Review Article

Jour Cas Stu Cas Rep, 4(1), 2025, 1-5

Journal of Case Studies and Case Reports

Open access peer reviewed international indexed journal Online ISSN: 2583-4428

Content Available at http://www.saapjournal.org/

A SYSTEMATIC REVIEW ON ACUTE RESPIRATORY TRACT INFECTION

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Received: 18 Dec 2024 Revised: 05 Feb 2025 Accepted 10 Mar 2025

Abstract

Observational studies and randomised controlled studies suggest that vitamin D plays a role in the prevention of acute respiratory tract infection (ARTI); however, findings are inconsistent and the optimal serum 25-hydroxyvitamin D concentration remains unclear. To review the link between concentration and ARTI, we searched EMBASE databases to identify observational studies reporting the association between 25-hydroxyvitamin D concentration and risk or severity of ARTI. We used random-effects meta-analysis to pool findings across studies. Twenty-four studies were included in the review, 14 were included in the meta-analysis of ARTI risk and five in the meta-analysis of severity. Serum 25(OH)D concentration was inversely associated with risk and severity of ARTI; pooled odds ratios (95% confidence interval) were 1.83, respectively, comparing the lowest with the highest 25(OH)D category. For each 10 nmol/L decrease in 25(OH) D concentration, the odds of ARTI increased by 1.02 (0.97–1.07). This was a non-linear trend, with the sharpest increase in risk of ARTI occurring at 25(OH) D concentration <37.5 nmol/L. In conclusion, there is an inverse non-linear association between 25(OH) D concentration and ARTI.

Keywords: Respiratory infection; vitamin D; systematic review; observational studies; 25-hydroxyvitamin D; meta-analysis; acute infection.

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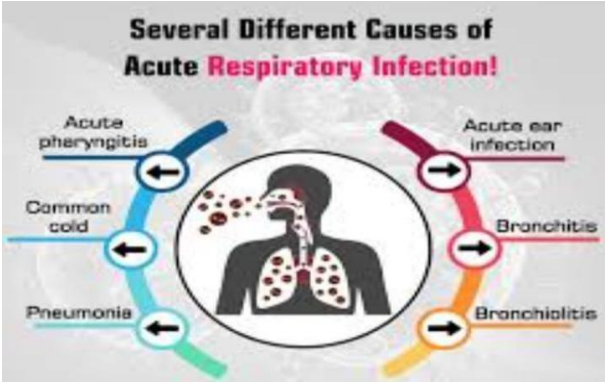
DOI: https://doi.org/10.37022/jcscr.v4i1.672

Introduction

Acute respiratory tract infection (ARTI) is very common, with most people experiencing at least one episode of ARTI each year [1]. ARTI includes upper respiratory tract infection (URTI) and lower respiratory tract infection (LRTI). The common cold and influenza are the most common ARTIs globally; the highest rate occurs during the winter months in temperate areas with little seasonal change in tropical regions [2]. During epidemic months, influenza can affect 20% to 50% of people worldwide [2]. Bronchitis and pneumonia are the two most common infections of the lower airways, and mortality due to LRTI is high [3]. In 2015, more than 2.8 million deaths worldwide were due to LRTI; children and the elderly are the most affected groups [3].

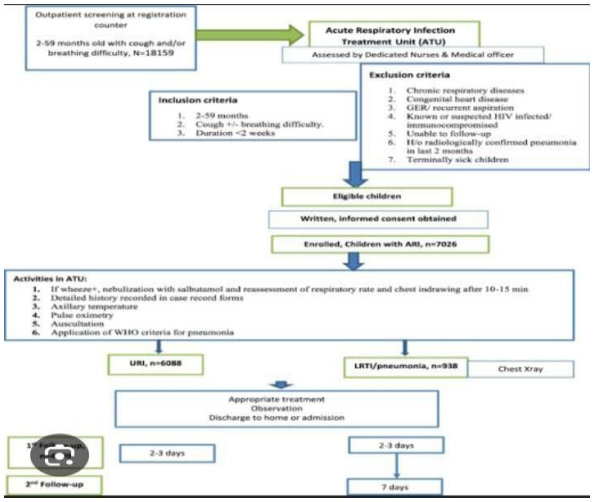
Vitamin D is critical for skeletal health and may play a role in other health outcomes, including infection. Vitamin D status is estimated by measuring the serum concentration of 25-hydroxyvitamin D, this varies seasonally and the lowest concentration in the winter/spring months coincides with the highest ARTI incidence, suggesting a link between vitamin D and ARTI [4]. This is supported by laboratory studies demonstrating an important role of vitamin D in the immune system. Vitamin D promotes the elimination of pathogens and suppresses prolonged inflammatory responses [5–7].

It enhances the production of antimicrobial peptides such as defensins and cathelicidins, which offer natural protection against microbial pathogens [8].

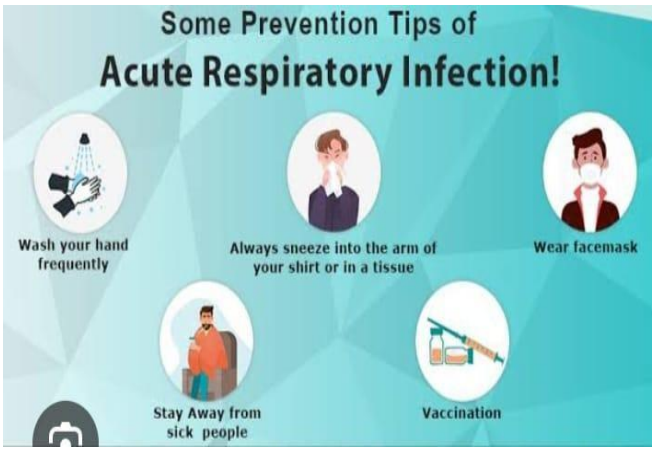


Many studies have investigated the link between 25(OH)D serum concentration and ARTI and the effect of vitamin D supplementation on ARTI. Two recent meta-analyses of observational studies considered associations between

25(OH)D concentration and ARTI incidence in children [9,10]. One included case-control studies in children aged ≤ 5 years and found higher odds of 25(OH)D deficiency in those with LRTI [9]. The other found an inverse association between prenatal maternal 25(OH)D concentration and risk of ARTI in the offspring [10]. The most recent systematic review and meta-analysis including older children and adults was published in 2015 as a conference abstract only—it included 19 observational studies and found a significant inverse association between 25(OH)D concentration and risk of ARTI [11]. A systematic review of 25 observational studies and 14 randomised-controlled trials (RCTs) was completed in 2013 [12]. It concluded that there was an inverse association between 25(OH)D concentration and risk of ARTI, but did not include a meta-analysis [12]. Some observational studies have found an inverse link between 25(OH)D concentration and severity of ARTI, as measured by duration of the illness, hospitalisation and severity index [13–16]; however, there has been no meta-analysis of these findings.



Results from RCTs investigating the effect of vitamin D supplementation on ARTI are inconsistent. Two meta-analyses found a significant benefit of vitamin D supplementation on ARTI [17,18] while another three did not [19–21]. There are indications of a greater protective effect in people with marked vitamin D deficiency [20,22], but the trials were unable to indicate an optimal concentration of 25(OH)D. We therefore conducted a systematic review and meta-analysis of observational studies to evaluate the link between serum 25(OH)D concentration and the risk and severity of ARTI in adolescents and adults. Findings from this meta-analysis will provide insights into the influence of vitamin D on ARTI risk and severity, and give an indication of the optimal 25(OH)D concentration for ARTI prevention and management.



Materials and Methods

The study protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews prior to commencement [23].

Search and Screening Strategy

PubMed databases were searched from their inception until Nov 2024. Keywords were chosen from the Medical Subject Headings terms in explosion of EMTREE terms in EMBASE. Essentially, we searched for the terms “vitamin d” or “25-hydroxyvitamin D” or “25OHD” or “25(OH)D” or “hypovitaminosis D” in combination with “respiratory tract infection or “respiratory infection or “respiratory disease or “pneumonia” or “influenza” or “bronchiolitis” or “common cold”. The complete search strategies are shown in the supplementary material.

Definition of Outcome

Primary outcome: The primary outcome was the risk of ARTI, defined as an acute infection of the respiratory tract in either the lower or upper airway or with the location not specified. ARTI was either self-reported via surveys or symptom diaries, or clinically confirmed with or without evidence from X-rays or laboratory tests.

Secondary outcome: The secondary outcome was the severity of ARTI, defined according to the duration of the illness, hospitalisation, admission to an intensive care unit, symptom severity score or index, or mortality.

Quality Assessment

They used the customised Newcastle-Ottawa scale (NOS) to assess the quality of each study [24]. The NOS tools are slightly different for each study design but generally include three main categories, namely: (1) selection of participants; (2) control for confounders; and (3) measurement of exposure or outcome.

Statistical Analysis Methods

A measure of association between 25(OH)D concentration and ARTI risk or severity (odds ratio (OR), relative risk (RR), hazard ratio (HR), mean difference (MD)) and their 95% confidence interval (CI) or standard deviation (SD); or Sufficient data to derive two by two tables of ARTI risk, comparing the lowest versus the highest 25(OH)D category.

We included the estimate from the most fully adjusted model for each study in the meta-analysis comparing the risk of ARTI in the lowest versus highest 25(OH)D category. When a study reported results using different 25(OH)D thresholds, we used 50 nmol/L as it was the most commonly used threshold. Two studies reported HRs as the measure of association between 25(OH)D concentration and risk of ARTI [25,26]; we included these two studies in the meta-analysis, considering the HR as an approximation of the OR. A random-effects model was used to pool the results.

We used a method described by Greenland and Longnecker to estimate trends across categories of exposure to calculate the effect of each 10 nmol/L decrease in 25(OH)D concentration on the risk of ARTI [27,28]. This method estimates the covariances between multivariable-adjusted odds ratios using the number of cases in each exposure category. We used variance least-squares regression to compute the trends in two studies in which the number of cases in each exposure category was not reported [25,29]. The representative value for each 25(OH)D category was assigned using either the midpoint of the range or by subtracting or adding the half width of the adjacent exposure category for open-ended categories [30]. We also used fixed effects to fit a restricted cubic spline model with 3 knots to evaluate a potential non-linear dose-response association between 25(OH)D concentration and ARTI risk [28].

For the overall analysis of severity, we defined a severe ARTI to be one that had a moderate-to-high severity score or resulted in death (no studies based on other severity outcomes were included). We also performed a separate meta-analysis to assess the association between 25(OH)D concentration (lowest versus highest category) and ARTI mortality.

Discussion

In this systematic review and meta-analysis, we observed significant associations between 25(OH)D concentration and both risk and severity of ARTI, but with significant heterogeneity and evidence of publication bias. There was a non-linear association between 25(OH)D concentration and risk of ARTI, with evidence of a more marked increased risk for 25(OH)D concentration below 37.5 nmol/L.

Findings from our meta-analysis of ARTI risk, which includes the largest number of participants, are consistent with results from previous reports. A meta-analysis published in 2015 as an abstract (n = 44,301) reported an increased risk of ARTI in those with 25(OH)D < 50 nmol/l compared with those ≥ 50 nmol/L.

The odds ratio was higher than we found (2.63 vs. 1.83); their analysis included children as well as adults and they did not present an estimate for adults and adolescents only [11]. A systematic review including 25 observational studies (10 in adults) reported significant inverse association between 25(OH)D concentration and risk of ARTI, but no formal meta-analysis was conducted [12]. The link between 25(OH)D concentration and risk of ARTI was also reported separately for children and LRTI; a meta-analysis showed a higher prevalence of vitamin D deficiency (< 50 nmol/L) in children with LRTI (n = 550) [9].

This is the first study to our knowledge which performed a meta-analysis of the association between 25(OH)D concentration and severity of ARTI. We found a stronger association between 25(OH)D concentration and severity of ARTI than with risk of ARTI (OR 2.46 vs. 1.83). The result accords with findings from a systematic review that highlighted the potential link between vitamin D deficiency and severe LRTI in children, but no meta-analysis was included [9]. It is difficult to meta-analyse the association between 25(OH)D concentration and severity of ARTI because of variability across studies with respect to variability in assay methods used to measure serum 25(OH)D; the cut points used to categorise 25(OH)D concentration; the scales used to measure severity; and the measures used to estimate effect. We could only include five studies in the severity meta-analysis so were unable to assess the association within subgroups or investigate a potential non-linear trend.

Results from RCTs are inconsistent. Some trials found that vitamin D supplementation reduced the risk of ARTI [48–50] while others did not [51–54]. The inconsistency may be due to differences in study design, vitamin D supplement doses and regimens, and different baseline 25(OH)D concentration. The most recent meta-analysis, using individual participant data, found that vitamin D supplementation reduced the risk of ARTI more strongly in people with 25(OH)D concentration < 25 nmol/L [22]. Our findings suggest that supplementation may be of most benefit in people with a 25(OH)D concentration ≤ 37.5 nmol/L, with some benefit up to 60 nmol/L, although these values should be considered with caution in light of the different assays and markedly varying cut point used across studies.

We observed high heterogeneity, and this mostly persisted in subgroup analyses. Despite this, the direction of effect was consistent; lower 25(OH)D concentration was associated with increased risk or severity of ARTI. There are indications of publication bias, indicating that small studies that showed no significant association were either not identified or not published. Publication bias has also been observed in meta-analyses of RCTs [17,22]. It is thus possible that the benefits of vitamin D for reducing risk or severity of ARTI have been over-estimated.

Conclusion

Their study is the largest to date and to the best of our knowledge, is the first to include a meta-analysis of the association between 25(OH)D concentration and severity of ARTI. Our findings suggest an important role of vitamin D in prevention of ARTI risk and severity, particularly in people with low 25(OH)D concentration. However, it is challenging to identify an optimal 25(OH)D concentration or a concentration below which supplementation would be of benefit due to the lack of consistency in both 25(OH)D assays and reporting across studies. It is important to improve consistency of reporting, as well as assays, to enable the field to move forward.

Funding

No Funding.

Acknowledgement

Nil

Conflict of Interest

No conflict of interest.

Informed Consent

Not applicable.

Ethical Statement

Not applicable

Author Contribution

All authors are contributed equally.

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