

# Association Between Vitamin D and Uric Acid in Adults: A Systematic Review and Meta-Analysis



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## ABSTRACT

Association between vitamin D and uric acid is complex and might be bidirectional. Our study aimed to determine the bidirectional association between vitamin D and uric acid in adults. Using MEDLINE via PubMed and Scopus, we systematically searched for observational or interventional studies in adults, which assessed the association between serum vitamin D and serum uric acid, extracted the data, and conducted analysis by direct and network meta-analysis. The present review included 32 studies, of which 21 had vitamin D as outcome and 11 had uric acid as outcome. Meta-analysis showed a significant pooled beta coefficient of serum uric acid level on serum 25(OH)D level from 3 studies of 0.512 (95% confidence interval: 0.199, 0.825) and a significant pooled odds ratio between vitamin D deficiency and hyperuricemia of 1.496 (1.141, 1.963). The pooled mean difference of serum 25(OH)D between groups with hyperuricemia and normouricemia was non-significant at 0.138 (–0.430, 0.707) ng/ml, and the pooled mean difference of serum uric acid between categories of 25(OH)D were also non-significant at 0.072 (–0.153, 0.298) mg/dl between deficiency and normal, 0.038 (–0.216, 0.292) mg/dl between insufficiency and normal, and 0.034 (–0.216, 0.283) mg/dl between deficiency and insufficiency. In conclusion, increasing serum uric acid might be associated with increasing 25(OH)D level, while vitamin D deficiency is associated with hyperuricemia. These reverse relationships should be further evaluated in a longitudinal study.

## ABBREVIATION

ABCG2	Adenosine triphosphate-binding cassette subfamily G member 2
BMI	Body mass index
CKD	Chronic kidney disease
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
HT	Hypertension
MD	Mean difference

NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
OR	Odds ratio
RoB2	Revised Cochrane risk of bias tool for randomized trials
ROBINS-I	Risk Of Bias In Non-randomized Studies of Interventions tool
SUA	Serum uric acid
T2D	Type 2 diabetes
VIT D	Vitamin D

## Introduction

Vitamin D (VIT D) deficiency is still a major public health problem in the world [1–3], with an estimation of over 1 billion people suffering from VIT D insufficiency or deficiency [4]. VIT D deficiency is not only a problem in areas with limited sunlight exposure such as the polar or temperate regions, but also in the tropics [3]. The prevalence of VIT D insufficiency was reported as 33.5–64.6% in Thailand [5] and 77.4% in Brazil [6], similar to the prevalence of 65% in near-polar Finland [7].

VIT D deficiency could cause bone-related diseases such as rickets and osteoporosis [8] and may increase the risk for cancer [9], tuberculosis [10], and several degenerative diseases such as type 2 diabetes (T2D) [11], hypertension (HT) [12], metabolic syndrome [13], and cardiovascular diseases (CVDs) [14]. VIT D deficiency occurs if there is a decreased intake or synthesis, or increased metabolism or excretion of VIT D. Sources of VIT D are from food and the synthesis by the skin when exposed to sunlight's ultraviolet B ray while it is minimally excreted in a healthy person [15, 16]. Several factors have been reported to be associated with VIT D level, including age, obesity, several diseases such as chronic kidney disease (CKD), liver disease, tuberculosis, sarcoidosis, and malignancies [17]. In addition, genetic factors may also regulate VIT D, for example, the Fok-I polymorphism of VIT D receptor gene [18] and the cytochrome P450 24A1 [19] and 2R1 [20–22] genes.

Previous evidence [23–27] showed that VIT D deficiency might increase the risk of high serum uric acid (SUA). On the other hand, some studies [28–32] showed that high SUA (hyperuricemia) could decrease VIT D level and/or induce VIT D deficiency. Therefore, we conducted a systematic review and meta-analysis to assess whether VIT D deficiency is associated with high SUA or vice versa.

## Materials and Methods

The study was conducted after registering with PROSPERO (CRD42 018105283). It has no funding source. A literature search was performed in MEDLINE via PubMed and Scopus databases to identify relevant studies published through July 31st, 2018. The search strategy was provided in Supplementary **Tables 1S** and **2S**.

### Selection of studies

Studies were included if they were comparative studies, which assessed the association between serum VIT D and SUA in adults. They were excluded if they were published in untranslatable languages, multiple publications of the same original research, or had incomplete data after 3 attempts of contacting the authors.

### Study factor and outcome of interest

The main exposure and outcome were VIT D and SUA level which were measured by any method according to the original studies. The SUA could be dealt with as a continuous variable or categorized using different cut-off points (i. e., 5.7, 6, or 6.6 mg/dl in females and 7 or 7.7 mg/dl in males). VIT D level could be measured as calcifediol [25(OH)D] and calcitriol [1,25(OH)<sub>2</sub>D] forms. The 25(OH) D level was categorized into deficiency, insufficiency, and normal if it was <20, 20–30, and > 30 ng/ml, respectively.

## Data extraction

Data extraction was done using a standardized data extraction form independently by 2 reviewers (RI and SB) and checked by senior reviewers (KT and AT). The data extraction form included characteristics of the article, study, and participants, exposure and outcome data of VIT D and SUA, and covariables, including mean age, body mass index (BMI), serum creatinine, serum glycosylated hemoglobin (HbA1c) levels, estimated glomerular filtration rate (eGFR), percentage of males, obesity, smoking, T2D, HT, CKD, and CVD. All disagreements were solved by discussion and reference to the original article with consent from a senior reviewer (KT).

## Risk of bias assessment

Two reviewers (RI and SB) assessed the risk of bias for each study independently. For observational studies, we used the Newcastle Ottawa Scale for cohort [33], adapted for cross-sectional [34] and case-control [33] studies, while the revised Cochrane risk of bias tool for randomized trials (RoB2) [35] and Risk Of Bias In Non-randomized Studies of Interventions tool (ROBINS-I) [36] were used for interventional studies. All disagreements were solved by discussion between the 2 reviewers (RI and SB) with consent from a senior reviewer (KT).

## Statistical analysis

### Direct meta-analysis

Direct meta-analysis was performed to pool the effect sizes, including beta coefficients (slopes) of SUA level on serum VIT D (25(OH) D) level, odds ratio (OR) between hyperuricemia and VIT D deficiency, and unstandardized mean difference (MD) of serum VIT D between the subjects with hyperuricemia and normal SUA. Heterogeneity was assessed and it was considered present if a Cochrane Q test p-value was <0.1 or Higgins I<sup>2</sup> ≥ 25% [37]. Effect sizes were pooled using DerSimonian and Laird method if they were heterogeneous, otherwise, the inverse-variance method was used [37].

We explored the source of heterogeneity using Galbraith plot and sensitivity or subgroup analysis where appropriate. A potential source (e. g., T2D, CVD, HT, CKD, age, BMI, and obesity) was fitted individually in a meta-regression model. If the  $\tau^2$  was decreased by ≥ 50%, a subgroup analysis was performed accordingly [38]. Publication bias was assessed by funnel plot and Egger test [39].

### Network meta-analysis

Network meta-analysis using two-stage approach was applied to estimate MDs of SUA between groups with different VIT D status (i. e., normal, insufficiency, and deficiency). Initially, linear regression analysis was applied to estimate the MD along with the variance-covariance for each individual study using normal VIT D status as the reference group. Then, a multivariate random-effects meta-analysis with a consistency model was used to pool the MDs across the studies [40, 41].

Inconsistency was assessed using the design-by-treatment interaction model [42]. Publication bias was assessed using a comparison-adjusted funnel plot [43].

All statistical analysis was performed using Stata version 15.1 SE by StataCorp (College Station, Texas, USA). A p-value <0.05 was

the threshold for statistical significance, except for heterogeneity where  $p$ -value  $< 0.1$  was used.

## Results

### Study Selection

There were 243 and 804 articles identified from the MEDLINE and Scopus databases, respectively. Thirty-two studies met our eligibility criteria (see Supplementary ► **Fig. 1S**). Characteristics of the studies are described in ► **Table 1**. Most of them (23) were cross-sectional studies. Their participants were either from the general population or had specific diseases, with mean age ranging from 36.9 to 76.9 years.

Among 32 studies, 21 [28–32, 44–59] and 11 [23–27, 60–65] considered VIT D and SUA as the outcome, respectively. Within the 21 studies with VIT D outcome, 6 [31, 32, 44, 48–50] provided data of SUA and VIT D levels as continuous variables, 14 [28–32, 45–47, 49, 52–54, 57, 59] assessed association between SUA level as continuous data and categorical VIT D status, while 3 [55, 56, 58] provided categorical data for both. For the 11 studies with SUA outcome, 1 [64] had continuous data for both VIT D and SUA levels, 9 [23–25, 27, 60–63, 65] provided continuous data for VIT D level and categorical SUA status, and 2 [25, 26] provided categorical data for both.

### Risk of bias assessment

The risk of bias assessment was performed and the results can be seen in Supplementary **Table 3S–5S**. For observational studies, 20 [23–27, 29, 30, 32, 45–47, 53, 57, 59–63, 65, 66], 4 [51, 52, 56, 58], and 6 [28, 44, 50, 54, 55, 64] were of low, moderate, and high risk of bias, respectively. The 2 interventional studies [31, 48] included had low risk of bias.

### Effects of SUA on VIT D outcome

#### Beta coefficient

Three studies [31, 32, 48] reported beta coefficient of SUA level on serum 25(OH)D level (see ► **Fig. 1** and Supplementary **Table 6S**) with the pooled coefficient (95% confidence interval) of 0.512 (0.199, 0.825;  $I^2 = 8.1\%$ ). In other words, there was a statistically significant, positive correlation between SUA and VIT D levels in that each mg/dl increase in SUA level was associated with an increase in 25(OH)D by 0.512 ng/ml. The funnel plot was symmetrical, corresponding to the non-significant Egger test (coefficient = 1.94, standard error = 2.19,  $p$ -value = 0.539).

#### Mean difference in SUA

Thirteen studies assessed associations between SUA and VIT D. Among them, 9 studies [29–32, 45–47, 49, 59] compared SUA levels between VIT D deficiency, insufficiency, and normal groups, whereas 4 [28, 53, 54, 57] reported SUA only between deficiency or insufficiency and normal groups. The most commonly used cut-offs for deficiency and insufficiency were  $< 20$  and  $< 30$  ng/ml, respectively (see Supplementary **Table 7S**). A network meta-analysis applied to estimate MDs of SUA levels among 3 groups across the studies yielded the non-significant pooled MDs of 0.072

( $-0.153, 0.298$ ), 0.038 ( $-0.216, 0.292$ ), and 0.034 ( $-0.216, 0.283$ ) mg/dl for deficiency vs normal, insufficiency vs normal, and deficiency vs insufficiency, respectively; all of them were not significant (see ► **Fig. 2** and **Table 8S**). Comparison-adjusted funnel plot from the network meta-analysis was symmetrical, indicating no significant publication bias.

Exploring the source of heterogeneity by subgroup analysis in the first direct meta-analysis (VIT D deficiency vs. normal) based on percentage of T2D patients showed that studies with partial T2D patients [29, 45] had a statistically significant pooled MD in SUA level of  $-0.379$  mg/dl ( $-0.552, -0.205$ ;  $I^2 = 0.0\%$ ), compared to the non-significant pooled MD of  $-0.247$  mg/dl ( $-0.874, 0.379$ ;  $I^2 = 74.9\%$ ) from studies with 100% T2D patients [28, 57] (see Supplementary **Tables 9S**). From the second direct meta-analysis (insufficiency vs normal), subgroup analysis by BMI showed that the studies with mean BMI  $< 30$  kg/m<sup>2</sup> [29, 49] had a non-significant pooled MD of 0.087 mg/dl ( $-0.306, 0.132$ ;  $I^2 = 0.0\%$ ) and those with higher mean BMI [45–47, 59] showed a non-significant pooled MD of 0.076 mg/dl ( $-0.240, 0.393$ ;  $I^2 = 58.8\%$ ) (see **Table 10S**). No specific source of heterogeneity was found in the direct meta-analysis of deficiency vs insufficiency groups.

### Effects of VIT D on SUA outcome

#### Odds ratio

Five studies [25, 26, 55, 56, 58] assessed association between VIT D deficiency and hyperuricemia (see **Table 11S**). ORs were estimated and pooled across studies, yielding the statistically significant pooled OR of 1.496 (1.141, 1.963;  $I^2 = 3.5\%$ ), indicating a significant association in which the odds for hyperuricemia of the group with VIT D deficiency was 1.496 times that of the group with normal VIT D. There is no evidence of publication bias by the funnel plot (see ► **Fig. 3**) and Egger test (coefficient =  $-0.188$ ; standard error = 0.593;  $p$ -value = 0.772).

#### Mean difference of VIT D

Eight studies [23–25, 27, 60–62, 65] compared 25(OH)D levels between hyperuricemia and normouricemia groups (see **Table 12S**). The MDs were moderately heterogeneous ( $I^2 = 30.0\%$ ) with the non-significant pooled MD of 0.138 ng/ml ( $-0.430, 0.707$ ; see ► **Fig. 4**). The funnel plot and Egger test showed no evidence of publication bias (coefficient =  $-0.726$ ; standard error = 1.162;  $p$ -value = 0.555).

## Discussion

We performed a systematic review and meta-analysis on the association between serum VIT D level and SUA level and vice versa, pooling the effect sizes of association between VIT D and SUA. We found that each mg/dl increase in SUA corresponded to an increase in serum 25(OH)D by approximately 0.5 ng/ml. Additionally, the odds for hyperuricemia of VIT D deficiency was approximately 1.5 times that of normal VIT D level.

According to our findings, high SUA might increase 25(OH)D level. This may be explained by the fact that hyperuricemia can inhibit 1 $\alpha$ -hydroxylase and prevent the conversion of the 25(OH)D form of VIT D into calcitriol [1,25(OH)<sub>2</sub>D] [25, 66], hence increasing the level of 25(OH)D but decreasing the level of calcitriol. Ge-

► **Table 1** Characteristics of included studies.

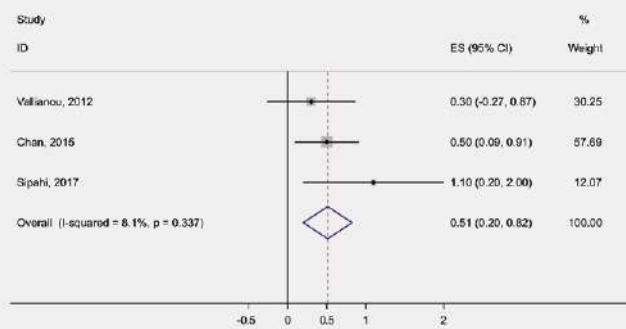
Author, Year [Ref]	Design	Country	Outcome	Mean age (years)	Mean BMI (kg/m <sup>2</sup> )	Mean serum creatinine (mg/dl)	Mean HbA1c (mmol/mol)	Mean eGFR (ml/min/1.73 m <sup>2</sup> )	Male%	Obese%	Smoking%	T2D %	HT%	CVD%	CKD %
Bakirdöğen, 2018 [44]	Cross-sectional	Turkey	25(OH) <sub>2</sub> D	53	28.2	9.9			52.1			22.9	52.1	0	100
Chen, 2017 [49]	Cross-sectional	China	25(OH) <sub>2</sub> D	43.7	22.6	0.67	78.0		12.6						
Faridi, 2017 [30]	Cross-sectional	US	25(OH) <sub>2</sub> D	60.4		0.9	39.5		54						
Jalali, 2017 [50]	Cross-sectional	Iran	25(OH) <sub>2</sub> D	36.8					55.8						
Pirro, 2017 [62]	Cross-sectional	Italy	Uric acid	66.5	26.0			80.56	0		25.6				
Sipahi, 2017 [31]	Interventional	Turkey	25(OH) <sub>2</sub> D	53.5		0.8	52.9	92.7	36.6						
Uzunova, 2017 [56]	Cross-sectional	Bulgaria	25(OH) <sub>2</sub> D	42.1					54.3	62.8					
Wang, 2017 [57]	Cross-sectional	China	25(OH) <sub>2</sub> D	52.4	25.4		81.3		62.4		32.5	100	41.1		
Bener, 2016 [47]	Case-control	Qatar	25(OH) <sub>2</sub> D	48.6	30.0	0.85	57.5		48.5						
Nardin, 2016 [53]	Cross-sectional	Italy	25(OH) <sub>2</sub> D	69.1	28.5	1.04	54.5		70.5		19.1		85.2	25.9	25.9
Sakoh, 2016 [63]	Cross-sectional	Japan	Uric acid	68.9	23.6			29.29	64.4			41.5	83.4		100
Takir, 2016 [26]	Cross-sectional	Turkey	Uric acid	54.8		0.79		88.37	18.9						
Xiao, 2016 [58]	Case-control	China	25(OH) <sub>2</sub> D	56.8					44.7		26.7				
Zhao, 2016 [27]	Cross-sectional	China	Uric acid	54.1	25.1	0.85			100						
Chan, 2015 [48]	Interventional	World	25(OH) <sub>2</sub> D	37.1					72						
Chien, 2015 [29]	Cohort	Taiwan	25(OH) <sub>2</sub> D	60.2	23.3				54.9		29.3	15.6	35.9	14.5	
Chin, 2015 [60]	Cross-sectional	Malaysia	Uric acid	42.9	24.3	0.93			100						
Hernandez, 2015 [61]	Cross-sectional	Spain	Uric acid	65	29	1.06		76.99	100						

▶ Table 1 Continued

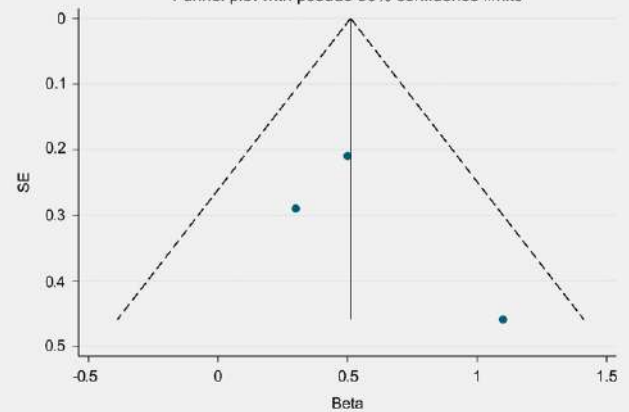
Author, Year [Ref]	Design	Country	Outcome	Mean age (years)	Mean BMI (kg/m <sup>2</sup> )	Mean serum creatinine (mg/dl)	Mean HbA1c (mmol/mol)	Mean eGFR (ml/min/1.73 m <sup>2</sup> )	Male %	Obese %	Smoking %	T2D %	HT %	CVD %	CKD %
Myrda, 2015 [52]	Cohort	Poland	25(OH) <sub>2</sub> D	53.4					85.6						
Parveen, 2015 [54]	Cross-sectional	Pakistan	25(OH) <sub>2</sub> D	60.0		1.19			75						
Veronese, 2015 [65]	Cohort	Italy	Uric acid	74.4	27.9			70.46	39.2		26.8	15.1		17.7	
Barker, 2014 [46]	Cross-sectional	USA	25(OH) <sub>2</sub> D	48.6	32.9				44.6						
Kim, 2014 [51]	Case-control	South Korea	1,25(OH) <sub>2</sub> D	45.8	24.5				62.6						
Lane, 2014 [23]	Case-control	USA	Uric acid	73.8	27.4	0.93		74.08	100		18.5	18.6			
Barcelo, 2013 [45]	Cross-sectional	Spain	25(OH) <sub>2</sub> D	52.3	31.3	0.99			76.9	54.6		17.7	16.5		
Peng, 2013 [25]	Cross-sectional	China	Uric acid		24.4				0		0.6	7.2	40.8		
Shrestha, 2012 [55]	Cross-sectional	Nepal	25(OH) <sub>2</sub> D						73.9						
Vallianou, 2012 [32]	Cross-sectional	Greek	25(OH) <sub>2</sub> D	45.9				105.01	39.4	57.8	34.7				
Yilmaz, 2012 [59]	Cross-sectional	Turkey	25(OH) <sub>2</sub> D	56.5	31.3	0.94	70.4		33.9		32.2	0	59.6	21.1	
Nabipour, 2011 [24]	Cross-sectional	Australia	Uric acid	76.9	27.8	1.08		68.7	100		62.7				
Sengül, 2011 [64]	Cross-sectional	Turkey	Uric acid	46.6	25.7	3.13			42.9						100
Bonakdaran, 2009 [28]	Cross-sectional	Iran	25(OH) <sub>2</sub> D	55.3	27.3	0.9	65.0	102.8	44			100			

**a**

## Association in slope coefficients between SUA and VIT D level

**b**

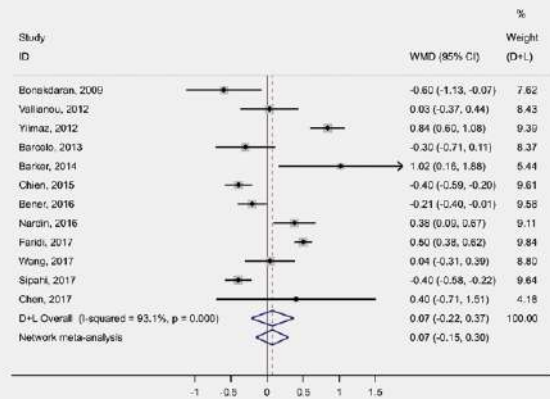
## Funnel plot with pseudo 95% confidence limits



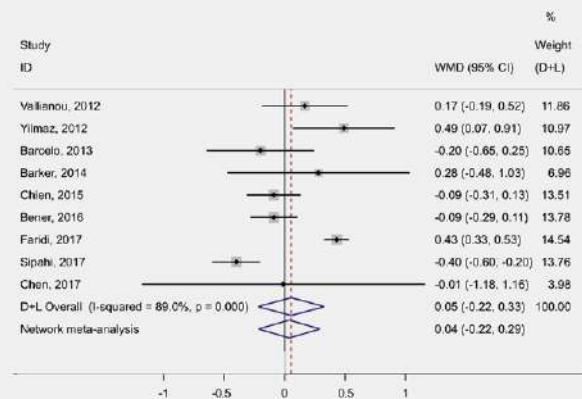
▶ **Fig. 1** Meta-analysis of beta coefficients of SUA level on serum VIT D level: **a** forest plot and **b** funnel plot.

**a**

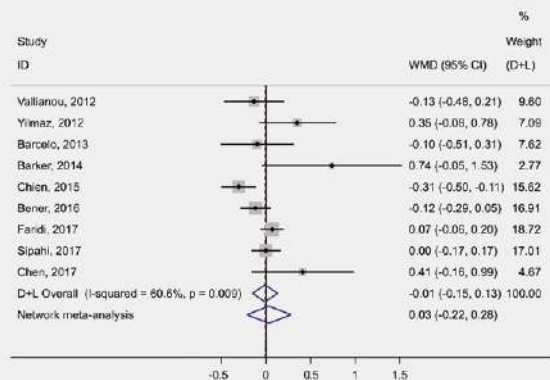
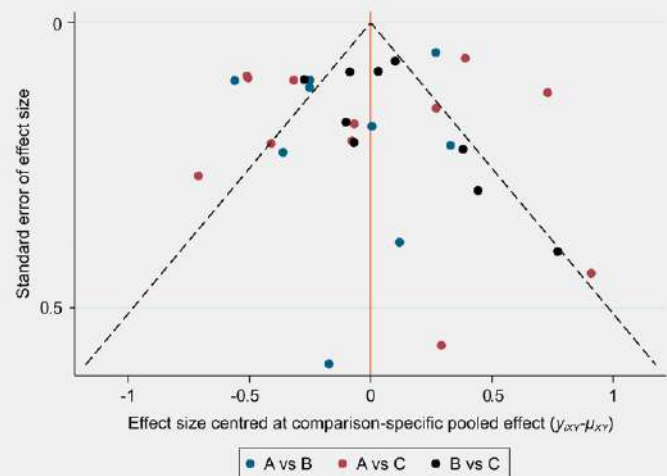
## Mean difference of SUA (mg/dl) in VIT D deficiency group vs normal

**b**

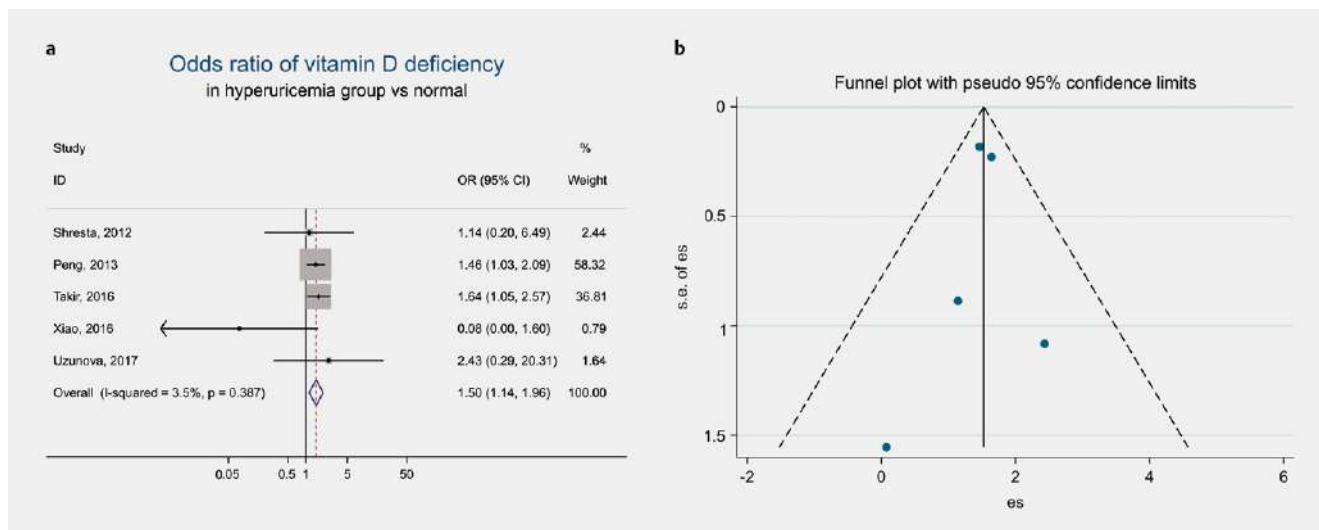
## Mean difference of SUA (mg/dl) in VIT D insufficiency group vs normal

**c**

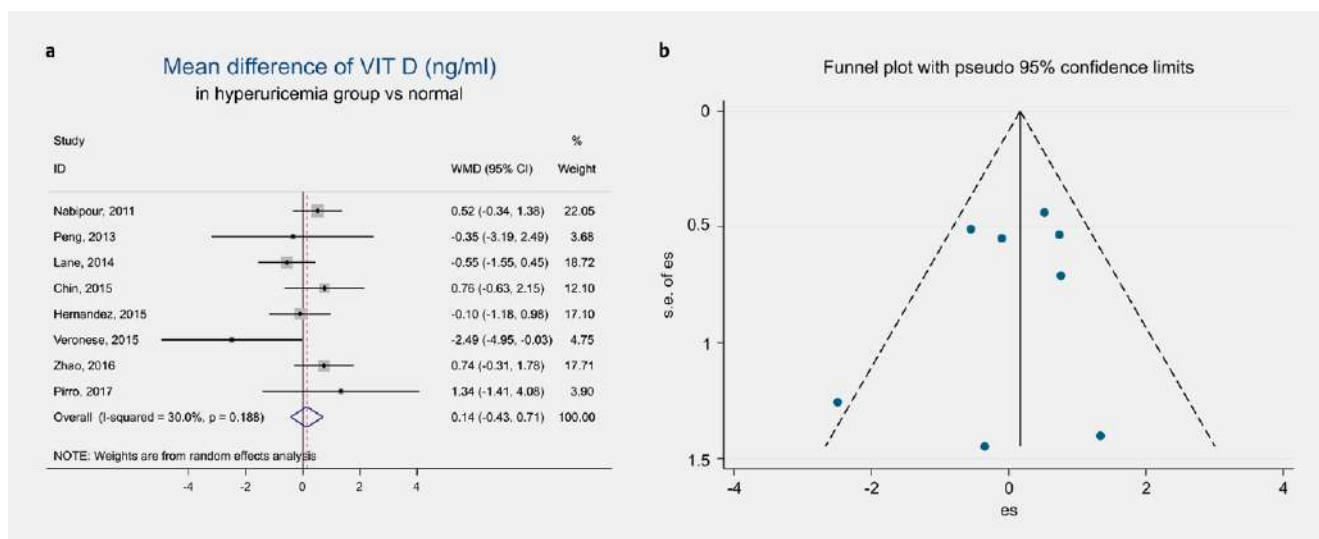
## Mean difference of SUA (mg/dl) in VIT D deficiency group vs insufficiency

**d**

▶ **Fig. 2** Meta-analysis of mean differences in SUA levels between categories of VIT D status: forest plots for **a** deficiency vs. normal, **b** insufficiency vs. normal, **c** deficiency vs. insufficiency, and **d** comparison-adjusted funnel plot from network meta-analysis.



► **Fig. 3** Meta-analysis of odds ratios between VIT D deficiency and hyperuricemia: **a** forest plot and **b** funnel plot.



► **Fig. 4** Meta-analysis of mean differences in serum VIT D levels between groups with hyperuricemia and normal SUA levels. **a** forest plot and **b** funnel plot.

netic backgrounds may also be involved in these metabolic pathways as shown by evidence from genome-wide association studies [67–71]. For instance, the rs4588 and rs2282679 polymorphisms of GC (VIT D binding protein) gene and rs10766197 polymorphism of cytochrome P450 2R1 gene were highly associated with VIT D level [72, 73], whereas the rs2231142 polymorphism of adenosine triphosphate-binding cassette subfamily G member 2 (ABCG2) gene was associated with increased SUA level [71]. A Mendelian randomization study [74] also showed a causal association between the rs2231142 polymorphism of ABCG2 gene and VIT D through SUA by reducing urate transporter in renal proximal tubules. In the same site, the increasing SUA is associated with an inhibition of CYP27B1 gene expression for the 1 $\alpha$ -hydroxylase enzyme, which converts 25(OH)D to calcitriol [66]. Furthermore, increased level of SUA might also lead to nephropathy in diabetic patients or initi-

ation and progression of renal disease in non-diabetic patients, manifested as microalbuminuria due to hyperuricemia [75], which might reduce the circulating VIT D binding protein and decrease VIT D level. Conversely, treatment with allopurinol, a xanthine oxidase inhibitor, in diabetic patients can decrease the SUA level and also increase the serum vitamin D level [76]. Therefore, the direction of the relationship between SUA and VIT D levels is still controversial.

It should be noted also that the study with the biggest weight for the pooled beta coefficient was a study using worldwide data on patients with chronic hepatitis B [48], which could, in turn, cause detrimental effects on serum VIT D level. However, this description might only explain a part of the bigger picture, since there are several other factors which could affect VIT D level such as diet, BMI, age, gender, geographical location, and season [21].

Meanwhile, for the association between VIT D and SUA outcome, the results from pooling ORs [25, 26, 55, 56, 58] showed a significant association between VIT D deficiency and hyperuricemia. This pooled OR is inconsistent with the above-mentioned pooled beta coefficient of SUA on serum 25(OH)D level. The mechanism behind this might be the secondary hyperparathyroidism caused by VIT D deficiency [77] which affects the ABCG2 gene [78] and thus decreases excretion or increases reabsorption of uric acid in the kidney tubules [60]. This VIT D deficiency could be caused by limited intake, insufficient ultraviolet exposure from sunlight, or genetic factors. It should be noted that as genetic factors can affect both VIT D and SUA levels as previously mentioned, each with their own specific gene polymorphisms, the fact that these genetic factors are not evenly distributed across different populations might also explain the conflicting results for the associations between SUA and VIT D, being pooled from a number of different populations.

This study is the first systematic review on the bidirectional association between SUA and VIT D which includes a total of 32 studies within the analysis. However, there are also some limitations in the present review, for example, the 2 significant pooled effect sizes are from a limited number of studies, whereas the other meta-analyses which consist of higher number of studies produce heterogeneous results.

In summary, increasing SUA might increase 25(OH)D VIT D level, while VIT D deficiency is associated with hyperuricemia. These reverse relationships should be further evaluated in a longitudinal study.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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