/L, the protective effect on blood sugar is the greatest [22]. These research results indicate that the protective effect of serum vitamin D concentration level on blood sugar is not a simple linear relationship, but there is an optimal treatment window, which shows that the serum vitamin D level at a specific concentration has different protective effects on different populations [23, 24].

4.3. Consistency and inconsistency

Our results revealed that the log-transformed vitamin D concentration was inversely correlated with the risk of developing diabetes. This is highly consistent with the results of a meta-analysis conducted in 2023, which indicated that appropriate serum vitamin D supplementation significantly reduced the incidence of diabetes [20]. Additionally, a 2025 review demonstrated that moderate vitamin supplementation at different age groups markedly reduced insulin resistance and impaired fasting glucose prevalence, further confirming the preventive and protective effect of serum vitamin D on blood sugar [23].

However, in Model 1, serum vitamin D levels were positively associated with abnormal blood sugar. This inconsistency was mainly due to the omission of BMI and age. A 2023 study on the effects of vitamin D supplementation on BMI and metabolism showed that the circulating serum vitamin D levels in individuals with high BMI were very low. This might be due to the distribution of vitamin D in adipose tissue, thereby weakening the protective effect of vitamin D on blood sugar in high BMI individuals [25].

Regarding the consistency of the RCS plots, this study, along with previous research, has demonstrated a nonlinear relationship between serum vitamin D concentrations and glucose abnormalities, indicating an optimal therapeutic window for protection against and prevention of glucose dysregulation. A systematic review and dose-response meta-analysis published in 2025 showed that correcting vitamin D deficiency helps reduce the risk of developing diabetes, with the best preventive and protective effects observed at levels between 100 and 200 nmol/L [23]. These findings further suggest that maintaining appropriate vitamin D levels contributes to stable blood glucose and cardiovascular health, thereby helping prevent impaired fasting glucose and diabetes.

Conversely, the RCS plots in our study also revealed some inconsistencies compared to prior research. First, earlier studies reported a negative association between vitamin D levels and glucose abnormalities in diabetic patients, whereas our results show a U-shaped curve. Beyond 200 nmol/L, excessively high vitamin D levels may even impair glucose control [24]. This could be due to excessive vitamin D increasing hepatic metabolic burden and inducing insulin resistance, thus worsening glycemic status. Additionally, our study found an inverted U-shaped curve in the impaired fasting glucose group, which contradicts the previously reported negative association [22]. These differences suggest that patients with impaired fasting glucose are in a transitional pathophysiological state, where the protective effect of vitamin D concentration follows an optimal window.

In the robustness analysis and subgroup analysis, the consistency of our research results with previous studies was manifested in that both moderate physical exercise and blood sampling in summer-autumn periods reflected higher levels of vitamin D protection and preventive effects. This is because physical exercise promotes blood circulation and metabolism, thereby increasing the vitamin D concentration in the circulatory system [26]. Moreover, blood sampling in summer-autumn promotes sun exposure and increases skin exposure to ultraviolet B, facilitating endogenous synthesis [27].

However, our results also showed inconsistency with previous studies. Firstly, in the IFG population with a BMI less than 25, the serum vitamin D content was positively correlated with abnormal blood glucose. This might be because in non-obese individuals, the strong confounding factor of obesity is weakened, and genetic variations in the vitamin D receptor gene may affect how individuals respond to vitamin D [28]. Additionally, although appropriate physical exercise has a significant protective effect on the diabetes group, it has almost no blood glucose protective effect on the IFG group. This might be because the pathological physiological core of IFG is hepatic liver insulin resistance and pancreatic β -cell dysfunction, while exercise mainly improves peripheral insulin sensitivity and has limited effect on improving liver insulin resistance [29].

4.4. Limitations

Firstly, because this study is a cross-sectional design using NHANES data, causal relationship cannot be established to obtain a direct relationship between serum vitamin D and abnormal blood sugar levels. Additionally, although we included the main confounding factors, the remaining confounding factors such as sleep duration and alcohol consumption were not fully considered.

4.5. Future suggestion

First, further research should pay greater attention to more refined, individualized vitamin D supplementation based on BMI stratification. Second, longitudinal cohort studies could be carried out to monitor the long-term effects of vitamin D levels on glucose abnormalities. Finally, future

research may explore the pathways through which vitamin D modulates blood glucose and its underlying molecular mechanisms at the medical and molecular level, further elucidating the personalized protective effects of vitamin D across different populations [30].

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