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Research Article

ARCHIVES OF INTERNAL MEDICINE RESEARCH

ISSN: 2688-5654

Vitamin D and respiratory infection in a rare genetic disorder. A systematic review and meta-analysis

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Abstract

Background: Vitamin D supplementation has been proposed as a capacity intervention to reduce respiratory infections. However, the evidence remains inconsistent across diverse populations and settings. This systematic review and meta-evaluation aimed to assess the efficacy of vitamin D supplementation in decreasing contamination occurrence, infection length, hospitalization charges, and upper respiratory infection (URI) severity.

Methods: A complete search of digital databases identified 4,597 articles, of which 16 randomized controlled trials (RCTs) met the inclusion criteria. Meta-analyses were carried out the usage of RevMan, and heterogeneity was assessed the use of the I^2 statistic. The hazard of bias was evaluated using the Cochrane ROB 2 tool.

Results: 1. Infection Incidence: The pooled threat ratio (RR) for contamination prevalence changed into 0.93 (95% CI: 0.83–1.03; p = 0.15), suggesting a non-large 7% discount in risk. Significant heterogeneity changed into found (I^2 = 77%).

2. Infection Duration: The standardized suggest difference (SMD) for contamination duration was 0.23 (95% CI: -0.49 to 0.94; p = 0.53), with extensive heterogeneity (I^2 = 83%).

3. Hospitalization Rates: The RR for hospitalization because of respiratory infections became 0.83 (95% CI: 0.56–1.21; p = 0.32), without heterogeneity (I^2 = 0%).

4. URI Severity: The pooled SMD for URI severity was -0.32 (95% CI: -1.17 to 0.52; p = 0.45), with slight heterogeneity (I^2 = 70%).

The normal threat of booklet bias became low, even though variability throughout research became obtrusive.

Conclusions: Vitamin D supplementation demonstrated a protective trend towards breathing infections, but didn't attain statistical significance in outcomes. Significant heterogeneity in contamination prevalence and duration highlights the need for similarly research to clarify its efficacy and become aware of populations most probably to benefit. Standardized methodologies and rigorous trial designs are critical to better understand the function of nutrition D in respiration contamination prevention.

Keywords: Vitamin D; Respiratory infections; Rare genetic disorders; Systematic review; Meta-analysis; Immunomodulation; Cystic fibrosis; Primary ciliary dyskinesia; Infection incidence

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Received: May 15, 2025
Accepted: May 22, 2024
Published: June 23, 2025

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DOI:10.26502/aimr.0209

Introduction

Respiratory tract infections (RTIs) are a common worldwide health difficulty, contributing considerably to morbidity and mortality. In 2010, on my own, RTIs were chargeable for 2.8 million deaths globally [1]. The maximum common pathogens encompass the bacterium Streptococcus pneumoniae and the influenza virus. While vaccines focused on these microbes are to be had in certain regions, their efficacy may be restricted due to vaccine non-responders and mechanisms that allow pathogens to prevent vaccine-precipitated immunity. Current treatment alternatives, including symptomatic therapies, antibiotics, and antivirals, face demanding situations like rising drug resistance, undoubtedly limiting their destiny effectiveness. Consequently, there's a need for added strategies to prevent or mitigate RTIs, and modulating the host immune response provides a promising opportunity. Emerging research highlights the role of nutrition D in modulating immune pathways, enhancing mucosal defenses, even as curtailing immoderate irritation [2]. For example, diet D upregulates the expression of the antimicrobial peptide LL-37 [3], which reveals strong bactericidal activity in opposition to key pathogens, together with Mycobacterium tuberculosis and the influenza virus [4,5]. Notably, human macrophages rely on the nutrition D/LL-37 axis for effective mycobacterial killing, an impact that diminishes while the LL-37 gene is silenced using RNA interference [6,7]. A large range of hospitalized patients with breathing infections require respiration aid and in-depth care (ICU) remedy [8,9]. Several factors contribute to sickness progression, with aged and frail individuals being at the highest risk for unfavorable outcomes and headaches. Additionally, conditions inclusive of cardiovascular sickness, diabetes, malignancy, and weight problems in addition increase the probability of headaches from COVID-19 and other respiratory infections [10–12]. One extremely good thing related to worse outcomes, increased severity, and a higher incidence of headaches is vitamin D deficiency [13,14]. Vitamin D plays a critical role in modulating each innate and adaptive immune responses. It promotes the production of antimicrobial proteins and well-known shows anti anti-inflammatory residences with the aid of lowering viral replication and pro-inflammatory cytokine synthesis [15,16]. Vitamin D also regulates numerous thrombotic pathways, which might also assist in mitigating coagulopathy associated with COVID-19 [17]. Low vitamin D levels are related to a higher occurrence of respiratory infections, along with a 64% extended risk of nosocomial-acquired pneumonia in patients with levels below 50 nmol/L [18,19]. Deficiency in vitamin D has also been related to higher rates of infections, sepsis, and mortality [20–22]. Observational studies have further demonstrated associations between low vitamin D levels and accelerated susceptibility, severity, and mortality in COVID-19 instances, with severe hypovitaminosis D correlating with poorer prognoses and higher mortality rates [23,24].

There is evidence supporting the protective impact of vitamin D supplementation towards respiratory tract infections [25]. However, findings concerning its blessings in COVID-19 sufferers have been inconsistent. While some research has found decreased ailment severity and quicker recovery with supplementation, others have observed no large effect on outcomes [26–32]. To address vitamin D deficiency, high-dose supplementation is frequently required [33]. A sort of dosing regimen is to be had, but bolus doses with longer intervals are generally discouraged because of an accelerated risk of unfavorable consequences [34]. Instead, daily supplementation has been proven to effectively lessen the incidence of respiratory infections in the general populace [35]. For ICU patients, fashionable doses may be inadequate, as it is able to take too long to accurately correct hypovitaminosis D. Higher day-by-day doses or an initial loading dose can be important for timely correction [36]. Different dosing regimens can produce various medical effects, with daily dosing presenting steady availability of vitamin D and its metabolites, probably influencing consequences.

While there may be no consensus at the higher limit for diet D supplementation, day-by-day doses generally range from four hundred to 2,000 IU, with the Endocrine Society recommending a higher restriction of 10,000 IU [37,38]. Studies suggest that long-term daily supplementation of up to 10,000 IU is safe and does not cause detrimental effects in human beings [39,40]. Furthermore, vitamin D supplementation is a cheaper and commonly secure intervention with rare side effects and a huge protection margin, making it a viable choice for hospitalized patients.

Rationale: Respiratory infections are a significant cause of morbidity and mortality globally, and individuals with rare genetic issues, including cystic fibrosis, primary ciliary dyskinesia, or other related situations, face a far greater danger because of their underlying respiratory and immune disorder. These infections regularly result in intense headaches, which include common hospitalizations and decreased nice of life. Emerging proof indicates that vitamin D, a key regulator of immune function, performs an essential function in enhancing mucosal defenses, modulating infection, and reducing the severity of breathing infections. Observational studies have related vitamin D deficiency to higher susceptibility and worse results in respiratory illnesses, highlighting the capability of vitamin D supplementation as a preventive or therapeutic approach. While the broader populace has been studied drastically, there is a lack of centered research examining the effect of vitamin D on breathing infections, especially within the context of rare genetic disorders. This systematic review and meta-analysis aim to synthesize available

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evidence, examine the efficacy of diet D supplementation in this high-risk population, and offer insights into its function in enhancing medical results, filling an essential gap in the literature.

Objectives: The number one objective of this systematic review and meta-evaluation is to assess the efficacy of nutrition D supplementation in lowering the occurrence, severity, and complications of breathing infections in individuals with uncommon genetic problems, which include cystic fibrosis and primary ciliary dyskinesia. Secondary targets encompass assessing the effect of diet D on immune modulation, biomarkers of respiratory fitness, and average great of lifestyles in this population. By synthesizing facts from present studies, the evaluation pursuits to become aware of styles, quantify effects, and provide evidence-based hints for scientific practice and destiny research. Additionally, it seeks to explore capacity versions in outcomes primarily based on dosing regimens, baseline diet D reputation, and look at design, imparting a complete information of the role of nutrition D in handling respiratory infections in this vulnerable group.

Methodology

The method follows the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Protocols and Registration

No registration or ethical approval was required for this systematic review and meta-analysis, as it is based on previously published studies.

Eligibility Criteria: Inclusion standards: Studies ought to include people of any age with uncommon genetic issues linked to respiratory headaches, which include cystic fibrosis or primary ciliary dyskinesia. The intervention of interest is Vitamin D supplementation or treatment, such as bureaucracy like cholecalciferol or vitamin D2. Comparators can consist of a placebo, no treatment, widespread care, or alternative treatments. Outcomes of hobby encompass the prevalence, severity, and duration of respiratory infections, in addition to biomarkers of breathing fitness and pleasant of life. Eligible observational designs consist of randomized controlled trials, observational studies with a control group, and systematic reviews presenting original or pooled records. Publications have to be peer-reviewed, written in English, and ideally posted within the closing 10–15 years.

Exclusion standards: Studies that concentrate on populations with rare genetic problems or on respiratory conditions not of non-genetic origin will be excluded. Research examining interventions other than Vitamin D, case reviews, editorials, animal research, in vitro experiments, and convention abstracts without full-text availability can also be excluded. Non-English publications without to be had translations will no longer be considered.

Table 1: PICOS framework

Population	Intervention	Comparison	Outcomes	Study Design
Adults with heart failure (HFrEF or HFpEF)	Vitamin D supplementation or treatment	Placebo, no treatment, standard care, or alternative therapies.	Incidence, severity, and duration of respiratory infections.	Randomized controlled trials

Table 2: Search strategy on individual databases

Sr No.	Databases	Search String	Number of studies
1	PubMed	("Vitamin D"[Mesh] OR "Cholecalciferol"[Mesh] OR "vitamin D supplementation" OR "vitamin D deficiency" OR "cholecalciferol" OR "ergocalciferol") AND ("Respiratory Tract Infections"[Mesh] OR "respiratory infection" OR "respiratory illness" OR "lung infection" OR "pneumonia" OR "bronchitis") AND ("Rare Diseases"[Mesh] OR "Genetic Disorders"[Mesh] OR "hereditary disease" OR "rare genetic disorder" OR "monogenic disorder" OR "Mendelian disorder") AND ("Clinical Trial" OR "Randomized Controlled Trial" OR "RCT" OR "meta-analysis" OR "systematic review")	1817
2	Cochrane Library	("Vitamin D" OR "Cholecalciferol" OR "Ergocalciferol") AND ("Respiratory Tract Infections" OR "respiratory infection" OR "lung infection") AND ("Rare Diseases" OR "Genetic Disorders" OR "rare genetic disorder" OR "monogenic disorder")	371
3	Google Scholar	"Vitamin D" AND "respiratory infection" AND ("rare genetic disorder" OR "hereditary disease" OR "monogenic disorder")	2409

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Information Sources: A complete search for studies on the efficacy of Vitamin D on respiratory infections was conducted across more than one digital database, consisting of PubMed, Google Scholar, ScienceDirect, and Cochrane Library. Independent journals and other scholarly guides have also been covered. The seek method adhered to PRISMA tips to ensure comprehensive coverage.

Search Strategy: The search method concerned the use of Boolean operators (AND/OR) to combine phrases related to the study title. Filters have been applied to attention in randomized controlled trials and human research. The search yielded sixteen studies (n=16) that met the inclusion criteria.

Selection Process: The article selection was accomplished in stages. First, titles and abstracts had been screened for relevance. In the second level, the full texts of the selected articles were reviewed to verify eligibility. Data on the primary creator, year of guide, observation layout, use of a sample size, results, and methods were extracted using a standardized records extraction tool.

Data Items: For every study, information on the sample size, study layout, effects, and statistical measures (means, standard deviations) was extracted. Data were synthesized and analyzed the usage of RevMan software for meta-analysis.

Study Risk of Bias Assessment: The Cochrane Risk-of-Bias (version 2) tool was used to evaluate the threat of bias throughout seven domains: random series era, allocation concealment, blinding, incomplete outcome records, selective reporting, and other biases. The risk of bias for every look was assessed as low, unclear, or excessive.

Statistical Analysis: Meta-analysis changed into completed the usage of Review Manager (RevMan) software (version 5.4). A random-consequences model was used due to predicted heterogeneity throughout the research. Heterogeneity was assessed the usage of the I^2 statistic, and meta-regression turned into performed where applicable.

Reporting Bias Assessment: Potential reporting biases have been minimized by means of selecting high-quality studies and undertaking a thorough search for all relevant publications. Funnel plots have been used to visually check for eBook bias.

Results

Study Selection and Screening

The initial search of the database yielded 4597 papers. After the removal of duplicates and applying the inclusion criteria total of 54 studies for selected for full-text analysis. Based on the methodological quality assessment and inclusion and exclusion criteria, a total of 16 articles finally met the criteria to be included in this systematic review and meta-analysis. Figure 1 presents the detailed PRISMA flowchart diagram of the selection process of the included studies.

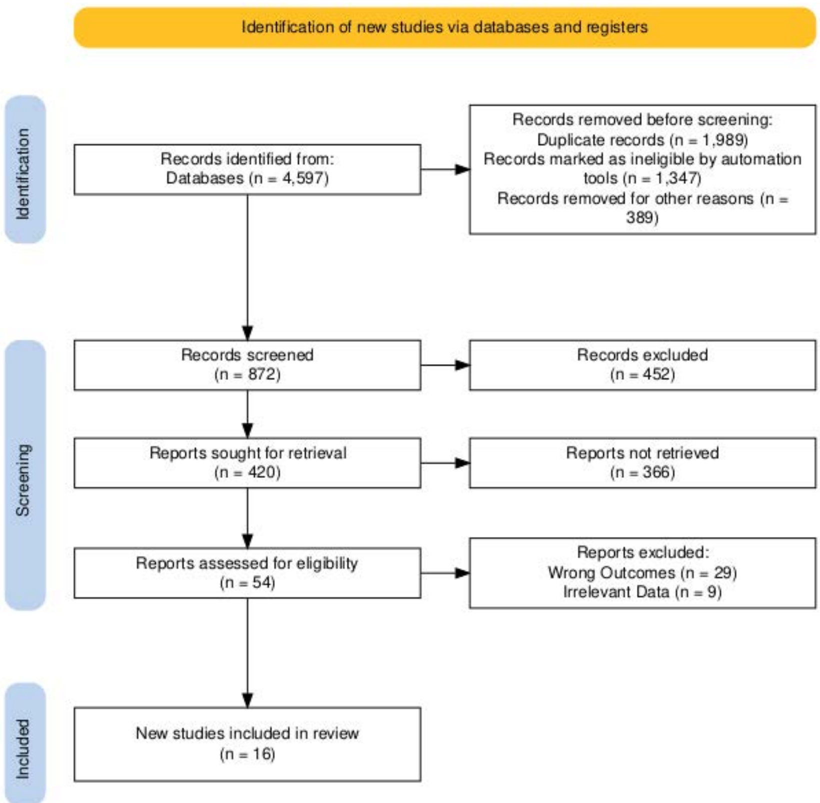

Figure 1: PRISMA Flow diagram of included studies [41].

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Study Characteristics: Study Characteristics of all the included studies are given in Table 3.

Table 3: Characteristics of included studies.

Sr No.	Study	Study Design	Location	Sample Size	Population	Intervention	Comparison	Outcome Measures
1	Tamara et al. [42]	RCT	Indonesia	84	Patients with vitamin D insufficiency and pulmonary tuberculosis who are between the ages of 6 and 18	Vitamin D supplementation	Placebo	Fever and Cough duration
2	Bugarin et al. [43]	RCT	Croatia	155	Patients with COVID-19 disease	Vitamin D supplementation	Placebo	Infections
3	Camargo et al. [44]	RCT	USA	15804	Older adults with high risk of upper respiratory tract infections	Vitamin D supplementation	Placebo	Infections
4	Dubnov et al. [45]	RCT	Israel	55	Adolescent Swimmers	Vitamin D supplementation	Placebo	Infections
5	Ganmaa et al. 46]	RCT	Mongolia	8851	children who had negative results for M. tuberculosis infection	Vitamin D supplementation	Placebo	Infections, Hospitalisation
6	Dilokpattanamongkol et al. [47]	RCT	Thailand	294	patients aged ≥ 18 years with COVID-19 pneumonia	Vitamin D supplementation	Placebo	Duration
7	Denlinger et al. [48]	RCT	USA	408	adults with mild to moderate asthma and vitamin D insufficiency	Vitamin D supplementation	Placebo	-
8	Jlliffe et al. [49]	RCT	UK	6200	people aged ≥16 years who were not taking vitamin D supplements at baseline	Vitamin D supplementation	Placebo	hospitalisation
9	Keever et al. [50]	RCT	Mexico	321	Frontline Healthcare Workers in COVID 19	Vitamin D supplementation	Placebo	-
10	Bergman et al. [51]	RCT	Sweden	124	adult patients with a high burden of RTIs	Vitamin D supplementation	Placebo	-
11	Huang et al. [52]	RCT	Taiwan	248	children aged two to five years	Vitamin D supplementation	Placebo	-
12	Singh et al. [53]	RCT	India	100	under-five children	Vitamin D supplementation	Placebo	infections, hospitalisation, URI severity
13	Harrison et al. [54]	RCT	UK	1644	patients doing military training	Vitamin D supplementation	Placebo	-
14	Loeb et al. [55]	RCT	Vietnam	650	healthy children and adolescents between the ages of 3 and 17 years	Vitamin D supplementation	Placebo	infections
15	Laaksi et al. [56]	RCT	Finland	412	healthy individuals	Vitamin D supplementation	Placebo	-
16	Camargo et al. [57]	RCT	USA	5110	older individuals	Vitamin D supplementation	Placebo	-

Risk of Bias: Risk of Bias [58] of the included studies was calculated using the Cochrane ROB 2 tool [59] since all of the included studies are Randomized Controlled Trials.

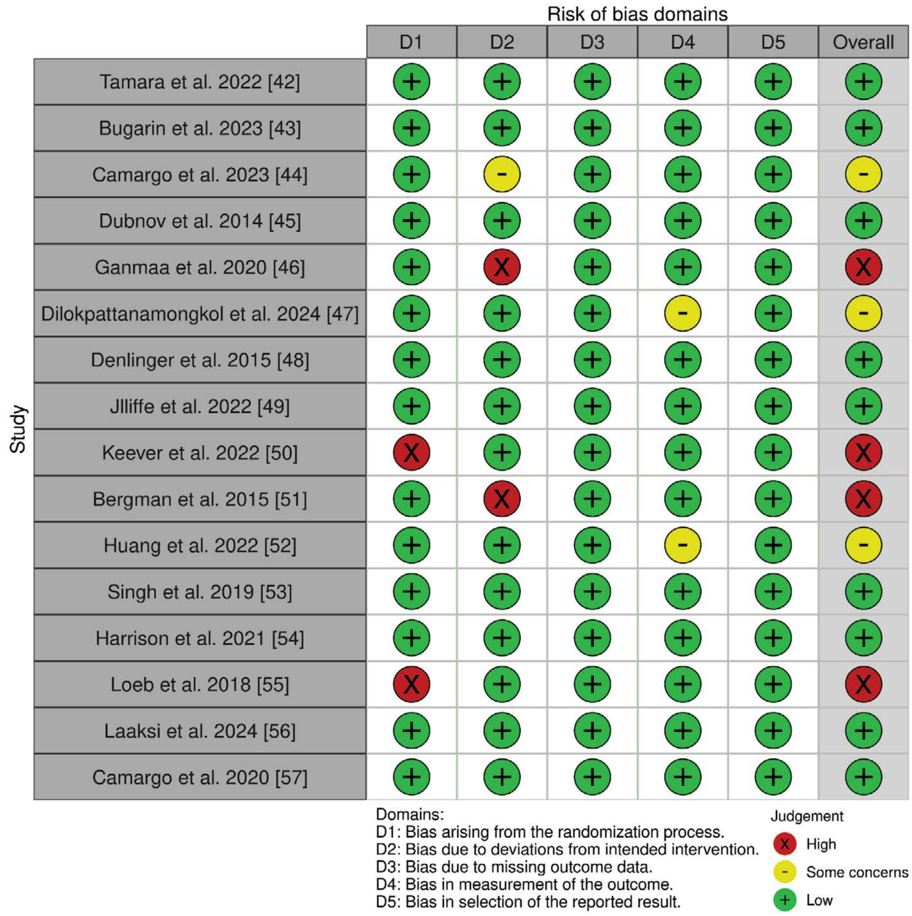

Figure 2: Traffic Light Plot of Risk of Bias of included studies

Meta-Analysis: RevMan was used to perform the meta-analysis for this study.

(i) Number of infections:

The forest plot illustrates the danger ratio (RR) for the number of infections in individuals receiving nutrition D supplementation in comparison to those receiving a placebo. The standard pooled risk ratio is 0.93 (95% CI: 0.83 to at least 1.03), indicating a 7% discount in the risk of infections with vitamin D supplementation, despite the fact that this result is not statistically significant ($p = 0.15$). Significant heterogeneity is present across the included studies ($I^2 = 77\%$, $p = 0.0002$), suggesting variability in the effect sizes that may be due to variations in look at design, population characteristics, or intervention protocols. While man or woman research like Loeb et al. (2018) and Keever et al. (2022) display statistically huge discounts in infection hazard with vitamin D, other research reports no substantial difference. The ordinary findings suggest a protective capacity effect of diet D supplementation against infections, but the excessive heterogeneity highlights the need for similarly research to clarify its function and perceive populations' maximum in all likelihood to advantage.

(ii) Duration of infection:

The Forest plot evaluates the effect of vitamin D supplementation as opposed to placebo on the length of infections, measured by the standardized suggest difference (SMD). The normal pooled SMD is zero.23 (95% CI: -0.49 to 0.94), indicating no statistically significant reduction in contamination duration with nutrition D supplementation ($p = 0.53$). High heterogeneity is located in most of the research ($I^2 = 83\%$, p = zero.003), suggesting sizable variability in the consequences. Individual studies show combined results, and do not use a consistent fashion favoring both institutions. For instance, Tamara et al. (2022) mentioned an advantageous effect of vitamin D supplementation, whilst different studies like Dubnov et al. (2014) verified no sizable difference. These findings recommend that diet D supplementation does not continuously lessen contamination length, and the high heterogeneity underscores the need for additional research with standardized methodologies to affirm those results.

(iii) Hospitalization:

The forest plot summarizes the effect of vitamin D supplementation versus placebo on hospitalization costs due

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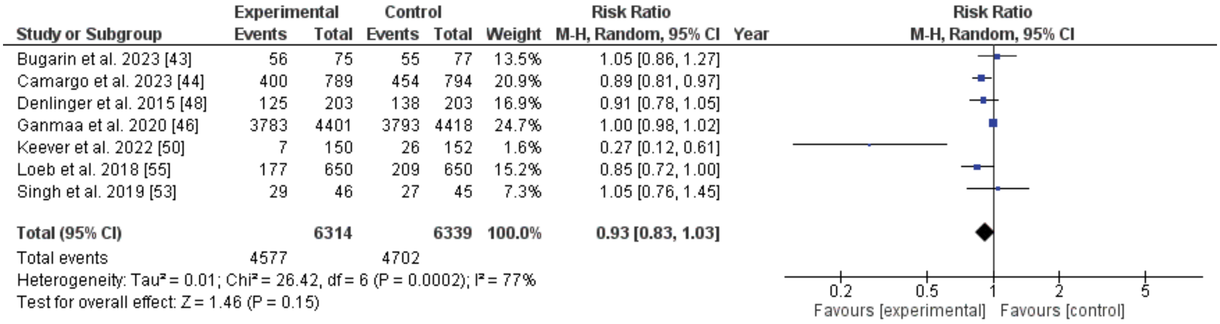

Figure 3: Forest Plot of the number of infections [43] [44] [46] [48] [50] [53] [55]

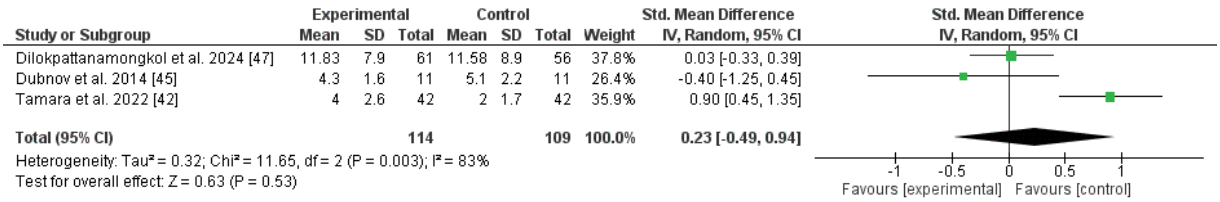

Figure 4: Forest Plot of the duration of infection [42], [45], [47]

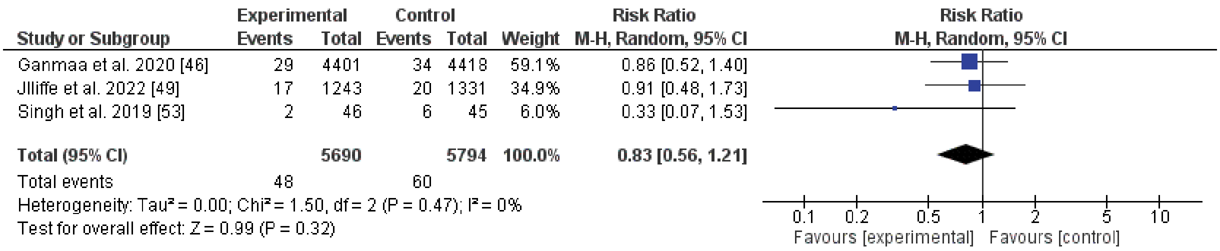

Figure 5: Forest Plot of Hospitalization [46],[49],[53]

to breathing infections. The pooled chance ratio (RR) is 0.83 (95% CI: 0.56 to at least 1.21), suggesting a 17% discount in hospitalization chance with nutrition D supplementation; however, this end result isn't always statistically significant (p = 0.32). Notably, there is no proof of heterogeneity in a few of the protected studies (I^2 = 0%, p = 0.47), indicating consistency in the impact sizes suggested. While character research, which includes Ganmaa et al. (2020) and Jolliffe et al. (2022), displays non-great developments favoring nutrition D, the general findings suggest insufficient proof to conclude a defensive impact of diet D supplementation on reducing hospitalizations. Further research with large pattern sizes and extra rigorous take a look at designs is warranted to establish the capability position of nutrition D in this context.

(iv) URI Severity:

The forest plot compares the standardized imply difference (SMD) in higher respiratory contamination (URI) severity between vitamin D supplementation and placebo groups. Two studies have been included in the evaluation, with Dubnov et al. (2014) showing a non-significant advantage of vitamin D (SMD: 0.19; 95% CI: -0.65 to at least one.03), at the same time as Singh et al. (2019) preferred the control group with a greater but still non-significant effect (SMD: -0.68; 95% CI: -1.11 to -0.26). The usual pooled impact estimate (SMD: -0.32; 95% CI: -1.17 to 0.52) suggests no statistically significant distinction in URI severity among the vitamin D and placebo groups (p = 0.45). Moderate heterogeneity was found (I^2 = 70%, p = 0.07), suggesting some inconsistency throughout research. Collectively, those findings mean that nutrition D supplementation won't appreciably reduce the severity of URIs as compared to placebo, even though variability among observed outcomes warrants further investigation.

Publication Bias:

The funnel plot assessing publication bias for studies comparing the relative risk (RR) of diet D supplementation on top of upper respiratory infection (URI) incidence seems largely symmetrical around the line of no effect (RR = 1), suggesting a low chance of full-size publication bias. Most research clusters carefully around the valuable axis, with a slight spread in effect sizes that is predicted due to sampling

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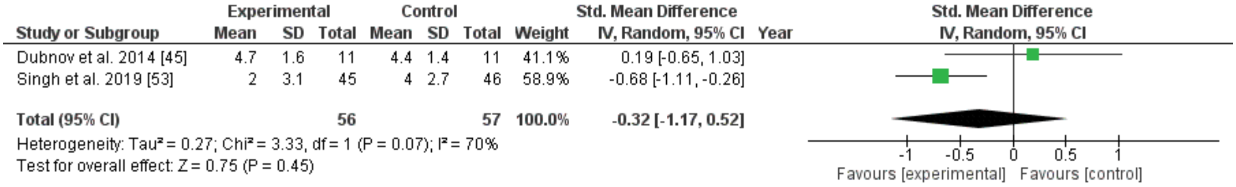

Figure 6: Forest Plot of URI severity [45],[53]

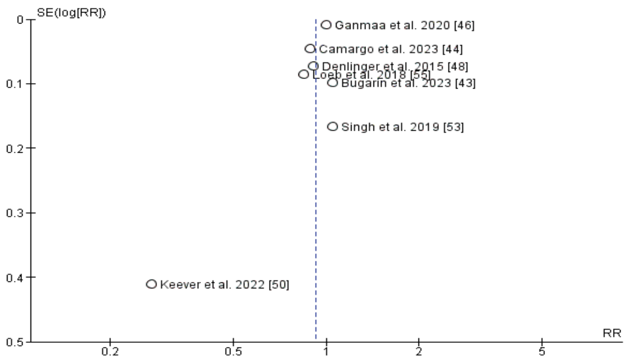

Figure 7: Funnel Plot of Publication Bias

variability. However, the study by means of Keever et al. (2022) seems as an outlier, located lower on the plot and in addition from the critical line, indicating a smaller scale look with bigger preferred errors and a more severe effect estimate. While this may improve some challenges for small-scale look at consequences, the overall distribution does not demonstrate the classic asymmetry function of big guide bias.

Discussion

This systematic review and meta-analysis assessed the impact of vitamin D supplementation on breathing infections, focusing on infection prevalence, contamination period, hospitalization, and top respiratory infection (URI) severity. While the findings propose ability advantages in some regions, the results have been commonly inconclusive, reflecting the heterogeneity of covered research and variability in the said outcomes.

The analysis of contamination incidence tested a 7% discount in danger with diet D supplementation (RR: 0.93; 95% CI: 0.83 to at least 1.03); however, this was not statistically significant ($p = 0.15$). Substantial heterogeneity ($I^2 = 77\%$) changed into observed, in all likelihood stemming from variations in study designs, populations, and intervention protocols. While person research, together with Loeb et al. (2018) and Keever et al. (2022), showed sizeable discounts, others showed no impact, suggesting that the ability of the protective position of diet D can also rely upon unique populations or contexts.

For the contamination period, the pooled evaluation revealed no big reduction with diet D supplementation (SMD: 0.23; 95% CI: -0.49 to 0.94; $p = 0.53$). The high heterogeneity ($I^2 = 83\%$) further complicates the translation of those findings. While some research, which includes Tamara et al. (2022), established a high-quality impact, others, like Dubnov et al. (2014), discovered no full-size distinction. This variability underscores the need for standardized methodologies and consistent outcome measures to better understand the position of vitamin D in reducing infection length.

Hospitalization rates because of respiratory infections have been additionally now not been extensively impacted by vitamin D supplementation (RR: 0.83; 95% CI: 0.56 to 1.21; $p = 0.32$), and not is no heterogeneity amongst research ($I^2 = 0\%$). Although tendencies favoring diet D were observed in individual studies, together with Ganmaa et al. (2020) and Jolliffe et al. (2022), the general findings suggest inadequate evidence to assist its function in reducing hospitalizations. These effects highlight the need for large, first-rate studies to explore this capability advantage further.

The evaluation of URI severity similarly did not show great differences among the diet D and placebo groups (SMD: -0.32; 95% CI: -1.17 to 0.52; $p = 0.45$), with slight heterogeneity ($I^2 = 70\%$). Notably, whilst Singh et al. (2019) said a trend favoring placebo, Dubnov et al. (2014) discovered no meaningful difference. This lack of consistency shows that vitamin D supplementation might not appreciably have an impact on URI severity, though similarly research is warranted to verify these findings.

A current systematic review and meta-analysis verified that vitamin D supplementation has a protective impact against respiratory tract infections (RTIs), with once-every-day dosing recommended because the simplest routine [61]. These findings align with the located developments in our analysis, which suggested a potential, though statistically non-enormous, protective role of vitamin D supplementation in opposition to contamination incidence and hospitalization. However, the heterogeneity discovered across blanket studies in both analyses underscores the demanding situations in drawing definitive conclusions. Differences in population characteristics, baseline diet reputation, dosing regimens, and study designs might also account for the range in results. Moreover, the ability for ebook bias, as stated in the preceding meta-analysis, in addition highlights the need for careful interpretation of these findings. Future studies have to focus on big, properly-designed trials with standardized methodologies to confirm these results and

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DOI:10.26502/aimr.0209

refine recommendations concerning the highest quality dosing techniques and target populations.

The low risk of guide bias located in the funnel plot analysis strengthens the validity of these findings. However, the presence of an outlier (Keever et al. 2022) highlights the capability have an effect on of small-scale research to have larger effect estimates.

Conclusion

In brief, this meta-analysis highlights mixed and largely non-significant consequences of nutrition D supplementation on breathing contamination effects, with high variability amongst studies. While some subgroups or specific populations can also benefit, the general proof remains inconclusive. Future studies have to focus on figuring out populations most likely to benefit from diet D supplementation, standardizing intervention protocols, and addressing the sources of heterogeneity to offer clearer guidance for medical practice.

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Citation: Ghazala S. Virk, Yusuf A. Siddique, Sarah Hack, Achbari Samia, Hemamalini Anand Murugesan, Huseyin Erdem Ak, Dinesh Aravind Rongali, Yousif Jihad, Manaswi Modali, Sana Afzal. Vitamin D and respiratory infection in a rare genetic disorder. A systematic review and meta-analysis. Archives of Internal Medicine Research. 8 (2025): 167-177.