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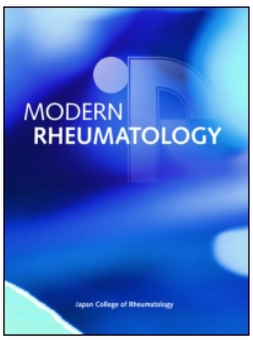

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Original Article

Vitamin D Insufficiency and Deficiency are Associated with a Higher Level of Serum Uric Acid: A Systematic Review and Meta-analysis

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Running Head: Vitamin D status and serum uric acid level

Keywords: Vitamin D deficiency, Vitamin D insufficiency, Uric acid, Hyperuricemia, Meta-analysis

Abstract

Introduction/objectives: Several epidemiological studies have suggested that patients with vitamin D insufficiency and deficiency tend to have a higher level of serum uric acid compared with those with adequate vitamin D level although the results were inconsistent across the studies. The current systematic review and meta-analysis was conducted with the aim to summarize all the available data.

Method: A systematic review was conducted using MEDLINE and EMBASE database from inception to May 2018 to identify all studies that compared the level of serum uric acid between individuals with normal vitamin D level and patients with vitamin D insufficiency/deficiency. Eligible studies must be cohort or cross-sectional studies that consisted of two groups of adult participants, one with normal level of vitamin D (vitamin D level >30 ng/ml) and one with vitamin D insufficiency (vitamin D level 20-30 ng/ml) or vitamin D deficiency (vitamin D level of <20 ng/ml). Mean serum uric acid level and standard deviation of participants were extracted from each study to calculate mean difference (MD). Pooled MD was then calculated by combining MDs of each study using random-effects model.

Results: A total of seven cross-sectional studies were eligible for the meta-analyses. Individuals with normal vitamin D level had a significantly lower serum uric acid level than patients with vitamin D insufficiency with the pooled MD of -0.33 mg/dL (95%CI, -0.61, -0.04), and also had a significantly lower serum uric acid level than patients with vitamin D deficiency with the pooled MD of -0.45 mg/dL (95%CI, -0.82, -0.08). The statistical heterogeneity of these meta-analyses was high with the I^2 of 78 % and 89%, respectively. Funnel plots of both meta-analyses were fairly symmetric and did not provide a suggestive evidence for the presence of publication bias.

Conclusions: Both patients with vitamin D insufficiency and patients with vitamin D deficiency had a significantly higher level of serum uric acid compared with individuals with normal vitamin D level.

Introduction

Hyperuricemia is a common medical problem affecting up to one-fifth of individuals in some population. (1) The persistently high level of serum uric acid can lead to several diseases such as gouty arthritis, nephrolithiasis, and chronic kidney disease. (2) In addition, studies have demonstrated that hyperuricemia is strongly associated with metabolic syndrome via the interaction with its components, including insulin resistance, hypertension, dyslipidemia, and central obesity. (3)

Vitamin D is a steroid hormone that regulates the normal homeostasis of calcium and phosphorus. The sources of vitamin D in human include endogenous synthesis by the skin and exogenous intake from diet. Vitamin D deficiency is a worldwide common health problem with the reported prevalence of up to 37 % in the United States. (4) Several studies have revealed a relationship between vitamin D status and a number of non-skeletal health conditions such as insulin resistance, metabolic syndrome, cardiovascular diseases, inflammatory diseases, infection and cancer. Still, whether the observed relationship is causal or vitamin D deficiency is just a surrogate for poor health status in general is still unclear. (5) A number of ongoing large randomized control trials are now being conducted with the aim to investigate the non-skeletal benefits of vitamin D supplement. (6-9)

The interaction between serum uric acid and vitamin D has been observed. A study found that uric acid can suppress 1-alpha-hydroxylase in vitro and in vivo, leading to the reduction in the conversion of the storage form of 25-hydroxyvitamin D (25-OHD) into the active form of 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D). (10) In fact, several epidemiological studies have suggested that patients with vitamin D insufficiency and deficiency tend to have a higher level of serum uric acid compared with those with adequate vitamin D level although the results were inconsistent across the studies. The current systematic review and meta-analysis was conducted with the aim to summarize all the available data to further clarify this potential relationship by comparing the serum uric level between individuals with normal vitamin D level versus patients with vitamin D deficiency and vitamin D insufficiency.

Methods

Search strategy

Three investigators (P.U., B.P., N.C.) independently searched published studies indexed in EMBASE and MEDLINE from inception to May 2018. Search terms were compiled from terms related to vitamin D and uric acid, including names of their derivatives and words representing their serum levels. The detailed search strategy is provided in the **Supplemental Material 1**. No language limitation was applied.

Inclusion criteria

Studies that were eligible to be included into the meta-analysis must be either cohort studies or cross-sectional studies that consisted of two groups of adult participants (age $\geq$ 18 years), one with normal level of vitamin

D (defined as vitamin D level of more than 30 ng/ml) and one with lower than normal level of vitamin D (either insufficiency, which was defined as vitamin D level of 20-30 ng/ml, or deficiency which was defined as vitamin D level of less than 20 ng/ml). The eligible studies must also report the mean level of serum uric acid of participants in both groups and its standard deviation (SD) or standard error of the mean.

Study eligibility was independently determined by the two investigators (B.P. and N.C.). Different opinions were resolved by conference with the senior investigator (P.U.). The quality of each study was evaluated by two investigators (N.C. and P.U.) using the Newcastle-Ottawa quality assessment scale for cohort studies (11) and the modified Newcastle-Ottawa quality assessment scale as described by Herzog et al. for cross-sectional studies. (12)

Data extraction

A standardized data collection form was used to extract the following information: last name of the first author, country where the study was conducted, study design, year of publication, total number of participants, recruitment of participants, average age of participants, percentage of female, definition of vitamin D status as well as mean and standard deviation of serum uric acid level in each group.

Statistical analysis

Mean serum uric acid level and SD of participants in both groups were extracted from each study and the mean difference (MD) was calculated. Pooled MD was then calculated by combining MDs of each study using random-effects model. The heterogeneity of the MDs across the included studies was quantified using the Q statistic, which is complimented with I^2 statistics. A value of I^2 of 0–25% indicates insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity and 76–100% high heterogeneity. (13) Visual inspection of funnel plots was used to assess for the presence of publication bias. Data analysis was performed using Review Manager 5.3 software from the Cochrane Collaboration (London, United Kingdom).

Results

Search results

A total of 1,269 articles were retrieved from EMBASE and MEDLINE databases in which 224 articles were duplication and were removed, leaving 1,045 articles for title and abstract review. Based on title and abstract review,

a total of 841 articles were excluded as they clearly did not fulfill the inclusion criteria on the basis of the type of article and study design. A total of 204 articles underwent full-length article review in which 194 articles were excluded as they did not report the outcome of interest while three articles were excluded as their participants were children. Finally, seven cross-sectional studies (14-20) met the inclusion criteria and were included into the meta-analysis (all seven studies were eligible for the meta-analysis of the comparison of serum uric acid level between individuals with normal vitamin D level and those with vitamin D insufficiency while six out of those seven studies were also eligible for the meta-analysis of the comparison of serum uric acid level between individuals with normal vitamin D level and those with vitamin D deficiency (14-17, 19, 20)). The study review and selection process are described in **Figure 1**. The basic characteristics of the included studies are summarized in **Table 1**.

Comparison of serum uric acid level between individuals with normal vitamin D level versus patients with vitamin D insufficiency

The meta-analysis found that individuals with normal vitamin D level had a significantly lower level of serum uric acid compared with patients with vitamin D insufficiency with the pooled MD of -0.33 mg/dL (95%CI, -0.61, -0.04). The statistical heterogeneity of this meta-analysis was high with I^2 of 78 % **(Figure 2)**.

Comparison of serum uric acid level between individuals with normal vitamin D level versus patients with vitamin D deficiency.

The meta-analysis also found that individuals with normal vitamin D level had a significantly lower level of serum uric acid compared with patients with vitamin D deficiency with the pooled MD of -0.45 mg/dL (95%CI, -0.82, -0.08). The statistical heterogeneity of this meta-analysis was high with I^2 of 89% **(Figure 3)**.

Evaluation for publication bias

Funnel plots were used for the assessment of publication bias. The plots for both meta-analyses were fairly symmetric and did not provide a suggestive evidence for the presence of publication bias **(Figure 4 and 5)**.

Discussion

The current study is the first systematic review and meta-analysis that summarizes the results of all available observational studies that compare the level of serum uric acid between vitamin D-insufficient patients and vitamin D-deficient patients versus adults with normal vitamin D level and found that the mean level of serum uric acid of patients with vitamin D deficiency and patients with vitamin D insufficiency was significantly higher than the mean level of serum uric acid of adults with normal vitamin D level. The meta-analyses found a pooled mean difference of -0.45 mg/dL in the analysis of normal vitamin D level versus vitamin D deficiency while the difference in the analysis of normal vitamin D level versus vitamin D insufficiency was slightly less pronounced (-0.33 mg/dL) which may suggest the dose-response relationship between the magnitude of deficit in vitamin D level and serum uric acid level. The observations may have clinical implications as they may suggest that vitamin D insufficiency/deficiency could be another modifiable risk factor for treatment and/or prevention of hyperuricemia. Nonetheless, this study alone cannot prove the causality between deficiency/insufficiency of vitamin D and hyperuricemia. Prospective-controlled studies are still required to determine whether the observed association is causal and to support this theoretical benefit before vitamin D supplement for this specific purpose can be recommended in clinical practice.

The exact mechanisms of this relationship are not known with certainty but there are some possible explanations. The first possible explanation is related to the metabolic effect of hyperparathyroidism as vitamin D deficiency is a known cause of secondary hyperparathyroidism (21) and several studies have suggested that elevated serum parathyroid hormone level can induce hyperuricemia. (22-24) Although the exact pathogenesis of this metabolic effect of parathyroid hormone is still unclarified, it is believed high level of serum parathyroid hormone may inhibit renal excretion of uric acid. (25) Second, patients with hyperuricemia often have gouty arthritis and may have a relatively limited outdoor activity (26, 27) compared with individuals without arthritis, leading to a lower endogenous vitamin D synthesis and a higher risk of vitamin D insufficiency/deficiency. Last, both vitamin D deficiency and hyperuricemia are known to be associated with several chronic diseases such as chronic kidney disease, metabolic syndrome and cardiovascular diseases (2, 3, 5). Therefore, without adjustment for associated comorbidities, it is also possible that the observed association is not causal and is confounded by the presence of such medical conditions. One of the particular concerns is kidney disease as decreased renal function can directly decrease uric acid excretion and cause hyperuricemia. Although renal function appeared to be comparable between

the groups based on three included studies that provided data on serum creatinine and/or glomerular filtration rate (GFR) of their participants (14, 15, 19) (**supplementary material 2**), we have no data on the other four studies and, therefore, cannot be certain whether renal function played a role as a confounder in this meta-analysis.

In general, measurement of serum vitamin D level is recommended for individuals with risk factors for vitamin D deficiency such as those with chronic kidney disease, chronic liver disease, fat malabsorption syndrome, limited physical activity, hypocalcemia, osteopenia, osteoporosis, history of non-traumatic fracture and low sunlight exposure (28). Based on the results of the current study, it may be reasonable to also consider hyperuricemia as another factor that can be used to identify those at a higher risk of vitamin D deficiency, although more studies are still needed to evaluate the benefits and cost-effectiveness of serum vitamin D measurement in patients with hyperuricemia.

It should be noted that this systematic review and meta-analysis has some limitations and caution is needed for the interpretation of the results. First, all of the studies are cross-sectional in nature and, thus, could not provide a temporal relationship between vitamin D insufficiency/deficiency and serum uric acid level. Studies with a more reliable design (such as prospective cohort study) are still needed before causality could be further substantiated. Second, the statistical heterogeneity in this study was high. We believe that the difference in the background populations across the included studies was the most likely explanation. Third, although the funnel plots for both meta-analyses were fairly symmetric and did not provide a suggestive evidence for the presence of publication bias, the reliability of the interpretation of the plots might be jeopardized by the relatively limited number of included studies. Finally, the current study only investigated the relationship between vitamin D status and serum uric acid level, not hyperuricemia-associated diseases. We still do not know with certainty if the observed higher level of serum uric acid among patients with vitamin D deficiency/insufficiency is of clinical significance and, thus, further studies are still required.

In summary, this study found that both patients with vitamin D insufficiency and vitamin D deficiency had a significantly higher level of serum uric acid compared with individuals with normal vitamin D level, but further studies are still needed to confirm the causality and to determine the role of vitamin D supplement for treatment and prevention of hyperuricemia.

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Conflict of interest: None.

Authors' contributions: All authors had access to the data and a role in writing the manuscript.

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Figure legend

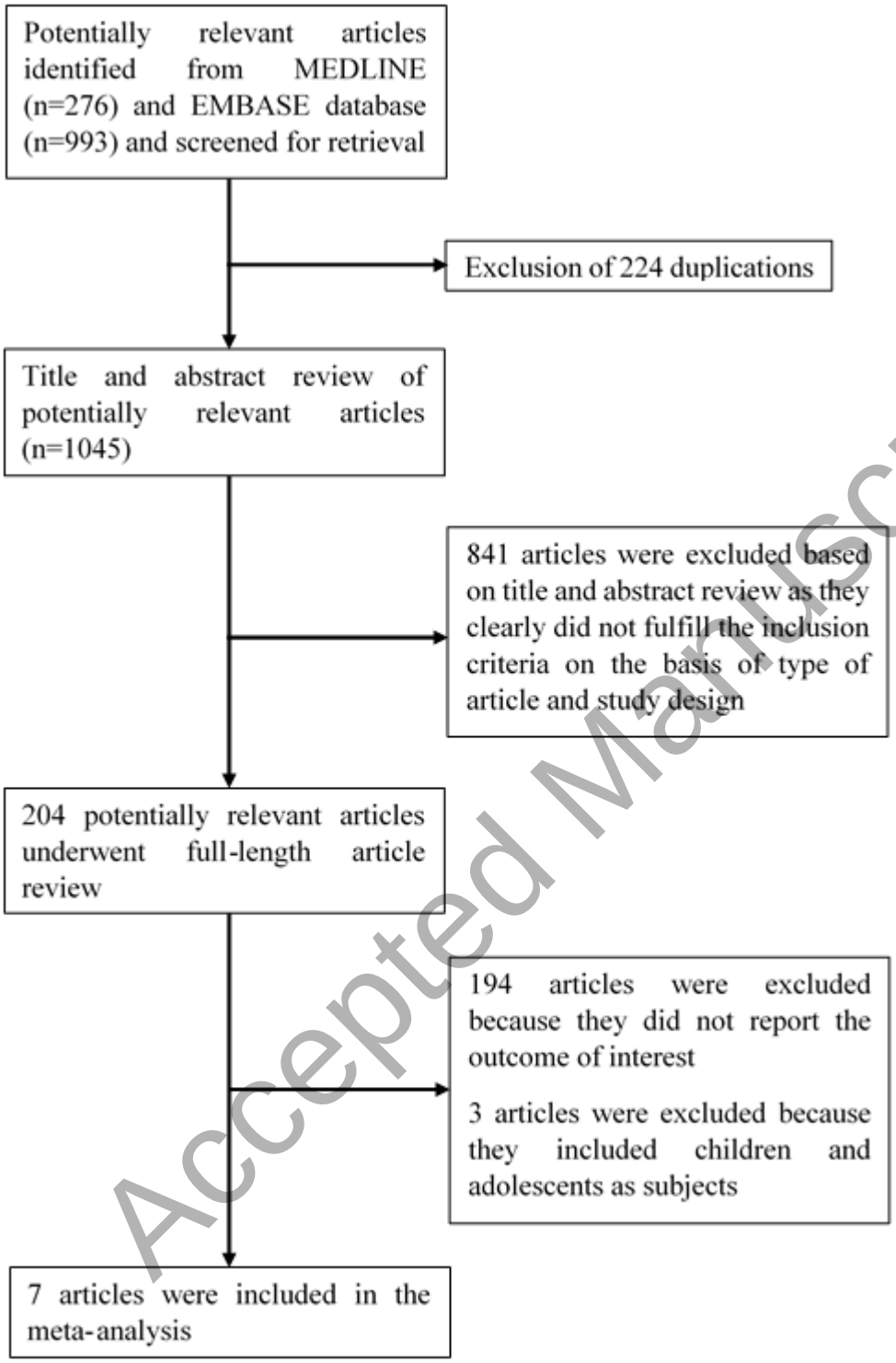
Fig. 1 Study identification and literature review process

Fig. 2 Forest plot of the meta-analysis of vitamin D insufficiency versus normal vitamin D level

Fig. 3 Forest plot of the meta-analysis of vitamin D deficiency versus normal vitamin D level

Fig.4 Funnel plot of the meta-analysis of vitamin D insufficiency versus normal vitamin D level

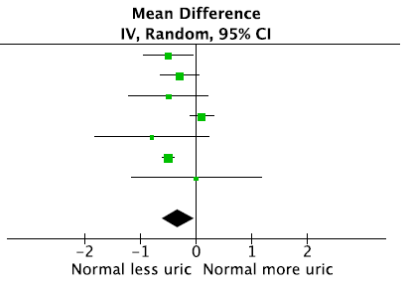
Fig. 5 Funnel plot of the meta-analysis of vitamin D deficiency versus normal vitamin D level



Study or Subgroup	Normal vit D level Mean	SD	Total	Vit D insufficiency Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Yilmaz et al.	4.4	0.4	32	4.9	0.8	14	15.6%	−0.50 [−0.94, −0.06]	2012
Vallianou et al.	4.7	1.6	120	5	1.5	217	18.1%	−0.30 [−0.65, 0.05]	2012
Barker et al.	5.1	1.3	18	5.6	0.9	21	9.8%	−0.50 [−1.21, 0.21]	2014
Bener et al.	5.6	1.8	412	5.5	1.7	806	21.8%	0.10 [−0.11, 0.31]	2016
Krysiak et al.	5.4	1.5	16	6.2	1.5	17	5.9%	−0.80 [−1.82, 0.22]	2016
Faridi et al.	5.1	1.6	2311	5.6	1.6	1430	23.9%	−0.50 [−0.61, −0.39]	2017
Chen et al.	5.2	1.8	11	5.2	1.5	36	4.8%	0.00 [−1.17, 1.17]	2017
Total (95% CI)			**2920**			**2541**	**100.0%**	**−0.33 [−0.61, −0.04]**	

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 26.74$, df = 6 (P = 0.0002); $I^2 = 78\%$

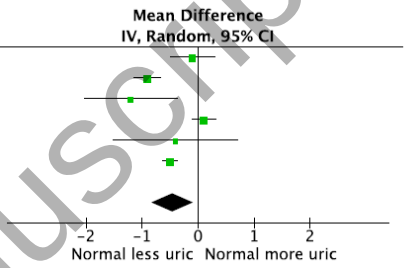
Test for overall effect: Z = 2.23 (P = 0.03)

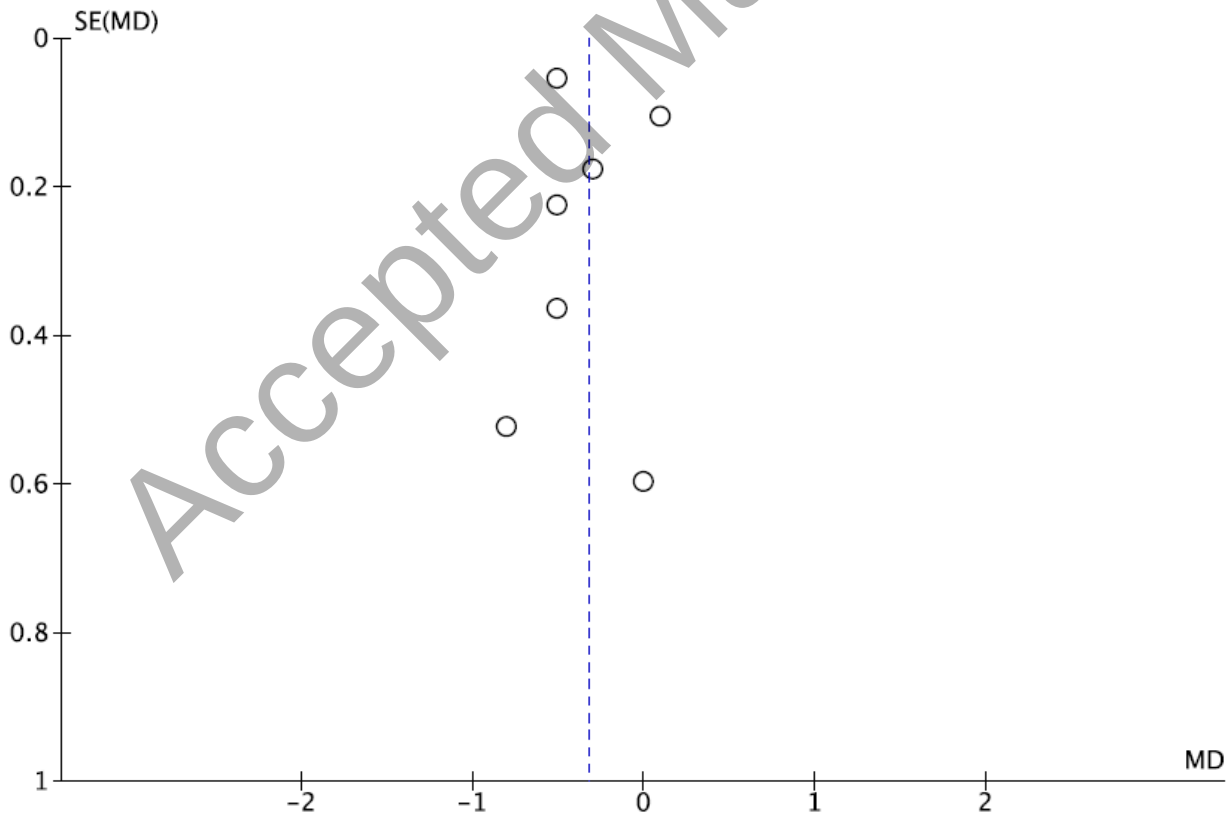


Study or Subgroup	Normal vit D level Mean	SD	Total	Vit D deficiency Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Vallianou et al.	4.7	1.6	120	4.8	1.6	135	18.0%	−0.10 [−0.49, 0.29]	2012
Yilmaz et al.	4.4	0.4	32	5.3	1.1	125	20.7%	−0.90 [−1.14, −0.66]	2012
Barker et al.	5.1	1.3	18	6.3	1.2	17	10.6%	−1.20 [−2.03, −0.37]	2014
Bener et al.	5.6	1.8	412	5.5	2	1026	21.1%	0.10 [−0.11, 0.31]	2016
Chen et al.	5.2	1.8	11	5.6	1.8	120	7.4%	−0.40 [−1.51, 0.71]	2017
Faridi et al.	5.1	1.6	2311	5.6	1.6	850	22.1%	−0.50 [−0.63, −0.37]	2017
Total (95% CI)			**2904**			**2273**	**100.0%**	**−0.45 [−0.82, −0.08]**	

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 46.14$, df = 5 (P < 0.00001); $I^2 = 89\%$

Test for overall effect: Z = 2.39 (P = 0.02)





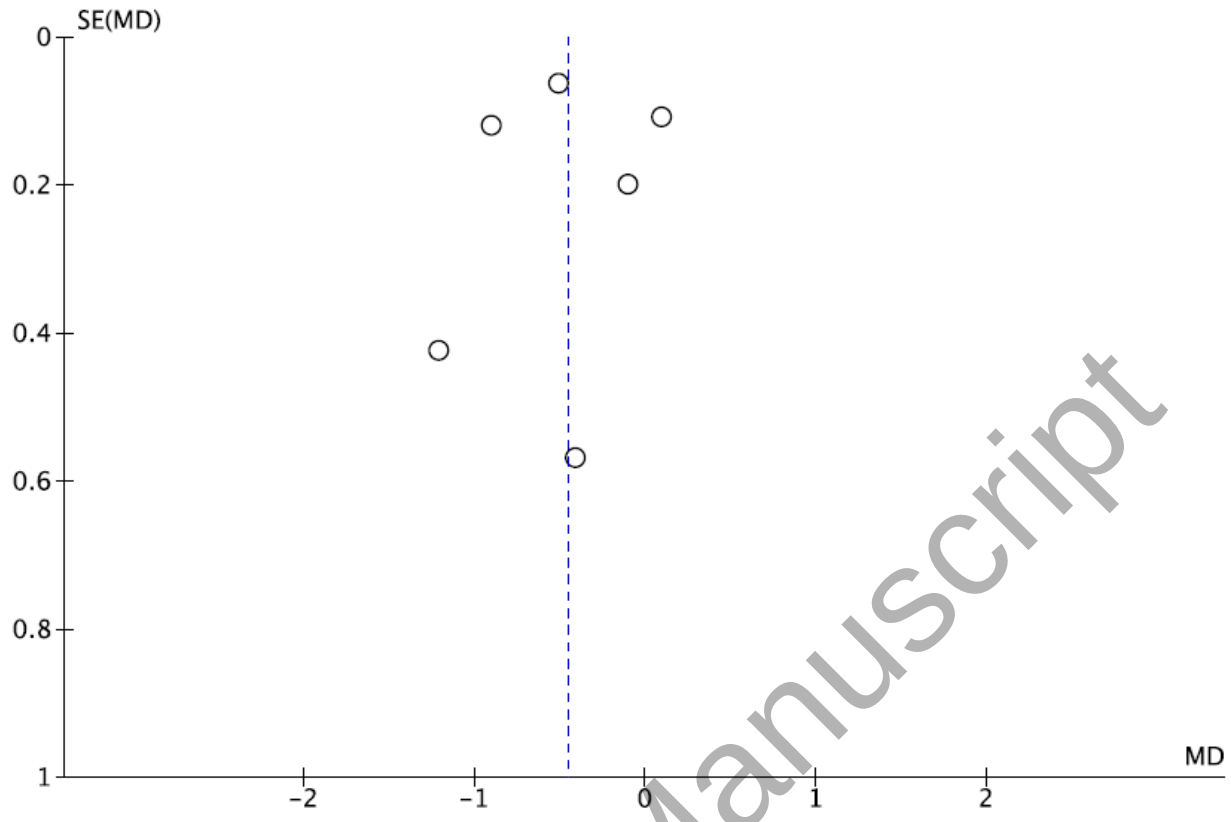


Table 1 Main characteristics of the studies included in the meta-analysis

	Yilmaz et al.(14)	**Vallianou et al.(15)**	**Barker et al.(16)**	**Bener et al.(17)**
Country	Turkey	Greece	United States	Qatar
Study design	Cross-sectional study	Cross-sectional study	Cross-sectional study	Cross-sectional study
Year of publication	2012	2012	2014	2016
Total number of participants	171	472	56	2,224
Recruitment of participants	Participants were adults with DM who were recruited from the Ankara diskapi training and research hospital from October 2010 to November 2010. All participants were tested for 25-OH vitamin D level and serum uric acid level.	Participants were 490 adults who had visited the Polykliniki General Hospital for annual health check-ups between April 2009 and January 2010. Individuals with history of cancer or recent infection were not included in the study. All participants were tested for 25-OH vitamin D level and serum uric acid level.	Participants were modestly active adults with age of 60 years or younger who were recruited from the practice of orthopedic surgeons at The Orthopedic Specialty Hospital (Murray, UT USA). The exclusion criteria were as follow: taking dietary supplement during the previous year, anti-inflammatory medication/other medications, lower leg injury during the previous year requiring clutches, tobacco use, and under physician guided treatment for known disease. All participants were tested for 25-OH vitamin D level and serum uric acid level.	Participant were diabetic patients and healthy control subjects aged 20 years or more attending Hamad General Hospital and Primary Health Care Centers in Qatar from November 2012 to July 2014. Only patients with Qatari or any other Arab country nationalities residing in Qatar were included in the study. All participants were tested for 25-OH vitamin D level and serum uric acid level.
Average age of participants (years)	56.5	45.9	48.6	48.6
Percentage of female	66.1	39.4	55.4	51.0
Definition of vitamin D status	Normal: > 30 ng/ml Insufficiency 20-30 ng/ml Deficiency < 20 ng/ml	Normal: > 30 ng/ml Insufficiency 20-30 ng/ml Deficiency < 20 ng/ml	Normal: > 30 ng/ml Insufficiency 20-30 ng/ml Deficiency < 20 ng/ml	Normal: > 30 ng/ml Insufficiency 20-30 ng/ml Deficiency < 20 ng/ml
Quality assessment (Newcastle-Ottawa scale)	Selection: 4 Comparability: 1 Outcome: 3	Selection: 4 Comparability: 1 Outcome: 3	Selection: 4 Comparability: 1 Outcome: 3	Selection: 4 Comparability: 1 Outcome: 3

(cont.)

Table 1 (cont.)

	Faridi et al.(18)	**Chen et al.(19)**	**Krysiak et al.(20)**
Country	United States	China	Poland
Study design	Cross-sectional study	Cross-sectional study	Cross-sectional study
Year of publication	2017	2017	2016
Total number of participants	4,591	167	49
Recruitment of participants	Participants were adults from Very Large Database of Lipids (VLDL), a dataset of 1,340,614 U.S. adults who were referred for Vertical Auto Profile (VAP) ultracentrifugation lipid analysis from 2009 to 2011. All participants had available measurements for 25-OH vitamin D and uric acid levels	Participants were adult Chinese non-obese type 2 diabetic patients who consecutively attended clinic during November and March. Participants who had acute illness, advanced liver or renal disease, medication known to affect vitamin D metabolism, abnormal thyroid or parathyroid hormone levels were excluded. All participants were tested for 25-OH vitamin D level and serum uric acid level.	Participants were men with age of 30 to 70 years with hypercholesterolemia. The exclusion criteria were as follows: CAD, stroke within 6 months preceding the study, symptomatic CHF, DM, moderate or severe HT, any acute or chronic inflammatory processes, autoimmune disorders, impaired renal or hepatic function, nephrotic syndrome, liver and biliary-tract diseases, BMI >35 kg/m^2, treatment with any hypolipemic agents within 6 months, treatment with calcium supplements, drugs affecting plasma lipid levels or calcium/phosphate homeostasis, treatment with drugs that interact with statins or vitamin D, and poor patient compliance. All participants were tested for 25-OH vitamin D level and serum uric acid level.
Average age of participants (years)	60.3	43.3	47.7
Percentage of female	46.4	52.6	0.0
Definition of vitamin D status	Normal: > 30 ng/ml Insufficiency 20-30 ng/ml Deficiency < 20 ng/ml	Normal: > 30 ng/ml Insufficiency 20-30 ng/ml Deficiency < 20 ng/ml	Normal: > 30 ng/ml Insufficiency 20-30 ng/ml Deficiency < 20 ng/ml
Quality assessment (Newcastle-Ottawa scale)	Selection: 5 Comparability: 1 Outcome: 3	Selection: 4 Comparability: 1 Outcome: 3	Selection: 4 Comparability: 1 Outcome: 3

Abbreviation: DM, diabetes mellitus; 25-OH vitamin D, 25-Hydroxyvitamin D; CAD, coronary artery disease; CHF, congestive heart failure; HT, hypertension; BMI, body mass index