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# Vitamin D Supplementation and Mortality Risk in Chronic Kidney Disease a Meta-Analysis

Atef H. Aljahdaly[1], KHALID S. ALMALKI[2], HIFTHI K.AL ALTHEEB[3], Dr. Shams Mohammed Alshehail[4], Wejdan Ali Sulieman Makki[5], Shaher Mohammed Aljedaani[6], Nora Abdullah Al-smari[7], Dalal Ali AlKhayri[8], ALI ABDUULAH ALGHAMDI[9], EBTHAL AHMED ALMEWALED[10], Jamaan Rajab Jamaan Azhrani[11], Tahani Abed Aboud Almuwallad[12], Abdullah Ali Almuntashiri[13]

***Abstract***

*Background: Chronic kidney disease (CKD) is a greatly prevalent condition worldwide in which the kidneys are functionally and/or structurally damaged. Vitamin D deficiency is very common in CKD, influencing over eighty percent of cases in pre-dialysis.Aim: To evaluate the impact of vit. D supplementation on mortality risk and related clinical results in patients with CKD.Patients and methods: Cochrane Library, PubMed, Embase, and Web of Science have been searched up to December 2021 for observational and interventional studies comparing vitamin D non-users and users in adult CKD cases. The 1ry result was all-cause mortality; 2ry results involved dialysis vintage, phosphorus, calcium, hemoglobin, intact parathyroid hormone (iPTH), alkaline phosphatase, lipid profile, and albumin. Data were pooled utilizing Review Manager 5.4.1, with fixed- or random-influences models regarding heterogeneity.Results: Eight studies involving 57,429 patients were included. Vit.D supplementation has been correlated with a significant reduction in mortality risk (OR = 0.54, 95% CI = 0.35–0.81, p = 0.003). Significant reductions in iPTH were observed, while other biochemical parameters showed insignificant variances between groups.Conclusion: Vitamin D supplementation in CKD is correlated with improved survival and favorable effects on parathyroid hormone, supporting its therapeutic role.*

***Keywords:*** *Chronic Kidney Disease, Mortality, Vitamin D.*

## Introduction

CKD is a widely frequent disorder globally characterized by functional and/or structural damage of the kidneys. Consequently, the kidneys diminish their capacity to effectively eliminate waste materials and execute key endocrine activities. The primary etiologies of chronic kidney disease involve diabetes mellitus, chronic pyelonephritis, hypertension, chronic glomerulonephritis,

[1] University medical services center, King Abdulaziz University,Jeddah ,Saudi Arabia.
[2] University medical services center, King Abdulaziz University.Jeddah .Saudi Arabia.
[3] University medical services center, King Abdulaziz University.Jeddah .Saudi Arabia
[4] University medical services center, King Abdulaziz University.Jeddah .Saudi Arabia
[5] Pharmacist- King Abdulaziz Hospital
[6] Pharmacist- Health Surveillance Centers – King Abdulaziz International Airport – Jeddah
[7] Nursing Technician- King Fahad General Hospital ( PHC Al Bawadi 1 )
[8] Lab technician- Medical services - MOI
[9] Radiology Technician- Health Surveillance Centers – King Abdulaziz International Airport – Jeddah
[10] Nurse- Health Surveillance Centers – King Abdulaziz International Airport – Jeddah
[11] Nurse- Health Surveillance Centers – King Abdulaziz International Airport – Jeddah
[12] Nursing Specialist- Health Surveillance Centers – King Abdulaziz International Airport – Jeddah
[13] Nursing Specialist- Health Surveillance Centers – King Abdulaziz International Airport – Jeddah

prolonged application of congenital anomalies, anti-inflammatory drugs, autoimmune disorders, polycystic kidney disease, Alport syndrome, and extended acute renal failure **(1)**.

Vit. D is a crucial steroid hormone in the body. Its primary role is the regulation of skeletal health and mineral homeostasis by modulating $Ca^{+2}$ and phosphate metabolism in key physiological organs, involving the colon, hepatic, bone, and kidneys **(2)**.

Vit. D insufficiency is prevalent in chronic kidney disease, impacting over eighty percent of pre-dialysis cases. Vit. D deficiency occurs early in the disease and typically exacerbates with the increasing decline of renal function (Al-Taie & Khattak, 2024). While the processes behind vitamin D insufficiency remain incompletely elucidated, data indicate a robust inverse correlation between blood vitamin D levels and morbidity and death in these populations **(3)**.

Numerous epidemiological studies indicate that insufficient vit. D levels may be correlated with all-cause mortality and various non-skeletal chronic diseases, including type II diabetes, cardiovascular disorders, and some types of cancer **(4)**.

Vit. D therapy has long been a significant and prevalent treatment for CKD and mineral and bone disorder (MBD). Vit. D compounds are categorized as nutritious or active based on their direct interaction with the vit. D receptor **(5)**.

Supplementation with vit. D, its analogues, or its active form is suggested based on the stage of chronic kidney disease and the existence or severity of secondary hyperparathyroidism (SHPT) **(6)**.

This meta-analysis aimed to assess the influence of vit. D supplementation on mortality risk and associated clinical results in cases with chronic kidney disease.

## Patients and Methods

### Search Strategy

We carried out a systematic literature search to recognize relevant studies on vitamin D supplementation and its association with mortality and clinical results in cases with CKD. Electronic databases involving Cochrane Library, Embase, PubMed/MEDLINE, and Web of Science have been searched from inception up to December 2021. The search terms involved combinations of keywords and MeSH terms like "vitamin D," "calcitriol," "alfacalcidol," "paricalcitol," "chronic kidney disease," "CKD," "end-stage renal disease," "ESRD," "hemodialysis," "mortality," "survival," "death," and "meta-analysis." No language restrictions were applied. Additional studies have been recognized by manually reviewing reference lists of relevant reviews, retrieved articles, and conference abstracts. The search has been carried out independently by two reviewers, with discrepancies resolved through consensus.

### Inclusion and Exclusion Criteria

**Inclusion criteria**: observational (cohort, cross-sectional, or case-control) or interventional studies involving adult patients (≥18 years) with CKD (any stage, including pre-dialysis and dialysis-dependent), comparison of vitamin D supplementation versus no supplementation or placebo, and reporting of at least one outcome of interest, including all-cause mortality (primary outcome) or secondary outcomes such as dialysis vintage, alkaline phosphatase, hemoglobin, calcium, phosphorus, iPTH, total cholesterol, HDL cholesterol, or albumin, provision of sufficient data for extraction, and inclusion of means with standard deviations (SD) for continuous outcomes or event counts for binary outcomes.

**Exclusion criteria included** animal studies, case reports, editorials, or reviews; studies focused solely on pediatric populations or non-CKD conditions; duplicate publications or overlapping patient cohorts; studies lacking a control group; and insufficient information for meta-analysis.

### Data Extraction

Two independent reviewers extracted information from eligible studies utilizing a standardized form. Extracted data involved research characteristics (author, year, country, design, research period, sample size), case demographics (age, BMI, sex, dialysis vintage), intervention details (type and period of vitamin D supplementation), and outcomes (means/SD for continuous variables, event rates for mortality). For mortality, data were extracted as odds ratios (OR) or converted to dichotomous events where possible.

**Quality Assessment:** The possibility of bias has been evaluated utilizing the ROB1 instrument for case-control studies.

### Statistical Analysis

All data analysis has been conducted utilizing Review Manager version 5.4.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. We computed the odds ratio with a ninety-five percent CI for binary findings. We computed the mean difference with a 95% confidence interval for continuous results. To determine the overall effect and estimate the ninety-five percent CI, we utilized a fixed-influence model utilizing the Mantel-Haenszel method in the lack of heterogeneity among studies. A random-influences model utilizing the DerSimonian and Laird approach was selected. The Q statistic and $I^2$ test were assessed to evaluate heterogeneity among studies, indicating the percentage of variability in the influence estimates. A P-value of below 0.05 has been deemed significant.

## Results

A total of 8 studies have been selected for the present analysis, involving a total of 57429 cases. The publication year ranged from 1990 to 2021. 3 studies have been conducted in Japan; baseline characteristics of involved studies are illustrated in **Table 1**.

| Last name of First Author | year | country | Study period | | Study design | Sample Size | |
|---|---|---|---|---|---|---|---|
| | | | from | to | | Vitamin D users' group | Vitamin D non-users' group |
| Mariko Ogawa, 2021(7) | 2021 | Japan | 2005 | 2010 | prospective clinical study | 89 | 101 |
| G. Jean, 2010 (8) | 2010 | France | 2005 | 2009 | cross-sectional analysis | 150 | 174 |
| Sachiyo Sugiura, 2009 (9) | 2009 | Japan | 1992 | 2008 | retrospective cohort study | 107 | 558 |
| Francesca | 2008 | Spain | 1996 | 2007 | Prospective | 20754 | 17312 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Tentori, 2008 (10) | | | | | observational cohort | | |
| Abigail B Shoben, 2008 (11) | 2008 | USA | | | | 429 | 989 |
| Manuel Naves-Dı´az, 2008 (12) | 2008 | Spain | | | | 7203 | 8801 |
| Csaba P. Kovesdy, 2008 (13) | 2008 | USA | 1990 | 2007 | | 258 | 262 |
| Tetsuo Shoji, 2004(14) | 2004 | Japan | | | observational study | 162 | 80 |

**Table 2. Case's characteristics:** The mean participants' age in the examined groups was 63.28, ranging from 24 to 79 years; BMI was 23.7, ranging from 18 to 37 kg/m²; and gender has been stated in 7 studies with 56909 females and males, as illustrated in table 2.

| **Last name of First Author** | **Age (year)** | | | | | | **Sex** | | | | | | **BMI (kg/m$^2$)** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Vitamin D users' group** | | | **Vitamin D non-users' group** | | | **Vitamin D users' group** | | | **Vitamin D non-users' group** | | | **Vitamin D users' group** | | | **Vitamin D non-users' group** | | |
| | **mean** | **SD** | **total** | **mean** | **SD** | **total** | **Male** | **Female** | **total** | **Male** | **Female** | **total** | **mean** | **SD** | **total** | **mean** | **SD** | **total** |
| Mariko Ogawa, 2021 | 60.9 | 11 | 89 | 61 | 12.5 | 101 | 60 | 29 | 89 | 57 | 44 | 101 | 21.1 | 2.8 | 89 | 21.8 | 4.8 | 101 |
| G. Jean, 2010 | 66 | 15 | 150 | 71.1 | 12 | 174 | 61 | 89 | 150 | 57 | 117 | 174 | 24.7 | 4 | 150 | 25.7 | 4 | 174 |
| Sachiyo Sugiu | 62 | 14.2 | 107 | 67.9 | 12.2 | 558 | 59 | 48 | 107 | 372 | 186 | 558 | 23 | 3.7 | 107 | 23.1 | 3.6 | 558 |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ra, 2009 | | | | | | | | | | | | | | | | | | |
| Francesca Tentori, 2008 | 61.3 | 14.8 | 20754 | 62.1 | 14.9 | 17312 | 9972 | 107822 | 20754 | 12017 | 5295 | 17312 | | | | | | |
| Abigail B Shoben, 2008 | 69 | 10.3 | 4299 | 70.3 | 10.3 | 9899 | 4200 | 9 | 4299 | 9974 | 15 | 9899 | 26.7 | 62.2 | 4299 | 564 | 57 | 9899 |
| Manuel Naves-Díaz, 2008 | 53.9 | 15.9 | 72003 | 55.6 | 16 | 88001 | 4199 | 3004 | 72003 | 51400 | 3661 | 88001 | 23.8 | 4.6 | 72003 | 23.7 | 4.7 | 88001 |
| Csaba P. Kovesdy, 2008 | 70.8 | 10.2 | 258 | 68.6 | 10.2 | 262 | | | | | | | 29.2 | 6 | 258 | 28.8 | 5.6 | 262 |
| Tetsuo Shoji, 2004 | 55.5 | 10.8 | 162 | 56.5 | 10.3 | 80 | 91 | 71 | 162 | 39 | 41 | 80 | 21.3 | 2.7 | 162 | 21.5 | 2.6 | 80 |

**Dialysis vintage (months):** Two studies reported (dialysis vintage) and all could be applied. An insignificant heterogeneity was observed. Therefore, a random-influence model has been applied for analysis ($I^2$ equal to 0%, p equal to 0.65). The combined mean variance & ninety-five percent

CI was 1.33 (-13.49 to 16.16). The combined outcome illustrates statistically non-significant variance between groups according to dialysis vintage (Z = 0.18, P = 0.86).

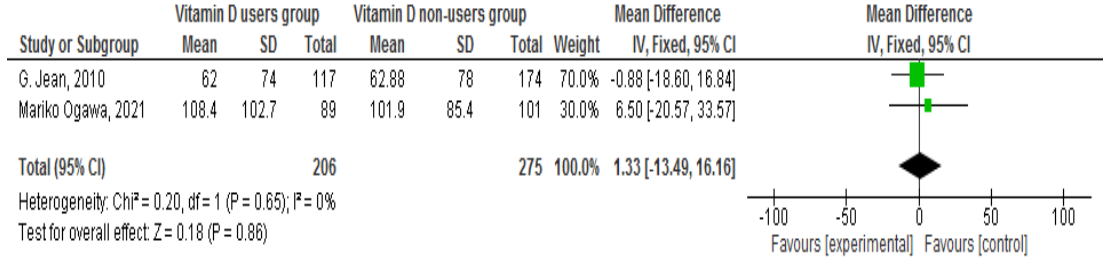


**Figure (1):** Forest plot of operative time illustrates statistically non-significant variance among Vit. D users' and Vit. D non-users' groups.

**Hemoglobin (g/dl):** Six studies stated (hemoglobin), and all could be utilized. A significant heterogeneity has been detected. Therefore, a random-influence model has been utilized for analysis ($I^2$ = 94%, p below or equal to 0.001). The combined mean variance and ninety-five percent CI was 0.13 (-0.04 to 0.30). The combined outcome illustrates statistically insignificant variance among groups according to hemoglobin (Z equal to 1.50, P equal to 0.13).

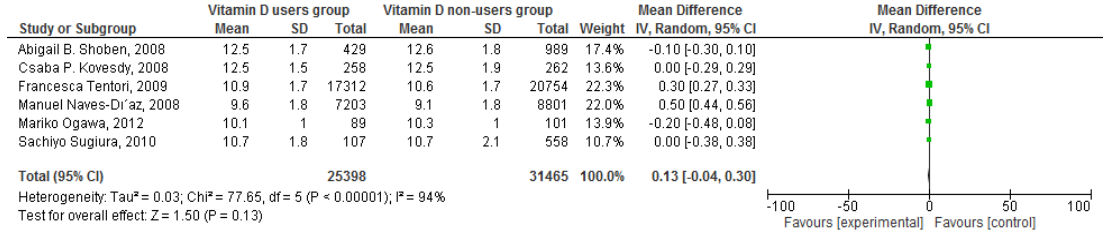


**Figure (2):** The forest plot of hemoglobin illustrates a statistically insignificant difference between the vitamin D users and the vitamin D non-users' groups.

**Calcium (mg/dL):** Seven studies stated (calcium), and all could be utilized. A significant heterogeneity was detected. Therefore, a random-influence model has been applied for analysis ($I^2$ = 94%, p < 0.0001). The combined mean variance and ninety-five percent confidence intervals were -0.03 (-0.12 to 0.05). The combined outcome shows statistically non-significant variance among groups according to calcium (Z equal to 0.77, P equal to 0.44).

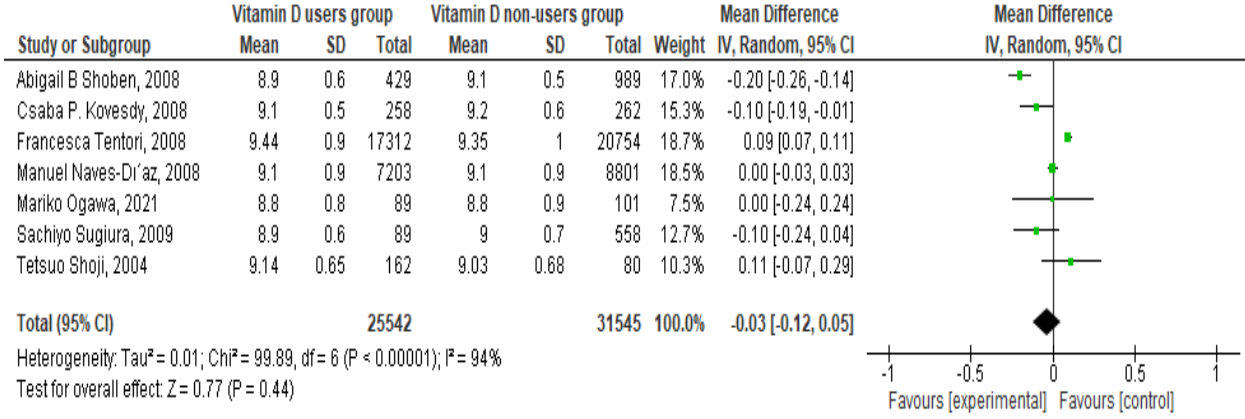


**Figure (3):** Forest plot of calcium illustrates statistically insignificant variance between Vit. D users and Vit. D non-users' groups.

**Phosphorous (mg/dL):** Seven studies stated (phosphorous), and all could be utilized. A significant heterogeneity has been observed. Therefore, a random-influence model has been applied for analysis ($I^2$ = 88%, p below 0.00001). The combined mean variance and 95% confidence intervals were -0.01 (-0.11 to 0.09). The combined outcome shows statistically insignificant variance among groups according to phosphorus (Z equal to 0.22, P equal to 0.83).

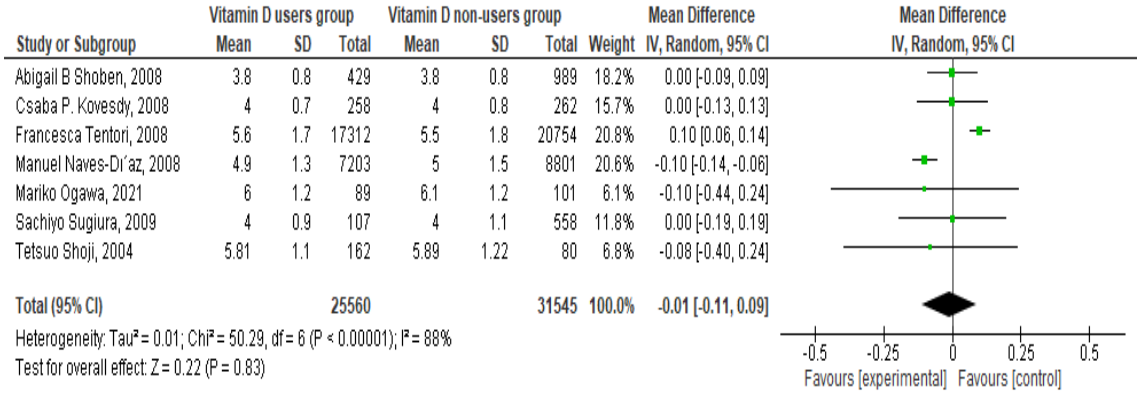


**Figure (4):** Forest plot of Phosphorous shows statistically non-significant variance among Vitamin D users and Vitamin D non-users' groups.

**Intact parathyroid hormone (pg/mL):** seven studies reported (intact parathyroid hormone), and all can be utilized. A significant heterogeneity has been observed. Therefore, a random-influence model was applied for analysis ($I^2$ = 99%, p below or equal to 0.001). The combined mean variance & ninety-five percent CI was 71.23 (36.10 to 106.36). The combined result shows statistically significant variance between groups according to intact parathyroid hormone (Z = 3.97, $P \leq 0.001$).

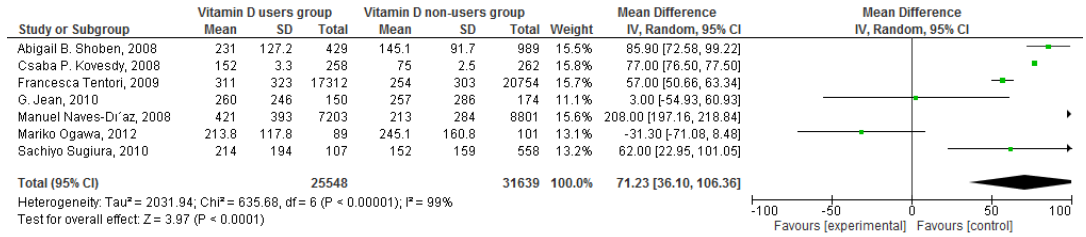


**Figure (5):** Forest plot of Intact parathyroid hormone shows statistically significant variance among Vitamin D users and Vitamin D non-users' groups.

**Total cholesterol (mg/dL):** 3 studies stated (total cholesterol), and all could be applied. An insignificant heterogeneity has been observed. Therefore, a fixed-influence model has been applied for analysis ($I^2$ = 26%, p = 0.26). The combined mean variance and ninety-five percent CIs was -0.21 (-1.76 to 1.34). The combined outcome shows statistically non-significant variance among groups according to hemoglobin (Z equals 0.27, P equals 0.79).

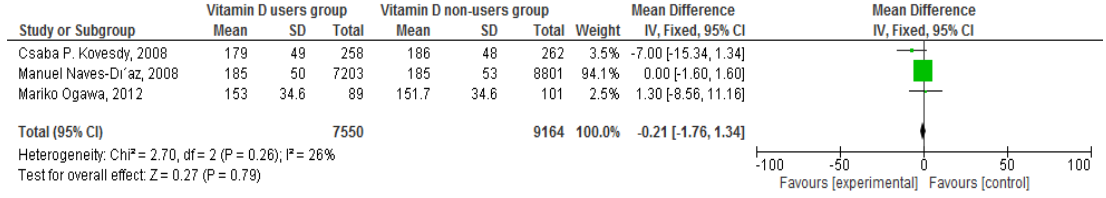


**Figure (6):** Forest plot of Total cholesterol shows statistically non-significant variance between Vit. D users and Vit. D non-users' groups.

**HDL cholesterol (mg/dL):** 3 studies stated (HDL cholesterol), and all can be applied. Insignificant heterogeneity has been observed. Therefore, a fixed-influence model has been applied for analysis ($I^2$ = 0%, p = 0.60). The combined mean variance & 95% confidence intervals were -0.21 (-1.91 to 1.49). The combined outcome shows statistically non-significant variance among groups according to HDL cholesterol (Z = 0.24, P equal to 0.81).

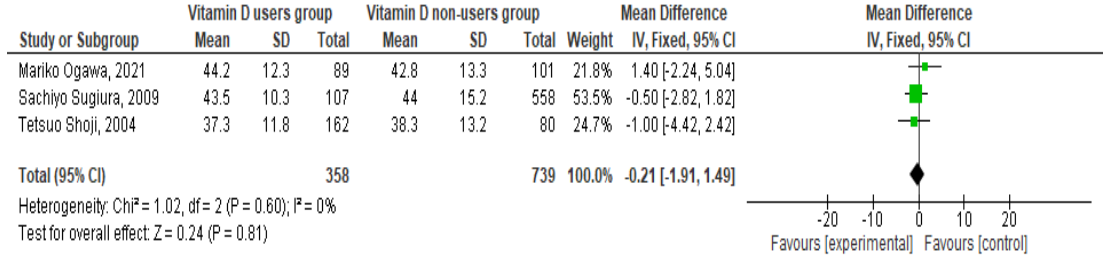


**Figure (7):** Forest plot of HDL cholesterol illustrates statistically insignificant variance among Vitamin D users and Vitamin D non-users' groups.

**Alkaline phosphatase (U/L):** Two studies stated (alkaline phosphatase) and all could be utilized. A significant heterogeneity has been observed. Therefore, a random-influence model has been applied for analysis ($I^2$ = 82%, p equal to 0.02). The combined mean variance and ninety-five percent CIs was -22.24 (-55.43 to 10.95). The combined result shows statistically insignificant variance among groups according to hemoglobin (Z equal to 1.31, P equal to 0.19).

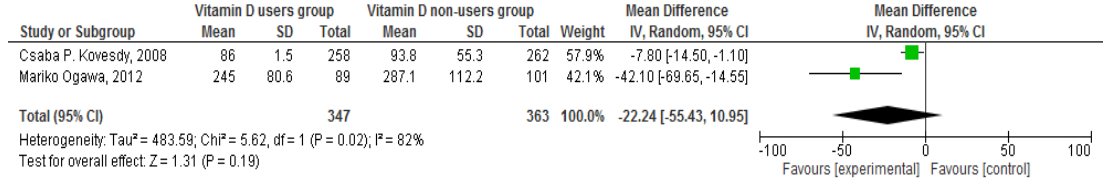


**Figure (8):** Forest plot of Alkaline phosphatase demonstrates statistically insignificant variance between Vit. D users and Vit. D non-users' groups.

**Albumin (g/dl):** Six studies stated (Albumin), and all can be utilized. Significant heterogeneity has been observed. Therefore, a random-influence model was applied for analysis ($I^2$ = 91%, p below 0.00001). The combined mean variance and ninety-five percent CIs was 0.06 (-0.02 to 0.13). The combined result shows statistically non-significant variance among groups according to albumin (Z equal to 1.43, P equal to 0.15).

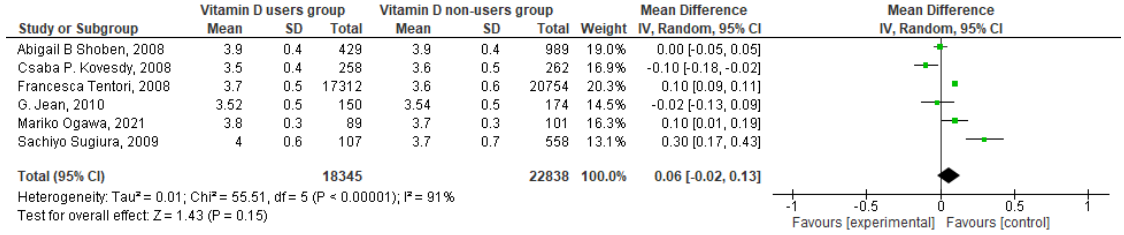


**Figure (9):** Forest plot of Albumin shows statistically non-significant variance among Vitamin D users and Vitamin D non-users' groups.

**Death:** Six studies stated (Death), and all may be utilized. Significant heterogeneity has been observed. Therefore, a random-influence model has been applied for analysis ($I^2$ = 98%, p below 0.00001). The combined mean variance and ninety-five percent confidence intervals were 0.54 (0.35 to 0.81). The combined result shows statistically significant variance among groups regarding death (Z equal to 2.93, P equal to 0.003).

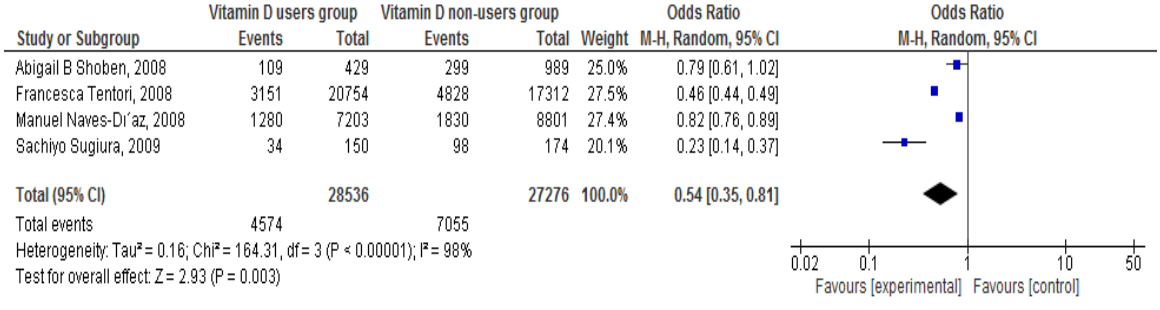


**Figure (10):** Forest plot of Death shows statistically significant variance among Vitamin D users and Vitamin D non-users' groups.

## Discussion

This systemic review and meta-analysis encompassed 8 studies, including approximately 57429 cases. The publication year ranged from 1990 to 2021.

**Outcomes:**

The combined result demonstrated a statistically insignificant difference among groups according to dialysis vintage (Z equal to 0.18, P equal to 0.86).

In agreement with our results, **Jean et al. (15)** aimed to determine the association among serum 25-hydroxyvitamin D (25-OHD) concentrations and alfacalcidol treatment with chronic hemodialysis cases' outcomes. They found that there was statistically non-significant variance among the examined groups regarding dialysis vintage.

Also, in alignment with our results, **Ogawa et al. (16)** determined the association among alfacalcidol treatment and the results of chronic hemodialysis (HD) cases. They stated that there was statistically non-significant variance among the studied groups according to dialysis vintage (P = 0.6350).

The combined outcome demonstrated statistically insignificant difference among groups according to hemoglobin (Z = 1.50, P = 0.13).

In agreement with our outcomes, **Ogawa et al. (16)** found that there was statistically insignificant variance among 2 groups regarding hemoglobin (P equal to 0.09).

As well, in alignment with our results, **Shoben et al. (17)** assessed correlations of oral calcitriol utilization with mortality and dialysis dependence in non-dialysis cases with chronic kidney disease. They found that there was statistically non-significant variance between the two groups regarding hemoglobin.

In addition, **Kovesdy et al. (18)** investigated the correlation of oral calcitriol treatment with mortality and the frequency of dialysis in cases with CKD stages three to five. They found that there was statistically non-significant variance among two groups according to hemoglobin (P = 0.8).

Moreover, in line with our results, **Sugiura et al. (19)** targeted to examine the association among the utilization of activated vitamin D, alfacalcidol, before initiation of dialysis, and CVD events. They stated that there was a statistically insignificant difference between the two groups regarding hemoglobin (P equal to 0.619).

The combined result demonstrated a statistically insignificant difference among groups regarding Ca+2 (Z = 0.77, P = 0.44).

In alignment with our results, **Ogawa et al. (16)** found that there was statistically non-significant variance among two groups according to Ca+2 (P = 0.685).

As well, in agreement with our results, **Shoben et al. (17)** found that there was statistically insignificant variance between two groups regarding Ca+2.

Moreover, in line with our results, **Sugiura et al. (19)** stated that there was statistically non-significant variance among two groups regarding Ca+2 (P = 0.228).

Furthermore, in accordance with our outcomes, **Shoji et al. (20)** hypothesized that treatment with vitamin D3 may be beneficial for survival in cases with end-stage renal disease (ESRD). They found that there was statistically insignificant variance among two groups according to Ca+2 (P = 0.192).

Also, in disagreement with our results, **Kovesdy et al. (18)** stated that there was a statistically

significant difference among the examined groups regarding Ca+2 (P = 0.03).

The combined result demonstrated statistically insignificant variance among groups regarding phosphorus (Z equal to 0.22, P equal to 0.83).

In agreement with our outcomes, **Ogawa et al. (16)** found that there was statistically insignificant variance among two groups according to phosphorus (P = 0.552).

Also, in alignment with our results, **Kovesdy et al. (18)** found that there was a statistically insignificant difference among the examined groups according to phosphorus (P = 0.56).

As well, in accordance with our results and **Sugiura et al. (19),** they stated that there was statistically insignificant variance among two groups regarding phosphorus (P = 0.625).

Moreover, in line with our results, **Shoji et al. (20)** found that there was statistically insignificant variance among two groups according to phosphorus (P = 0.638).

The combined outcome demonstrated statistically significant variance among groups regarding intact parathyroid hormone (Z = 3.97, P below or equal to 0.001).

In agreement with our outcomes, **Shoben et al. (17)** found that there was statistically significant variance among two groups according to parathyroid hormone (PTH).

Furthermore, in line with our outcomes **Sugiura et al. (19)** stated that there was statistically significant variance among two groups regarding intact parathyroid hormone (P < 0.0001).

Unlike our results, **Ogawa et al. (16)** found that there was statistically non-significant variance between two groups according to intact parathyroid hormone (P equal to 0.132).

Also, in contrast with our results, **Shoji et al. (20)** found that there was statistically non-significant variance among two groups according to parathyroid hormone (P equal to 0.471).

The combined outcome demonstrated statistically insignificant difference among groups according to total cholesterol (Z = 0.27, P equal to 0.79).

In agreement with our outcomes, **Ogawa et al. (16)** found that there was statistically insignificant variance among two groups according to total cholesterol (P = 0.797).

As well, in accordance with our results and **Kovesdy et al. (18),** they stated that there was statistically non-significant variance among the studied groups according to total cholesterol (P = 0.12).

The combined outcome demonstrated a statistically non-significant difference between the two groups regarding HDL cholesterol (Z = 0.24, P = 0.81).

In agreement with our outcomes, **Ogawa et al. (16)** found that there was statistically insignificant variance among two groups regarding HDL cholesterol (P equal to 0.469).

In addition, **Sugiura et al. (19)** stated that there was statistically insignificant variance among two groups according to HDL cholesterol (P = 0.747).

Also, in accordance with our results and **Shoji et al. (20),** they found that there was statistically non-significant variance among two groups according to HDL cholesterol (P = 0.567).

The combined outcome demonstrated statistically insignificant variance among groups regarding alkaline phosphatase (Z equal to 1.31, P equal to 0.19).

In alignment with our results, **Kovesdy et al. (18)** stated that there was statistically insignificant variance among the examined groups regarding alkaline phosphatase (P = 0.09).

In contrast with our results, **Ogawa et al. (16)** found that there was statistically non-significant variance among two groups according to alkaline phosphatase (P = 0.003).

The combined outcome demonstrated statistically insignificant variance among groups according to albumin (Z equal to 1.43, P equal to 0.15).

In alignment with our results, **Ogawa et al. (16)** found that there was a statistically insignificant difference among two groups according to albumin (P = 0.125).

As well, in accordance with our results, **Shoben et al. (17)** found that there was statistically non-significant variance among two groups according to albumin.

Moreover, in agreement with our outcomes, **Kovesdy et al. (18)** stated that there was a statistically insignificant difference among the examined groups according to albumin (P = 0.64).

The combined result demonstrated statistically significant variance between groups regarding death (Z equal to 2.93, P equal to 0.003).

In agreement with our outcomes, **Shoben et al. (17)** reported that there were 299 deaths among non-users and 109 deaths among calcitriol users (p > 0.05).

## Conclusion

In conclusion, this meta-analysis and systemic review found that vitamin D supplementation significantly reduced all-cause mortality and effectively lowered intact parathyroid hormone levels, without notable changes in other biochemical parameters. These findings suggest a potential survival benefit of vitamin D in CKD, warranting confirmation through high-quality randomized controlled trials.

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