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PII: S1568-9972(23)00231-8

DOI: https://doi.org/10.1016/j.autrev.2023.103497

Reference: AUTREV 103497

To appear in: *Autoimmunity Reviews*

Received date: 12 November 2023

Accepted date: 29 November 2023

Please cite this article as: W. Rojas-Carabali, J.S. Pineda-Sierra, C. Cifuentes-González, et al., Vitamin D deficiency and non-infectious uveitis: A systematic review and Meta-analysis, *Autoimmunity Reviews* (2023), https://doi.org/10.1016/j.autrev.2023.103497

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ABSTRACT

Background: Vitamin D plays a critical role in immunomodulation, and its deficiency is implicated in the pathogenesis of several autoimmune diseases. Nevertheless, its relationship with non-infectious uveitis (NIU), an inflammatory ocular disorder, remains inconclusive.

Methods: A systematic search was conducted in three databases from database inception until May 8, 2023, to investigate the potential relationship between vitamin D deficiency and non-infectious uveitis. We included observational studies reporting the measurement of vitamin D levels in patients with NIU and healthy controls without restriction of language or date of publication. Three pairs of authors independently screened the title and abstracts for potential eligibility and then in full text. A third author resolved disagreements. Three pairs of independent reviewers abstracted the data from the fully reviewed records and evaluated the risk of bias. We followed The MOOSE and PRISMA guidelines. Random effects meta-analyses were used for primary analysis. Studies not included in the meta-analysis were summarized descriptively. This review was registered in PROSPERO: CRD42022308105.

Findings: Of 933 records screened, 11 studies were included, and five were meta-analyzed, encompassing 354 cases and 5,728 controls (mean participant age ranging from 7.1 to 58.9 years). Patients with vitamin D deficiency exhibited an Odds Ratio of 2.04 (95% CI = 1.55-2.68, P < 0.00001) for developing NIU compared to controls. Overall, potential sources of bias were low across most studies.

Interpretation: Our findings suggest that vitamin D may play an essential role in the pathophysiology of NIU. While the included studies demonstrated generally low potential bias, additional rigorous prospective studies are necessary to confirm these findings and further elucidate the underlying mechanisms involved. Vitamin D supplementation could represent a possible therapeutic strategy for preventing or managing NIU if substantiated. Clinicians should consider screening for and addressing vitamin D deficiency in patients with or at risk for NIU.

Funding: None

Keywords: Vitamin D, Risk Factor, Uveitis, Autoimmunity, Rheumatology, Ophthalmology.

1. INTRODUCTION

Vitamin D is an essential cofactor for calcium homeostasis. However, its biological functions are not limited to this, and its pleiotropic nature has been described extensively[1,2], with particular interest in its immunomodulatory and anti-inflammatory actions.[3–7]

Vitamin D binds the intracellular vitamin D receptor (VDR) found in lymphocytes, macrophages, and dendritic cells to act as a transcriptional factor and create a tolerogenic immune environment [7]. This is achieved by inhibiting dendritic cell differentiation, reducing pro-inflammatory cytokines, such as IL-6, IL-12, and IL-23, and enhancing the production of anti-inflammatory cytokines like IL-8 and IL-10. Additionally, vitamin D inhibits cytokine production in T-helper 1 and T-helper 17 lymphocytes while inducing the differentiation of T-helper 2 and T-regulatory lymphocyte [4][5] (**Figure 1**). Alterations in these immunological pathways explain the association between vitamin D and various immune-mediated diseases, including rheumatoid arthritis, juvenile idiopathic arthritis, multiple sclerosis, Crohn's disease, spondyloarthropathies, and ocular inflammatory diseases, among others [5–8].

Recent publications have linked serum vitamin D levels with the development, inflammatory activity, and remission of non-infectious uveitis (NIU)[8,9]. Uveitis, an inflammatory eye condition, responsible for 10% to 15% of blindness globally and 67% to 90% of cases in developed countries[10], thus, generating a significant socio-economic impact worldwide[11–13]. Although Grotting et al.[9] associated the hypovitaminosis D (<30 ng/mL) with idiopathic noninfectious anterior uveitis when described that individuals with hypovitaminosis D had 2.53 times more chance to develop it, most evidence about the impact of hypovitaminosis D on NIU development and activity is still inconclusive.

Therefore, this aimed to evaluate the association between vitamin D levels and NIU through a systematic review and meta-analysis. Our primary outcome was to assess the impact of vitamin D on the development of NIU. Secondary outcomes included the level of inflammatory activity, the effect of seasonality on NIU diagnosis and activity, the impact of latitude on vitamin D deficiency, and the influence of race on vitamin D deficiency NIU diagnosis and disease activity.

2. METHODS

This review was registered in PROSPERO under the reference CRD42022308105 and followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[14] and The Meta-analysis of Observational Studies in Epidemiology Reporting (MOOSE) Guideline[15] (**Supplementary Material 1**).

2.1. Eligibility criteria: We include all articles published that reported 1) patients with non-infectious uveitis and 2) measurement of vitamin D levels, including 25 hydroxyvitamin D and 1,25 hydroxyvitamin D. The data was collected in nanograms per milliliter; therefore, reports in nanomoles per liter were converted by multiplying by 2,596 as suggested by Grotting et al.[9]. NIU diagnosis was as our primary outcome. We included observational studies (case-control, cohort, and cross-sectional studies) without language restrictions or publication dates.

2.2. Search methods and strategy: We conducted a systematic literature search in the following databases: Embase, PubMed, and Lilacs. Search algorithms included a combination of terms reflecting the disease of interest (uveitis) in combination with the exposure factor (vitamin D) (available in **Supplementary Material 2**). The search was initially done on January 25, 2022, and updated on May 8, 2023, in the same databases (available in **Supplementary Material 2**). The authors reviewed the references of the eligible studies to identify any potentially missed relevant observational studies. The entire search process was documented following the PRISMA statement and is available in **Figure 2**[14].

2.3. Study selection: Titles and abstracts from the initial search were randomly assigned and independently screened by three pairs of reviewers: WRC-PTMV, MSM-MAFM, and LFPP-JSPS. The same was done for the results of the updated search by JSPS-CHCG. The relevant articles to our research question were retrieved for full-text review, which was also performed in a paired way. Inclusion criteria were: (1) report patients with non-infectious uveitis; (2) reported mean serum levels 25(OH)D or 1,25(OH)D; (3) include study participants of all ages, ethnicities, and sexes. Studies were excluded if they were: (1) case reports, review articles, experimental studies on animals or *in-vitro* studies with human blood cells, conference abstracts, economic studies, systematic reviews, and meta-analysis; or (2) studies that included individuals with infectious uveitis, pregnant women, and participants with baseline alterations of vitamin D metabolism. Any articles that did not meet the criteria

for systematic review but were relevant to the study question were reviewed, and pertinent findings were reported in the discussion section.

2.4. Data collection: A standardized, validated form in Microsoft Excel was used to extract data from the included studies. The form collected data about (1) the author's name, (2) study sites/locations, (3) the year of publication, (4) population, (5) study methodology, (6) sampling method, (7) sampling size, (8) age, (9) gender; (10) definition of vitamin D deficiency and insufficiency, (11) laboratory method used to measure vitamin D levels, (12) Serum vitamin D levels in cases and controls, and (13) primary outcomes of the study (OR, RR, p, β, or r). A second investigator reviewed all extracted data to ensure accuracy and completeness. We could find the relevant information we needed in all the selected articles.

2.5. Risk of bias assessment: The risk of bias assessment was conducted using the Newcastle-Ottawa Scale for observational studies such as cohort and case-control studies[16], Hoy et al.[17] tool for prevalence and cross sectional studies. Each article was assessed by two independent reviewers (JSPS and MRC) using all domains of each tool as explained in **Supplementary material 3**.

2.6. Data synthesis and analysis

All articles that provided relevant data for qualitative analysis were summarized in a narrative way. For meta-analyses, we used the standardized mean differences for the quantitative synthesis and only did Odds Ratio (OR) analysis for the low vitamin D levels measured one year before uveitis onset due to the heterogeneity in the definitions for hypovitaminosis D across the included studies. Additionally, we converted nanomoles per liter to nanograms per milliliter multiplying by 2.596, as recommended by Grotting et al.[9]. Only variables that were reported in at least two studies underwent meta-analysis. In most meta-analyses, we use the random effects model to capture uncertainty resulting from significant statistical, clinical, sociodemographic, and methodological heterogeneity between studies. However, a sensitivity analysis was performed to estimate the contribution of each study to heterogeneity by sequentially excluding one study and recalculating the pooled standardized mean difference, thus reducing the number of studies and using the model of fixed effects to obtain a more precise estimate of the between-study variance[18]. The I2 statistic was used to calculate the studies' heterogenicity, which also influences the use of random effects or fixed effects models, and values of <24%, 25% to 49%, 50% to 74%, and ≥ 75% denote no, low, moderate and high heterogeneity respectively[19]. We used Review Manager (RevMan 5.4; The Nordic Cochrane Centre, The Cochrane Collection, Copenhagen, Denmark) to elaborate the forest plots.

3. RESULTS

Our search strategy showed 1227 studies, of which 933 were screened after duplicates removal and 11 were included after the screening process (**Figure 2**). Six were case-control studies conducted in the USA (n=3), Turkey (n=1), Romania (n=1), and China (n=1), two cohort studies from Germany and Denmark, and three cross-sectional studies from the USA (n=1), Australia (n=1) and Brazil (n=1). There were 1,681 uveitis patients with 25(OH)D measurements and a mean age of patients ranging between 7.1 and 58.9 years.[8,9,20–28] **Table 1** summarizes the characteristics and findings from the included studies. Overall, most studies had a low-moderate risk of bias, only the studies by Yi et al.[28], and Dadaci et al.[23], were identified as high risk of bias due to potential selection and comparability bias owing to an insufficient description of case definition, control definition, and selection of controls (**Figure 3A**). The risk of bias assessments for the studies included are presented in **Table 1, Figure 3, and Supplementary Material 3.**

3.1. PRIMARY OUTCOME:

3.1.1. Association of low 25(OH)D serum levels with development of uveitis

Nine studies investigated the relationship between vitamin D levels and NIU development. The studies varied in their specific diagnoses, timing for blood sampling of 25(OH)D, and definition of low vitamin D levels. Their sample sizes (between 39 and 12,555 individuals) and female ratios varied (from 20.5 to 75.5%.). [8,9,20] (**Table 1**) Among these, three reported odds ratios, two compared mean 25(OH)D levels, [21,23] and two reported an inverse correlation with NIU development. [21,27]. Likewise, two studies documented hazard ratios[25], only one being statistically significant[24].

On the other hand, four studies analyzed vitamin D levels as a continuous variable, revealing the effects of increasing 25(OH)D levels on the risk of NIU.[8,9,24,25]. Grotting et al. [9] and Llop et al.[8] found decreased odds of NIU development with every increase in 25(OH)D levels after adjusting for age, gender, race, smoking, history of vitamin D supplementation, and presence a systemic autoimmune disease associated with low vitamin D. Sengler et al.[24] noted a reduced risk for JIA patients. In contrast, Skaaby et al.'s results weren't statistically significant.[25] Lastly, Al-Barry et al.'s research on VKH uveitis patients indicated most were vitamin D deficient. [29]

Similarly, Sengler et al. reported a 5% reduction in the risk of developing uveitis in JIA patients for every ng/mL increase in 25(OH)D levels from 22.1 ng/mL when analyzing samples drawn before developing uveitis (HR 0.95, 95% CI 0.92; 1.00, *P*= 0.03). Skaaby et al. executed a similar analysis for anterior NIU and four ng/mL increases in 25(OH)D levels; however, their results were not statistically significant (HR 1.00 95% CI 0.86-1.17 *P*= 0.999). Moreover, Al-Barry et al. reported the 25(OH)D levels of 39 patients with VKH uveitis and 50 controls. Their findings show that most uveitis patients were vitamin D deficient and reported individual measurements for each patient, with a mean of 18.70 ng/mL. The latter contrasts with the 50 controls, where only 12 had vitamin D deficiency, 23 had insufficiency (21-29 ng/mL), and 15 were vitamin D sufficient; unfortunately, they do not report the measurements for the controls.

Our meta-analysis of five studies with 6,082 patients showed that patients with uveitis had significant lower 25(OH)D levels in serum compared with controls (SMD= -0.39; 95%CI=-0.71, -0.08; *p* 0.0007). However, there was substantial heterogeneity among the studies (I2=79%) (**Figure 4A**). Sensitivity analyses showed changes in results when omitting each study (range -0.53, -0.28). Two studies (González et al.[21] and Dadaci et al.[23]) significantly influenced heterogeneity (**Figure 4B**). The former due to its design and the latter because of its population's unusually low serum 25(OH)D levels.

When only examining studies that measured vitamin D levels at any time before the onset of uveitis (n=786 patients), those who developed uveitis had significant lower levels of vitamin D than controls (SMD=-0.37; CI= -0.56, -0.17) (**Figure 5A**). Similar results (SMD=-0.67; CI= -0.93, -0.41; I2 0%) were obtained when analyzing studies that only measured vitamin D levels one year before uveitis onset (=377 patients) (**Figure 5B**). Moreover, meta-analysis of studies reporting Odds Ratios (n=862 patients) demonstrated that patients with uveitis had more chance of having low vitamin D levels one year before of the disease onset (OR= 2.04; 95% CI=1.55-2.68, p= 0.00001) (**Figure 6**). However, there were slight differences in defining low vitamin D levels among the studies. [8],[9]

3.2. SECONDARY OUTCOMES:

3.2.1. Vitamin D and inflammatory activity of uveitis.

Only one case-control study assessed the relationship between 25(OH)D and NIU inflammatory activity. In that study, Chiu et al.[22] reported that patients with active uveitis had significantly lower serum levels of 25(OH)D with a mean of 18.43 ng/mL (IQR 11.62 –

28.04 ng/mL), compared with the inactive uveitis group, who had a mean of 25.64 ng/mL (IQR 20.83 – 31.65 ng/mL) *(p <0.001).* They also found reduced odds of active uveitis as 25(OH)D serum levels increased (OR 0.98, 95% CI 0.96-0.99). Furthermore, the active group had a higher rate of hypovitaminosis D (<20 ng/mL) compared to the local population-based studies data, with a rate of 54.1% vs. 28.6% *(p<0.001)*.

Moreover, Koller et al.[26] reported lower levels of 25(OH)D levels in patients with active NIU, with a mean of 21.7 ± 9.1 ng/mL, compared with inactive NIU, with a mean of 27.7 ± 11.3 ng/mL with statistical significance (*p= 0.017).* They also found that levels of 25(OH)D <30 ng/mL and <20 ng/mL were associated with increased odds of active disease with odds ratios of 5.963 (95% CI 1.257 - 28.281; p=0.025) and 7.4 (95% CI 1.441 - 37.883; p=0.016) respectively. In addition, they found that the odds of active disease decreased by 6% for every unit increase in 25(OH)D levels (OR=0.944, 95% CI 0.894 - 0.996; p=0.034).

3.2.2. Impact of seasons on NIU diagnosis and activity

Only one study evaluated the impact and association between seasons, 25(OH)D serum levels, and uveitis activity status. Chiu et al.[22], in a prospective case-control study in Australia, found that patients with active uveitis had higher rates of vitamin D deficiency than the local population regardless of the season. No significant difference in UV light exposure was demonstrated between active and inactive group; however, direct sunlight was the most potent mechanism for increasing vitamin D levels and decreased uveitis activity in the fall (active uveitis median, 47 nmol/l; inactive uveitis median, 66 nmol/l; p= 0.022) and winter (active uveitis median, 40 nmol/l; inactive uveitis median, 60 nmol/l; p < 0.01).

3.2.3. Impact of seasons and latitude on vitamin D deficiency

Sobrin et al.[20] analyzed the association between the demographic characteristics of cases and matched controls, including indicators of geographic region and the season in which the laboratory analysis was performed (November to March with less daylight, contrary to April to October). However, similar ORs were found among regions (Northeast OR: 1; Southeast OR: 1.31 (1.02-1.67); West OR: 1.16 (0.86-1.56); unknown geographic region: OR 0.91 (0.20-4.11) p= 0.18).

3.2.4. Influence of race on vitamin D deficiency and non-infectious uveitis diagnosis and disease activity.

Sobrin et al.[20] analyzed the influence of low 25(OH)D levels on NIU development among different races finding that black patients had a lower risk (OR 0.49; 95% CI 0.30-0.80; p= 0.004). Additionally, although Koller et al.[26] did not compare races, they grouped skin phototypes based on the Fitzpatrick Classification and found no statistically significant association between them and uveitis activity.

3.2.5. Impact of the time of deficiency 25(OH)D diagnosis and the diagnosis of non-infectious uveitis.

Four studies detailed 25(OH)D measurement timings. Three were case-control, and one was a prospective multicenter study. In case-control studies, 25(OH)D was measured within a year before NIU diagnosis. The prospective study measured it twice; first between baseline and 9 months, and second between 3 and 36 months, distributing collection times equally between seasons. This study used the first-measured 25(OH)D level to analyze possible correlation with disease activity [24]. Grotting et al.[3] found NIU odds 2.5 times higher with low vitamin D, a fact consistent across various measurement times and after adjusting for demographics. Furthermore, Llop et al.'s [8] analysis associated NIU with low vitamin D levels before or after uveitis onset (OR = 1.92, *p 0.000232*) at any time before uveitis onset (OR = 1.84, *p 0.007*), and within one year before uveitis onset (OR = 2.53, *p 0.001*).

4. DISCUSSION

Our systematic review and meta-analysis aimed to investigate the relationship between vitamin D levels and uveitis diagnosis and activity. Joltikov and Lobo-Chan[30] conducted a systematic review in 2021 on the epidemiology and risk factors associated with non-infectious uveitis. They included studies related to vitamin D and found six studies, comprising three retrospective case-control and three prospective case-control studies, that reported an association between either low vitamin D levels and a higher risk of uveitis or lower vitamin D levels in uveitis cases. These studies were also included in our review. Based on the collective findings, they concluded that there is sufficient evidence to support further investigation into vitamin D supplementation as a possible preventive measure for uveitis development and flares, ideally through experimental studies.

Chan and Zhang et al.[31] conducted a systematic review examining the association between vitamin D and various ocular diseases, including dry eye disease, thyroid eye disease, and uveitis, among others. Their analysis of 11 observational studies found consistent evidence suggesting an association between vitamin D deficiency and uveitis development and severity. We included 10 of the 11 aforementioned studies in our review, with the only exemption being Rohmer et al.[32], which examined vitamin D measurements in patients with sarcoid uveitis. This was excluded from our analysis due to the potential impact of sarcoidosis on vitamin D levels.

The association between vitamin D levels and NIU has been reported in many studies, with most of them indicating an increase in uveitis risk with low vitamin D levels. However, a study by González et al.[25] stands out as the only exemption. None of the 25 uveitis patients in this study had low vitamin D levels. There are a few possible explanations for this outlier. First, hypovitaminosis D is not the only putative risk factor for uveitis and it is clearly possible to develop uveitis having normal levels of vitamin D. This sample size of 25 patients was small and there could be a sampling bias and diminished power to detect an effect of vitamin D on uveitis risk. Taken together, the available studies provide compelling evidence for a relationship between hypovitaminosis D and NIU. However, due to the observational nature of the studies, a causal relationship cannot be definitively established. Nonetheless, a recent case-control study by Susarla et al.[33] utilized Mendelian Randomization (MR) to demonstrate an association between genetic variants that lower 25(OH)D levels and the risk of NIU/scleritis. This study further supports a possible causal relationship between vitamin D deficiency and NIU, considering that MR is not subject to residual confounding or reverse causation.

The role of vitamin D in modulating immune responses is pivotal, and its deficiency might culminate in immune dysregulation[34]. This can potentially spark or worsen uveitis due to the disruption in the balance between immune activation and suppression, causing chronic ocular inflammation. Furthermore, there is a known correlation between vitamin D deficiency and a heightened vulnerability to autoimmune diseases[25]. One hypothesis based on this posits that a lack of vitamin D might either kick-start or expedite autoimmune reactions against ocular tissues, leading directly to uveitis. Another viewpoint focuses on how vitamin D deficiency impacts diverse inflammatory pathways within the body. Such a deficiency might mediate specific inflammatory signaling pathways tied to uveitis, possibly escalating its onset or intensity.

Emerging studies underline the connection between gut microbiota, immunity, and autoimmune disorders. The role of Vitamin D in modulating gut microbiota composition and diversity suggests that its deficiency might tweak the gut flora in ways that perturb immune reactions, potentially steering the onset of uveitis through interactions between microbiota and immunity[35]. Moreover, there is a confluence between certain genetic determinants linked to both uveitis risk and vitamin D metabolism[33]. This raises the speculation that vitamin D deficiency could interplay with these genetic elements, heightening uveitis susceptibility during prolonged periods of low levels of systemic vitamin D. It is also essential to recognize that vitamin D levels can be shaped by factors such as sun exposure and dietary patterns. Hence, those who, due to lifestyle choices or geographical constraints, have minimal sun exposure or inadequate vitamin D in their diet might face a magnified uveitis risk. Nevertheless, establishing a direct causal relationship between vitamin D paucity and uveitis still demands rigorous clinical trials and detailed prospective studies. Often, medical conditions emerge from a mixture of genetic, environmental, and immune-centric factors, and uveitis is likely no exception.

4.1. Potential biases and limitations

The present review possesses some limitations. Firstly, our data are derived from observational studies, which may introduce considerable heterogeneity into the analyses. Nevertheless, we endeavoured to control for this heterogeneity using various sensitivity analyses. A second limitation pertains to the relatively small sample size. However, this should be understood in the context of the specific scenario under study and the low prevalence of uveitis. The third limitation is the inherent heterogeneity of the data, which may confound the interpretation of the results. This variability arises from factors such as the type

of test employed in the studies, the clinical status of the patients, and the sociodemographic variables within each study. To further bolster the evidence for potential treatment recommendations regarding vitamin D supplementation and target values in the future, it is advised to measure 25(OH)D levels, as proposed by the Endocrine Society Clinical Practice Guideline (ESCPG).[36] Additionally, patients should be classified as having vitamin D insufficiency when 25(OH)D levels range from 21-29 ng/mL and as having vitamin D deficiency when levels are ≤20 ng/mL, in accordance with the ESCPG. This standardization will ensure that study analyses are both homogeneous and comparable.

5. Conclusion

Current evidence supports a significant association between hypovitaminosis D and the development of NIU. Our results show that patients with hypovitaminosis D are 2.04 times more likely to develop NIU than subjects with vitamin D sufficiency. However, these conclusions are based on limited data from a few studies, suggesting that further research in this field is necessary. In future investigations, authors should standardize the measurement technique and cut-off values of serum vitamin D to reduce heterogeneity in meta-analysis.

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FIGURE LEGENDS:

Figure 1. Immunomodulation mediated by Vitamin D under Normal Conditions. The 1,25(OH)2VD impacts a range of immune cells including macrophages, dendritic cells (DCs), as well as T and B lymphocytes. While macrophages and DCs inherently have the vitamin D receptor (VDR) present, T lymphocytes only exhibit increased VDR expression after being activated. The presence of $1,25(OH)_2VD3$ enhances its own action in macrophages and monocytes by amplifying the VDR expression and the CYP27B1 protein. Some signals transmitted by Toll-like receptors (TLRs) can further enhance VDR expression. Moreover, $1,25(OH)_2VD3$ plays a role in stimulating monocyte growth and boosting the release of interleukin-1 (IL-1) and the antimicrobial peptide cathelicidin in macrophages. Dendritic cells undergo a reduction in their maturation due to 1,25(OH)2VD3, leading to restrained expression of MHC class II, CD40, CD80, and CD86. It also curtails the IL-12 secretion in DCs but encourages IL-10 production. In the context of T lymphocytes , $1,25(OH)_2VD$ suppresses the release of IL-2, IL-17, and interferon-γ (IFNγ) while also moderating the cytotoxic actions and growth of both CD4+ and CD8+ T lymphocytes. It is suggested that $1,25(OH)_2VD$ may also foster the rise of FOXP3+ regulatory T lymphocytes and IL-10-producing regulatory T lymphocytes of type 1. Additionally, this vitamin impedes the growth of B lymphocytes, their evolution into plasma cells, and the synthesis of immunoglobulins. Adapted from Mora et al.[42]

Figure 2. PRISMA flowchart of the systematic review

Flowchart of the literature databases search of the systematic review.

Figure 3.A Risk of bias of case-control: D1: Bias due to Selection – Domain scoring: 0-1 (High); 2(Some Concerns); 3+(Low); D2: Bias due to Comparability – Domain scoring: 0 (High); 1(Some Concerns); 2+(Low); D3: Bias due to Exposure – Domain scoring: 0(High); 1(Some Concerns); 2+(Low) **B.** Risk of bias of Cross-Sectional: D1: Bias due to External Validity – Domain scoring: 0-1 (High); 2(Some Concerns); 3+(Low); D2: Bias due to Internal Validity – Domain scoring: 0-2 (High); 3(Some Concerns); 4+(Low) **C.** Risk of bias of cohorts: D1: Bias due to Selection – Domain scoring: 0-1 (High); 2(Some Concerns); 3+(Low); D2: Bias due to Comparability – Domain scoring: 0 (High); 1(Some Concerns); 2+(Low); D3: Bias due to Outcome – Domain scoring: 0(High); 1(Some Concerns); 2+(Low).

Figure 4. Meta-analysis of mean vitamin D levels measured at any moment before or after uveitis onset. **A.** Forrest plot of meta-analysis of the mean vitamin D levels measured at any moment before or after uveitis onset from the five included studies with a heterogeneity of I2=79% (*P*= 0.01*).* **B.** Forrest plot of meta-analysis of the mean vitamin D levels measured at any moment before or after uveitis onset after excluding González et al.[21] and Dadaci et al.[23] studies for achieving a heterogeneity of I2=56% (*P*= 0.0006).

Figure 5. A. Meta-analysis of mean vitamin D levels measured at any moment before uveitis onset. Forrest plot of meta-analysis of the mean vitamin D levels measured at any moment before uveitis onset, with heterogeneity of I2=27% (*p < 0.0001*). **B.** Meta-analysis of mean

vitamin D levels measured one year before uveitis onset. Forrest plot of meta-analysis of the mean vitamin D levels measured one year before uveitis onset with heterogeneity of I2=0% (*p 0.0001*).

Figure 6. OR meta-analysis of low vitamin D levels measured one year before uveitis onset and uveitis.

Forrest plot of odds ratio meta-analysis, evidencing the association between low vitamin D levels one year before uveitis onset and uveitis with an OR of 2.04 (95%, CI=1.55-2.68, *P*= 0.00001).

DECLARATIONS

Authors contribution

WRC, JSPS and MSM conceived and drafted the study. JSPS, MSM, PTMV, LFPP, MAFM collected all data. CCG, WRC, DLC, and JSPS analyzed and interpreted the data. JSPS, MSM, PTMV, MAFM, and CCG prepared the initial draft of the manuscript. ADLT supervised the project. ADLT, RA, LS, IP provided critical insights, reviewed the draft and edited the final version. All authors revised the manuscript for important intellectual content and approved the final manuscript.

Declaration of competing interest

None

Funding/Support: This study did not receive funding or financial support.

Data availability

Data will be made available on request.

Acknowledgements

None

Table 1. Observational studies meeting inclusion criteria

Author; Country; Year	Study design	Follow-up period	Sample size	Age Mean ± SD or Median (IQR) years	% Female	Risk of bias
Sobrin et al. USA 2018	Case-control	January 1, 2000, to December 31, 2016	558 cases (NIU) 2790 controls	58.9 +/- 14.7 years	75.4	Low risk
A Grotting et al. USA 2017	Case-control	March 1, 2008, to December 12, 2015.	100 cases (NIU) 100 controls	Cases: 51.8 +/- 16.2 years Controls: 53.6 +/- 15.9	73.5	Low risk
M Llop et al. USA 2019	Case-control	2005-2016	NIU 333 Controls 329	Cases: 51.5 +/- 16.4 years Controls: 51.5 +/- 15.1	NIU 54.6 Controls 72.6	Low risk
Mitulescu et al. Rumania 2016	Case-Control	March 2014 and April 2015	52 total 34 AS (Only 11 have AAU)	AS: 42.5 +/- 13 Controls: 34.25 +/- 13	AS: 20.5 Controls: 55.5	High risk
Yi et al. China 2011	Case-Control	November 1, 2009 to March 31, 2010	41 Total, 25 cases with VKH 16 healthy controls	Cases: mean 38.4 years Controls: mean 40.5 years	Cases: 48 Controls: 43.7 Total: 46.3	Low risk
Chiu et al. Australia 2020	Cross Sectional Study.	From January to August 2017	151 Cases (NIU) 74 (Active NIU) 77 (Inactive NIU) 594 Controls	NIU Cases 43 years (33+/- 55) Active NIU 40 years (31+/- 51) Inactive NIU 46 years (34 +/- 61) Controls 52 years (39 +/- 65)	Active NIU 56.8 Inactive NIU 55.8 Controls 56.7	Low risk
Dadaci et al. Turkey 2017	Observational case-control study	Between May and October 2015	40 Total 20 Cases of idiopathic or HLA-B27-associated AAU 20 Controls	AAU Cases (43.5 +/- 16.25 years) Controls (36.3 +/- 13.59 years)	AAU Cases 75 Controls 57.1	High Risk
González et al. USA 2018	Cross-sectional Population-based study.	2009-2010	5106 Subjects 27 cases (NIU)	No self-reported uveitis 44 +/- 14 years Self-reported uveitis 53 +/- 13 years	No self-reported uveitis 51.5 Self-reported uveitis 63	Low risk
Sengler et al. Germany 2018	Prospective observational, controlled multicenter study	2003 - 2006	A total of 954 patients, of which 360 had 25(OH)D measurements (61 with NIU and 299 without NIU)	Patients with JIA with 25(OH)D measurement 7.1 ± 4.6 years All patients 7.9 ±4.8 years	Patients with JIA with 25(OH)D measurement 67.5 All patients 67.2	

Skaaby et al. Denmark 2014	Prospective population-based study	1993–1994 1999–2001 2006 - 2008	Total: 12.555 29 NIU Monica10: 2,649 Inter99: 6,497 Health2006: 3409	55.4 ± 10.8 46.1 ± 7.9 49.4 ± 13.0	Monica10: 49.8 Inter99: 50.8 Health2006: 55.1	Low risk
Koller et al. Brazil 2023	Cross-sectional study	July 2019 to December 2021	67 cases (NIU) 45 (Active NIU) 22 (Inactive NIU)	All cases 41.6 ± 11.7	70.1	Low risk

AAU: Acute anterior uveitis; AS: Ankylosing Spondylitis; NIU: Non-Infectious uveitis; VKH: Vogt-Koyanagi-Harada syndrome.

- Recent publications have linked vitamin D with non-infectious uveitis (NIU).
- Hypovitaminosis D has been associated with 2.5 times more chance to develop NIU.
- In this study, vitamin D levels were found to be lower at any time before NIU onset.
- Hypovitaminosis D shows an OR of 2.04 ($p < 0.00001$) for NIU development.
- Evidence on hypovitaminosis D impact in NIU still inconclusive.
- Consider screening for hypovitaminosis D in NIU patients or at-risk individuals.

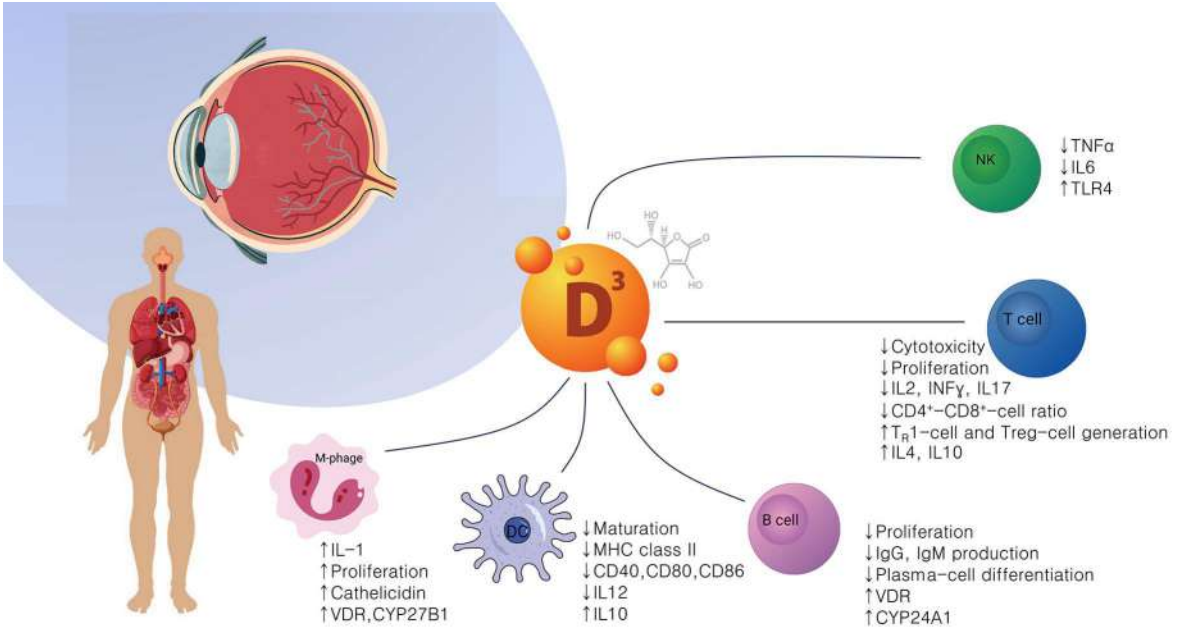
NK
↓TNFα
↓IL6
↑TLR4
D3
T cell
↓Cytotoxicity
↓Proliferation
↓IL2, INFγ, IL17
↓CD4+–CD8+–cell ratio
↑TR1–cell and Treg–cell generation
↑IL4, IL10
M-phage
↑IL–1
↑Proliferation
↑Cathelicidin
↑VDR,CYP27B1
DC
↓Maturation
↓MHC class II
↓CD40,CD80,CD86
↓IL12
↑IL10
B cell
↓Proliferation
↓IgG, IgM production
↓Plasma–cell differentiation
↑VDR
↑CYP24A1

Figure 1

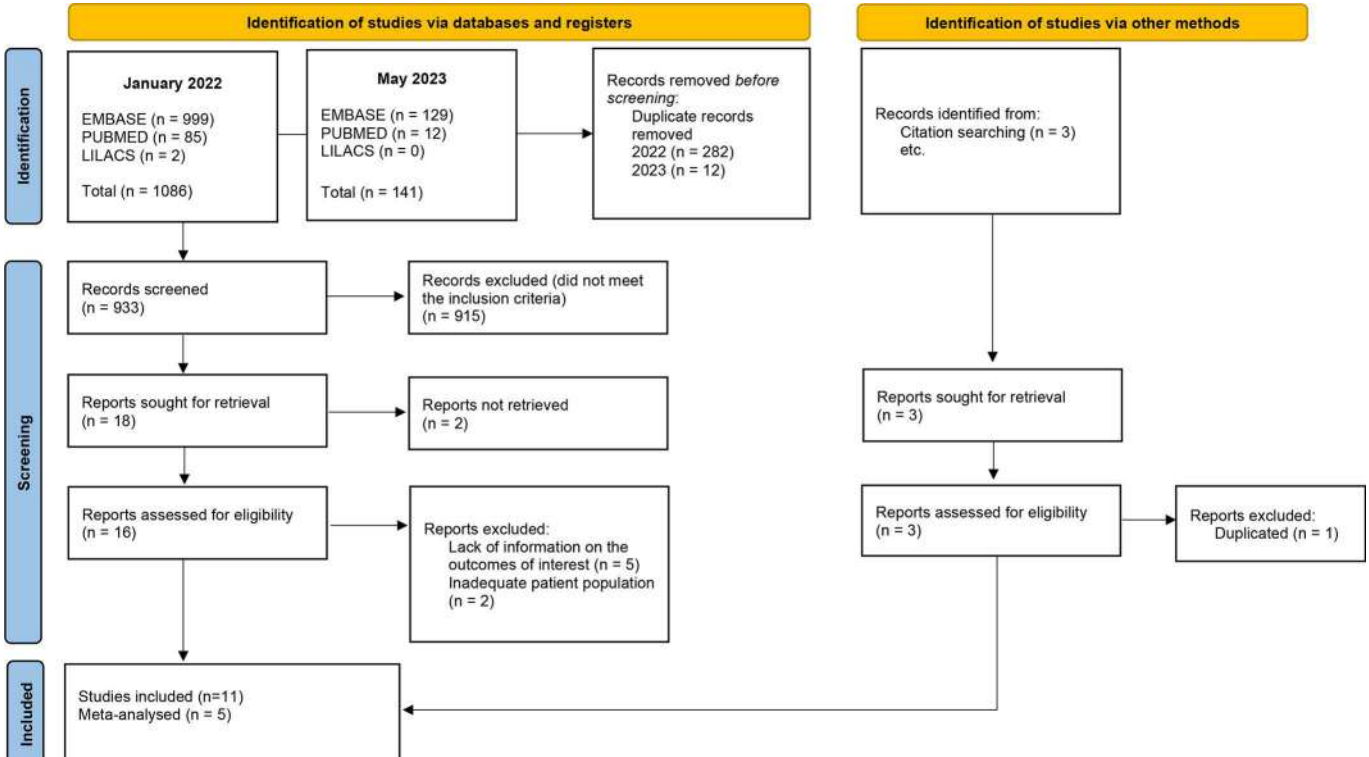
Identification of studies via databases and registers
Identification of studies via other methods
Identification
Screening
Included
January 2022
EMBASE (n = 999)
PUBMED (n = 85)
LILACS (n = 2)
Total (n = 1086)
May 2023
EMBASE (n = 129)
PUBMED (n = 12)
LILACS (n = 0)
Total (n = 141)
Records removed before screening:
Duplicate records removed
2022 (n = 282)
2023 (n = 12)
Records identified from:
Citation searching (n = 3)
etc.
Records screened
(n = 933)
Records excluded (did not meet the inclusion criteria)
(n = 915)
Reports sought for retrieval
(n = 18)
Reports not retrieved
(n = 2)
Reports sought for retrieval
(n = 3)
Reports assessed for eligibility
(n = 16)
Reports excluded:
Lack of information on the outcomes of interest (n = 5)
Inadequate patient population (n = 2)
Reports assessed for eligibility
(n = 3)
Reports excluded:
Duplicated (n = 1)
Studies included (n=11)
Meta-analysed (n = 5)

Figure 2


A
Risk of bias Newcastle–Ottawa
D1
D2
D3
Overall
Study
Yi et al. (2011)
Grotting et al. (2016)
Dadaci et al. (2016)
Llop et al. (2018)
Sobrin et al. (2018)
D1: Bias due to Selection - Domain scoring: 0-1 (High); 2(Some Concerns); 3+(Low)
D2: Bias due to Comparability - Domain scoring: 0 (High); 1(Some Concerns); 2+(Low)
D3: Bias due to Exposure - Domain scoring: 0(High); 1(Some Concerns); 2+(Low)
Judgement
High
Some Concerns
Low
B
Risk of bias Hoy et al
D1
D2
Overall
Study
Mitulescu et al. (2016)
González et al. (2018)
Chiu et al. (2019)
K Koller et al. (2023)
D1: Bias due to External Validity - Domain scoring: 0-1 (High); 2(Some Concerns); 3+(Low)
D2: Bias due to Internal Validity - Domain scoring: 0-2 (High); 3(Some Concerns); 4+(Low)
Judgement
High
Some Concerns
Low
C
Risk of bias Newcastle–Ottawa
D1
D2
D3
Overall
Study
Skaaby et al. (2015)
Sengler et al. (2018)
D1: Bias due to Selection - Domain scoring: 0-1 (High); 2(Some Concerns); 3+(Low)
D2: Bias due to Comparability - Domain scoring: 0 (High); 1(Some Concerns); 2+(Low)
D3: Bias due to Outcome - Domain scoring: 0(High); 1(Some Concerns); 2+(Low)
Judgement
Some Concerns
Low

Figure 3

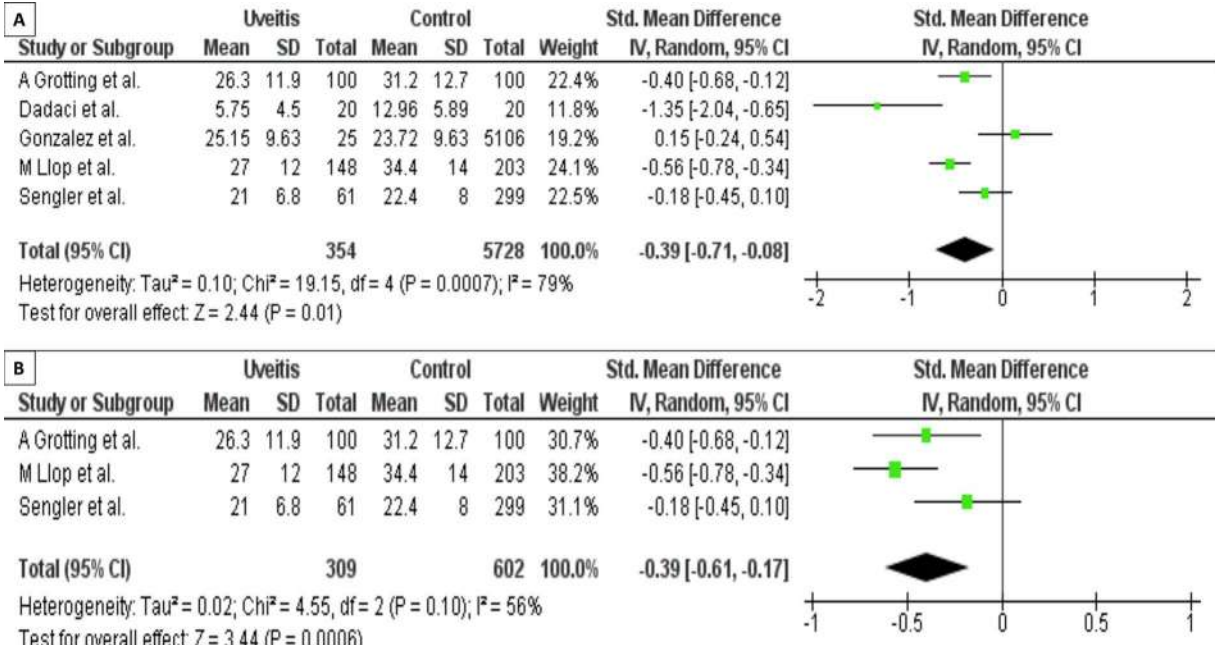
A
Uveitis
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
A Grotting et al. 26.3 11.9 100 31.2 12.7 100 22.4% -0.40 [-0.68, -0.12]
Dadaci et al. 5.75 4.5 20 12.96 5.89 20 11.8% -1.35 [-2.04, -0.65]
Gonzalez et al. 25.15 9.63 25 23.72 9.63 5106 19.2% 0.15 [-0.24, 0.54]
M Llop et al. 27 12 148 34.4 14 203 24.1% -0.56 [-0.78, -0.34]
Sengler et al. 21 6.8 61 22.4 8 299 22.5% -0.18 [-0.45, 0.10]
Total (95% CI) 354 5728 100.0% -0.39 [-0.71, -0.08]
Heterogeneity: Tau² = 0.10; Chi² = 19.15, df = 4 (P = 0.0007); I² = 79%
Test for overall effect: Z = 2.44 (P = 0.01)
-2
-1
0
1
2
B
Uveitis
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
A Grotting et al. 26.3 11.9 100 31.2 12.7 100 30.7% -0.40 [-0.68, -0.12]
M Llop et al. 27 12 148 34.4 14 203 38.2% -0.56 [-0.78, -0.34]
Sengler et al. 21 6.8 61 22.4 8 299 31.1% -0.18 [-0.45, 0.10]
Total (95% CI) 309 602 100.0% -0.39 [-0.61, -0.17]
Heterogeneity: Tau² = 0.02; Chi² = 4.55, df = 2 (P = 0.10); I² = 56%
Test for overall effect: Z = 3.44 (P = 0.0006)
-1
-0.5
0
0.5
1

Figure 4

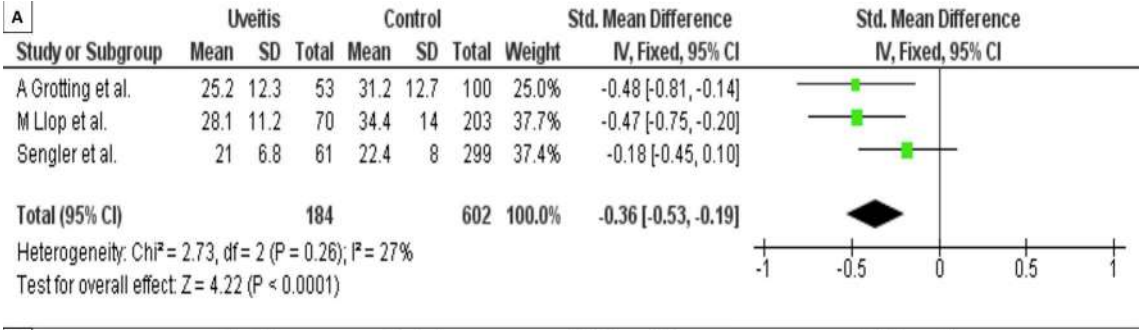
A
Uveitis
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
A Grotting et al. 25.2 12.3 53 31.2 12.7 100 25.0% -0.48 [-0.81, -0.14]
M Llop et al. 28.1 11.2 70 34.4 14 203 37.7% -0.47 [-0.75, -0.20]
Sengler et al. 21 6.8 61 22.4 8 299 37.4% -0.18 [-0.45, 0.10]
Total (95% CI) 184 602 100.0% -0.36 [-0.53, -0.19]
Heterogeneity: Chi² = 2.73, df = 2 (P = 0.26); I² = 27%
Test for overall effect: Z = 4.22 (P < 0.0001)
-1
-0.5
0
0.5
1
B
Uveitis
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
A Grotting et al. 22.8 10.4 33 31.2 12.7 100 41.8% -0.69 [-1.09, -0.28]
M Llop et al. 25.5 10.4 41 34.4 14 203 58.2% -0.66 [-1.00, -0.32]
Total (95% CI) 74 303 100.0% -0.67 [-0.93, -0.41]
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 5.05 (P < 0.00001)
-1
-0.5
0
0.5
1

Figure 5

Study or Subgroup	Uveitis Events	Uveitis Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
A Grotting et al.	67	100	44	100	20.3%	2.58 [1.46, 4.59]
M Llop et al.	167	333	114	329	79.7%	1.90 [1.39, 2.59]
Total (95% CI)		**433**		**429**	**100.0%**	**2.04 [1.55, 2.68]**
Total events	234		158			

Heterogeneity: $Chi^2 = 0.86$, $df = 1$ ($P = 0.35$); $I^2 = 0\%$

Test for overall effect: $Z = 5.08$ ($P < 0.00001$)

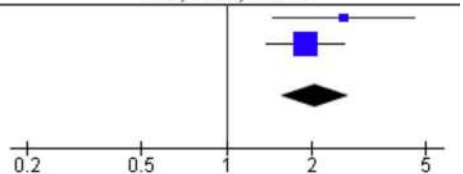

Figure 6