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Review Article

Vitamin D Supplementation and the Risk of Acute Respiratory Infection: A Metadata-Driven Synthesis of Randomized Evidence

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ABSTRACT

Vitamin D metabolites regulate antimicrobial peptide expression in the respiratory epithelium, providing a biological rationale for supplementation as a means of preventing Acute Respiratory Infections (ARIs). Observational data have consistently linked low circulating 25-Hydroxyvitamin D (25[OH]D) with greater infection risk, but trial results have been heterogeneous. To synthesize randomized evidence on whether Vitamin D supplementation reduces ARI risk, and to characterize the factors that modify this effect. Peer-reviewed Randomized Controlled Trials (RCTs) and meta-analyses of RCTs were retrieved from PubMed and PubMed Central. Study characteristics, pooled effect estimates, and subgroup findings were extracted into an evidence matrix and summarized narratively and quantitatively. Across successive meta-analyses the pooled Odds Ratio (OR) for experiencing at least one ARI drifted toward the null as large trials accrued: 0.88 (95% CI 0.81-0.96) in the 2017 individual-participant-data analysis, 0.92 (0.86-0.99) in 2021, and 0.94 (0.88-1.00; *p*=0.057) in the 2025 update. Early benefit was concentrated in profoundly deficient participants given daily or weekly (non-bolus) regimens. Several large, well-powered trials in unselected or replete populations reported null effects. Supplementation was consistently safe. Vitamin D supplementation is safe and may confer a small reduction in ARI risk that is most plausible among deficient individuals receiving regular physiological doses; it is not supported as a broad preventive measure in Vitamin-D-replete populations. A precision-prevention framing-correcting deficiency rather than universal supplementation-best fits the current evidence.

Keywords: 25-hydroxyvitamin D, acute Respiratory Infection, Cholecalciferol, Innate Immunity, Meta-analysis, Randomized Controlled Trial, Vitamin D.

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INTRODUCTION

Acute respiratory infections remain among the most common reasons for primary-care visits, antibiotic prescriptions, work and school absence, and-at the severe end-hospitalization and death worldwide. The search for safe, inexpensive, and scalable preventive strategies has repeatedly turned to micronutrients, and Vitamin D has attracted particular attention because of its dual role in skeletal and immune physiology. Beyond its classical function in calcium homeostasis, the active metabolite 1,25-dihydroxyvitamin D modulates innate immunity, including the induction of antimicrobial peptides such as cathelicidin (LL-37) and β-defensins in airway epithelial cells, which provide a first line of defense against inhaled pathogens (Hiemstra, 2007). This mechanistic plausibility, together with the seasonal coincidence of wintertime Vitamin D deficiency and respiratory-virus circulation, framed the central hypothesis that correcting low Vitamin D status might reduce infection risk.

Observational studies have repeatedly reported inverse associations between serum 25(OH)D concentrations and the incidence of respiratory infections, but such associations are vulnerable to reverse causation-acute and chronic illness lowers circulating 25(OH)D-and to confounding by outdoor activity, adiposity, and overall health (Autier *et al*., 2017; Ganmaa *et al*., 2021). Randomized controlled trials are therefore the decisive source of evidence, and these have multiplied over the past fifteen years. Yet individual trials have reached strikingly different conclusions, ranging from a halving of infection risk in Vitamin-D-deficient children (Camargo *et al*., 2012; Urashima *et al*., 2010) to clearly null findings in replete or unselected adults (Camargo *et al*., 2024; Murdoch *et al*., 2012). This heterogeneity-driven by differences in baseline Vitamin D status, dosing regimen, age, and outcome ascertainment-has made the literature unusually dependent on careful quantitative synthesis.

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The purpose of this review is to compile and interpret the randomized evidence on Vitamin D supplementation for the prevention of ARIs using metadata drawn from PubMed-indexed publications. Three questions organize the synthesis: (1) What is the overall pooled effect of supplementation on ARI risk, and how has it evolved as larger trials have been added? (2) Which participant- and intervention-level factors modify that effect? (3) What are the implications for clinical and public-health practice? By tracing the trajectory of the pooled estimate across successive meta-analyses, the review highlights a methodologically instructive case in which an apparently settled positive finding has been progressively attenuated by the accumulation of well-powered trials.

METHODOLOGY

Literature search and information sources

Bibliographic metadata were retrieved from PubMed and full texts, where openly licensed, from PubMed Central. Searches combined controlled vocabulary and free-text terms for the exposure ("Vitamin D," "cholecalciferol," "ergocalciferol," "25-hydroxyvitamin D") with terms for the outcome ("acute respiratory tract infection," "respiratory infection," "influenza," "upper respiratory tract infection") and for study design ("randomized controlled trial," "meta-analysis," "systematic review"). Reference lists of the major pooled analyses were inspected to ensure that landmark primary trials were captured. The corpus reflects literature indexed through mid-2026.

Eligibility criteria

Eligible primary studies were randomized, placebo- or lower-dose-controlled trials administering Vitamin D (D_3 or D_2) for any duration in which incidence of acute respiratory infection was a prospectively collected, pre-specified outcome. Eligible secondary studies were systematic reviews with meta-analysis of such trials. Reviews of Vitamin D for non-respiratory endpoints were used only for background and mechanistic context. Open-label designs, bolus-only follow-up reports, and trials without usable ARI data were noted but de-emphasized in the quantitative narrative, mirroring the exclusion logic of the principal pooled analyses.

Data extraction and synthesis

For each included study the following fields were extracted: first author and year, design, sample size, population and baseline Vitamin D status, dosing regimen, primary outcome definition, the principal effect estimate with its 95% confidence interval, and, where reported, heterogeneity (I^2) and serious-adverse-event data. Because the underlying trials measure related but non-identical outcomes (e.g., "proportion with ≥1 ARI" versus "infection rate ratio"), results are presented as reported rather than re-pooled, and emphasis is placed on the three sequential meta-analyses that share a common analytic lineage. Effect estimates below 1.0 indicate fewer infections with Vitamin D. The study-selection process is summarized in Figure 1.

RESULTS

Characteristics of the evidence base

The randomized evidence spans more than fifteen years and a wide range of ages, latitudes, and baseline Vitamin D states-from severely deficient Mongolian schoolchildren with median 25(OH)D near 7 ng/mL (Camargo *et al*., 2012) to largely replete older adults in the Vitamin D and OmegA-3 TriaL (VITAL), whose mean baseline 25(OH)D approached 31 ng/mL (Camargo *et al*., 2024). Table 1 summarizes the landmark primary trials and the principal pooled analyses that anchor this synthesis.

Early trials: large effects in deficient populations

The earliest rigorously designed trials were conducted in young, often Vitamin-D-deficient populations and reported sizeable benefits. In Japanese schoolchildren, daily winter supplementation with 1,200 IU reduced laboratory-confirmed influenza A from 18.6% to 10.8% (relative risk 0.58, 95% CI 0.34-0.99), with a more pronounced effect in children not already taking supplements (Urashima *et al*., 2010). Among severely deficient Mongolian children, Vitamin-D-fortified milk roughly halved parent-reported ARIs (rate ratio 0.52, 95% CI 0.31-0.89) over a winter season (Camargo *et al*., 2012). These trials established proof of concept but were modest in size and conducted in populations with low baseline status-precisely the conditions later identified as most favorable to benefit.

The 2017 individual-participant-data meta-analysis

The pivotal synthesis pooled individual participant data from 25 RCTs comprising 11,321 participants aged 0-95 years, with data obtained for 96.6% of enrollees (Martineau *et al*., 2017). Overall, supplementation reduced the risk of at least one ARI (Adjusted Odds Ratio [aOR] 0.88, 95% CI 0.81-0.96). The same dataset was reported in expanded form as a Health Technology Assessment monograph (Martineau *et al*., 2019). Crucially, the benefit was not uniform. Protection was confined to regimens delivering Vitamin D daily or weekly without large bolus doses (aOR 0.81, 0.72-0.91), whereas bolus regimens showed no effect (aOR 0.97, 0.86-1.10). Within the daily/weekly stratum, the effect was dramatic among the profoundly deficient (baseline 25[OH]D < 25 nmol/L: aOR 0.30, 0.17-0.53) and attenuated among the relatively replete (≥ 25 nmol/L: aOR 0.75, 0.60-0.95). Serious adverse events were not increased (aOR 0.98, 0.80-1.20). These subgroup contrasts, displayed in Figure 2, became the interpretive lens for all subsequent work.

Successive updates and the drift toward the null

As the trial base expanded, the same investigator group produced two updates. The 2021 aggregate-data analysis incorporated 46 eligible RCTs, with primary-outcome data for 48,488 participants across 43 studies, and found a smaller but still significant effect (OR 0.92, 95% CI 0.86-0.99; I^2 = 35.6%) (Jolliffe *et al.*, 2021). Protection persisted in pre-specified strata-daily dosing (OR 0.78, 0.65-0.94), daily-equivalent doses of 400-1,000 IU (OR 0.70, 0.55-0.89), trial duration ≤ 12 months (OR 0.82, 0.72-0.93), and ages 1.00-15.99 years (OR 0.71, 0.57-0.90)-though formal interaction tests were no longer significant.

The 2025 stratified update added six further RCTs (19,337 participants), including one large trial of 15,804 individuals, bringing the pooled total to 40 studies and 61,589 participants (Jolliffe *et al.*, 2025). The overall estimate moved to OR 0.94 (95% CI 0.88-1.00), with the confidence interval now touching 1.00 and the p-value reaching only 0.057-i.e., no longer statistically significant. Pre-specified subgroup analyses no longer detected effect modification by age, baseline status, dosing frequency, or dose size, and a funnel plot showed left-sided asymmetry (Egger's test p=0.0020), consistent with small-study effects or publication bias. Serious adverse events again did not differ from placebo (OR 0.96, 0.90-1.04). Table 2 and Figure 3 trace this trajectory.

Large null trials in unselected or replete populations

Several individually well-powered trials reported null results, and these drove much of the attenuation. The VIDARIS trial randomized 322 healthy New Zealand adults to high-dose monthly Vitamin D and found no reduction in the number, duration, or severity of upper respiratory infections (RR 0.97, 95% CI 0.85-1.11) (Murdoch *et al.*, 2012)-a regimen that,

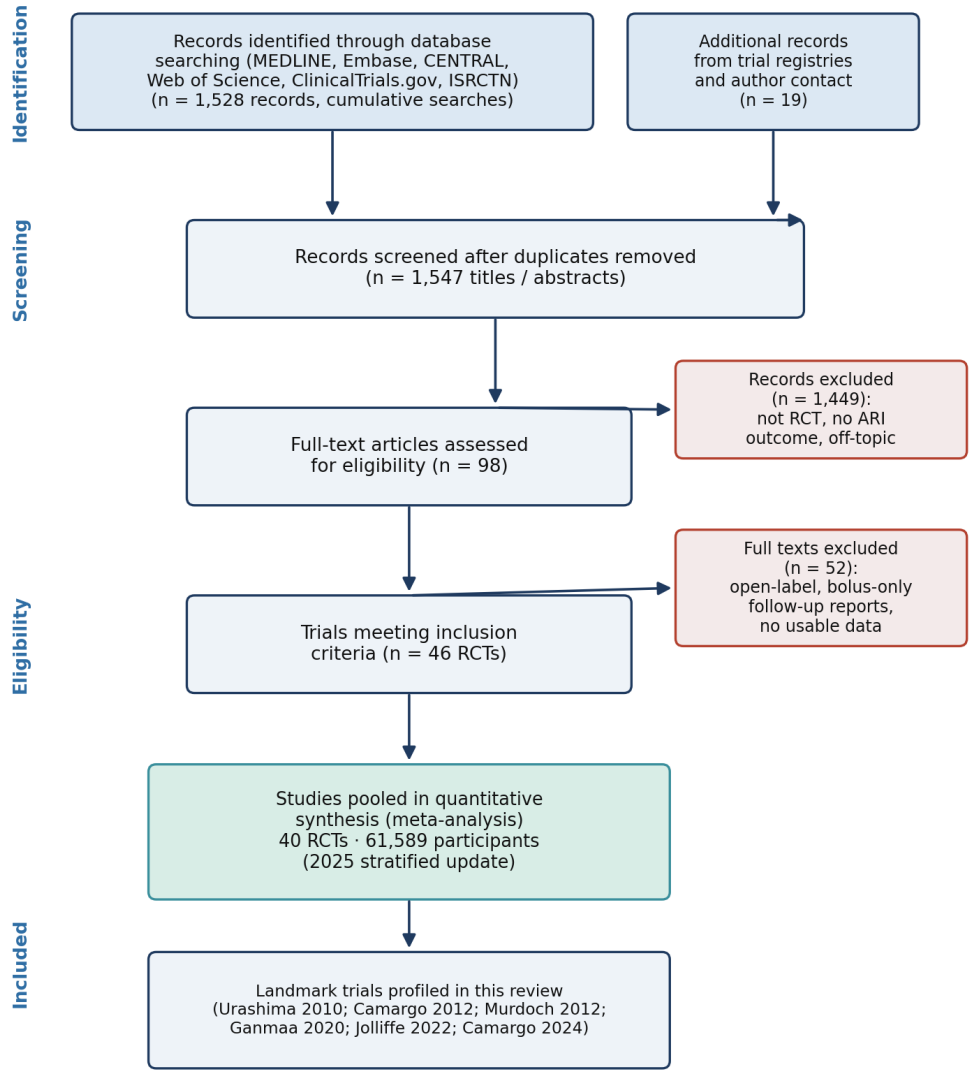


Figure 1: PRISMA-style schematic of study identification, screening, and inclusion. Counts reflect the cumulative search underlying the principal pooled analyses synthesized here.

Table 1: Characteristics and principal findings of landmark trials and pooled analyses.

Study (year)	Design	N	Population / baseline 25(OH)D	Regimen	Principal finding
Urashima *et al.* (2010)	RCT	334	Japanese School Children	1,200 IU/day (winter)	Influenza A 10.8% vs 18.6%; RR 0.58 (0.34-0.99)
Camargo *et al.* (2012)	RCT (cluster)	247	Mongolian children; median 7 ng/mL	300 IU/day fortified milk	ARI rate ratio 0.52 (0.31-0.89)
Murdoch *et al.* (2012) - VIDARIS	RCT	322	Healthy NZ adults; mean 29 ng/mL	200,000 IU ×2 then 100,000 IU/month	URTI RR 0.97 (0.85-1.11); null
Ganmaa *et al.* (2020)	RCT	8,851	Deficient Mongolian children; 95.6% <20 ng/mL	14,000 IU/week × 3 y	ARI hospitalization RR 0.86 (0.52-1.40); null
Jolliffe *et al.* (2022) - CORONAVIT	RCT (test-and-treat)	6,200	UK adults ≥16 y; suboptimal status	800 or 3,200 IU/day × 6 mo	ARI OR 1.09-1.26; null
Camargo *et al.* (2024) - VITAL	RCT	15,804	Older US adults; mean 31 ng/mL	2,000 IU/day	URI OR 0.96 (0.86-1.06); null
Martineau *et al.* (2017)	IPD meta-analysis	11,321	25 RCTs, ages 0-95	Mixed	ARI aOR 0.88 (0.81-0.96)
Jolliffe *et al.* (2021)	Aggregate meta-analysis	48,488	43 RCTs	Mixed	ARI OR 0.92 (0.86-0.99)
Jolliffe *et al.* (2025)	Stratified meta-analysis	61,589	40 RCTs	Mixed	ARI OR 0.94 (0.88-1.00); p = 0.057

Note. RCT = Randomized Controlled Trial; IPD = Individual Participant Data; ARI = Acute Respiratory Infection; URTI/URI = Upper Respiratory Tract Infection; aOR = Adjusted Odds Ratio; RR = Risk/Rate Ratio; CI = 95% confidence interval. To convert 25(OH)D from ng/mL to nmol/L, multiply by 2.496.

in retrospect, used the bolus-style dosing later shown to be ineffective. In deficient Mongolian schoolchildren, three years of weekly 14,000 IU did not reduce tuberculosis infection or acute respiratory infection (hospitalization RR 0.86, 0.52-1.40) despite robust biochemical repletion (Ganmaa *et al.*, 2020). The pragmatic CORONAVIT test-and-treat trial in 6,200 UK adults found no reduction in all-cause ARI or COVID-19 with either 800 or 3,200 IU/day (Jolliffe *et al.*, 2022). Finally, a pre-specified analysis of 15,804 VITAL participants-generally replete older adults-showed no overall effect of 2,000 IU/day on upper respiratory infection (OR 0.96, 0.86-1.06), with only a non-significant signal in the small, profoundly deficient subgroup (OR 0.60, 0.28-1.30; *n*=255) (Camargo *et al.*, 2024).

Population-specific and micronutrient syntheses

Syntheses restricted to particular populations reinforce the picture of a small, conditional effect. In healthy children, neither an earlier review of seven RCTs (ARI RR 0.79, 95% CI 0.55-1.13) (Xiao *et al.*, 2015) nor a later analysis of eight RCTs (OR 0.98, 0.90-1.08) found an overall reduction, although both noted ancillary signals-reduced asthma exacerbations in the former and fewer influenza A episodes with higher doses in the latter (Fang *et al.*, 2023). Among older adults, a synthesis of twelve trials (41,552 participants) found essentially no effect (RR 0.99, 0.97-1.02; I^2 = 0%), with at most a non-significant trend in those starting below 50 nmol/L (Jia *et al.*, 2024). A broader micronutrient meta-analysis estimated a marginal benefit for the Vitamin D arm (RR 0.97, 0.94-1.00) alongside a modest shortening of symptom duration (Abioye *et al.*, 2021). An umbrella review of Vitamin D and non-skeletal outcomes likewise concluded that prevention of upper respiratory infection was among the few endpoints with suggestive support (Autier *et al.*, 2017). Table 3 consolidates the quantitative signal by population stratum.

DISCUSSION

Principal findings

Three conclusions emerge from the randomized evidence. First, Vitamin D supplementation is safe: across tens of thousands of randomized participants, serious adverse events were not increased (Jolliffe *et al.*, 2025; Martineau *et al.*, 2017). Second, any benefit for ARI prevention is small in the general population and has become statistically uncertain as the trial base has grown, with the pooled odds ratio migrating from 0.88 in 2017 to a borderline 0.94 (p=0.057) in 2025 (Jolliffe *et al.*, 2021, 2025; Martineau *et al.*, 2017). Third, the most credible benefit is conditional-concentrated among people who are genuinely deficient at baseline and who receive Vitamin D in regular daily or weekly physiological doses rather than infrequent large boluses (Martineau *et al.*, 2017).

Table 2: **Evolution of the pooled estimate across the three sequential meta-analyses sharing a common analytic lineage.**

Meta-analysis	RCTs (*n*)	Participants	Pooled OR (95% CI)	Interpretation
Martineau *et al.* (2017), IPD	25	11,321	0.88 (0.81-0.96)	Significant overall protection; strong effect modification
Jolliffe *et al.* (2021), aggregate	43	48,488	0.92 (0.86-0.99)	Smaller but significant; effect in daily / low-dose strata
Jolliffe *et al.* (2025), stratified	40	61,589	0.94 (0.88-1.00)	No longer significant (p=0.057); no subgroup signal

Note. OR = Odds Ratio for experiencing ≥1 acute respiratory infection; IPD = Individual Participant Data. Participant counts reflect those contributing to the primary outcome. The progressive widening toward 1.00 illustrates how accumulating well-powered trials can attenuate an initially significant pooled estimate.

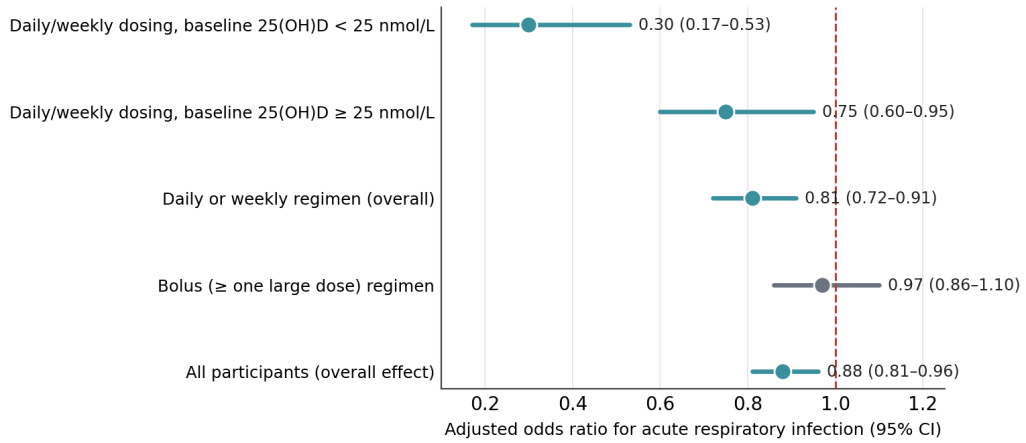


Figure 2: Effect modification by dosing regimen and baseline Vitamin D status in the 2017 individual-participant-data meta-analysis (Martineau *et al.*, 2017). Benefit concentrates in daily/weekly regimens and in the most deficient participants.

Why did the effect attenuate?

The drift toward the null is itself instructive. Part of the explanation is statistical: early meta-analyses were weighted by small trials in deficient populations, where effects are largest, whereas later updates added very large trials in replete or unselected groups, where effects are negligible (Camargo *et al.*, 2024; Jolliffe *et al.*, 2022). The 2025 funnel-plot asymmetry (Egger's p=0.0020) further suggests that small-study effects or selective publication inflated earlier estimates (Jolliffe *et al.*, 2025). This pattern-an initially significant pooled estimate eroded by the arrival of well-powered trials-is a recurring motif in nutritional epidemiology and a caution against over-interpreting early syntheses dominated by small studies.

Biological reasoning aligns with the statistics. If Vitamin D acts permissively-enabling normal antimicrobial-peptide responses that are impaired only when status is low (Hiemstra, 2007)-then supplementing already-replete individuals would not be expected to help, exactly as the replete-population trials show. Under this model, the relevant clinical question is not "does everyone benefit from Vitamin D?" but "does correcting deficiency restore a defense that deficiency had compromised?" The dosing contrast points the same way: daily or weekly regimens maintain steady 25(OH)D concentrations, whereas large boluses produce supraphysiological peaks and troughs and may perturb Vitamin D catabolism, plausibly explaining their lack of benefit (Martineau *et al.*, 2017).

Comparison with existing literature

Population-specific syntheses are consistent with a conditional, modest effect. Reviews in healthy children and in older adults found no overall reduction in ARIs but preserved hints of benefit in deficient or higher-dose subgroups (Fang *et al.*, 2023; Jia *et al.*, 2024; Xiao *et al.*, 2015), while broader appraisals of Vitamin D and non-skeletal health single out respiratory infection as one of the more defensible-if still uncertain-indications (Autier *et al.*, 2017; Ganmaa *et al.*, 2021). No major synthesis reports net harm, and the safety signal is reassuringly stable across analyses.

Implications for practice and policy

The evidence supports a precision-prevention rather than a mass-supplementation stance. Identifying and correcting genuine Vitamin D deficiency-common in winter, at high latitudes, and in housebound, darker-skinned, or institutionalized individuals-is a defensible, low-cost intervention with an excellent safety profile and benefits that extend beyond respiratory infection. By contrast, the data do not support routine high-dose or bolus

supplementation of Vitamin-D-replete people for the express purpose of preventing colds or influenza (Camargo *et al.*, 2024; Jolliffe *et al.*, 2022). Where supplementation is used, daily or weekly physiological dosing is preferable to infrequent large boluses on both efficacy and pharmacological grounds.

Limitations

This review compiles published trial-level and pooled metadata rather than re-analyzing individual participant data, so it inherits the limitations of its sources: heterogeneous outcome definitions (laboratory-confirmed influenza versus self-reported colds), variable adherence, differing assays for 25(OH)D, and inconsistent reporting of baseline status. The constituent trials differ in latitude, season, and co-interventions, and pooled estimates carry non-trivial statistical heterogeneity. The funnel-plot asymmetry noted in the most recent update implies that even the pooled literature may overstate benefit. Finally, the corpus reflects publications indexed at the time of compilation; ongoing and future trials-particularly those enrolling deficient participants and using daily dosing-could refine these conclusions.

Future research

The decisive trials have not yet been done in the population the evidence implicates. What is needed is adequately powered randomization of genuinely deficient individuals (e.g., baseline 25[OH]D below 25-30 nmol/L) to daily or weekly physiological Vitamin D versus placebo, with laboratory-confirmed respiratory outcomes and pre-registered subgroup hypotheses. Mechanistic substudies linking on-treatment 25(OH)D, antimicrobial-peptide induction, and infection outcomes would help convert an association into a defensible causal account. Until such targeted trials report, the prudent reading is that Vitamin D corrects a deficiency-related vulnerability rather than acting as a general-purpose prophylactic.

Table 3: Quantitative synthesis of effect by population and modifying factor.

Stratum / factor	Representative source	Effect estimate (95% CI)	Direction
Profoundly deficient (<25 nmol/L), daily/weekly	Martineau *et al.* (2017)	aOR 0.30 (0.17-0.53)	Strong benefit
Daily dose 400-1,000 IU	Jolliffe *et al.* (2021)	OR 0.70 (0.55-0.89)	Benefit
Children aged 1-16 y	Jolliffe *et al.* (2021)	OR 0.71 (0.57-0.90)	Benefit
Bolus (large intermittent) dosing	Martineau *et al.* (2017)	aOR 0.97 (0.86-1.10)	No effect
Replete / unselected older adults	Camargo *et al.* (2024)	OR 0.96 (0.86-1.06)	No effect
Overall, most recent pooling	Jolliffe *et al.* (2025)	OR 0.94 (0.88-1.00)	Borderline / null
Serious adverse events	Jolliffe *et al.* (2025)	OR 0.96 (0.90-1.04)	No excess harm

Note. Estimates are reproduced as reported in the cited sources and are not re-pooled here. aOR = adjusted odds ratio; OR = odds ratio. Benefit is most evident where baseline deficiency is severe and dosing is regular and physiological.

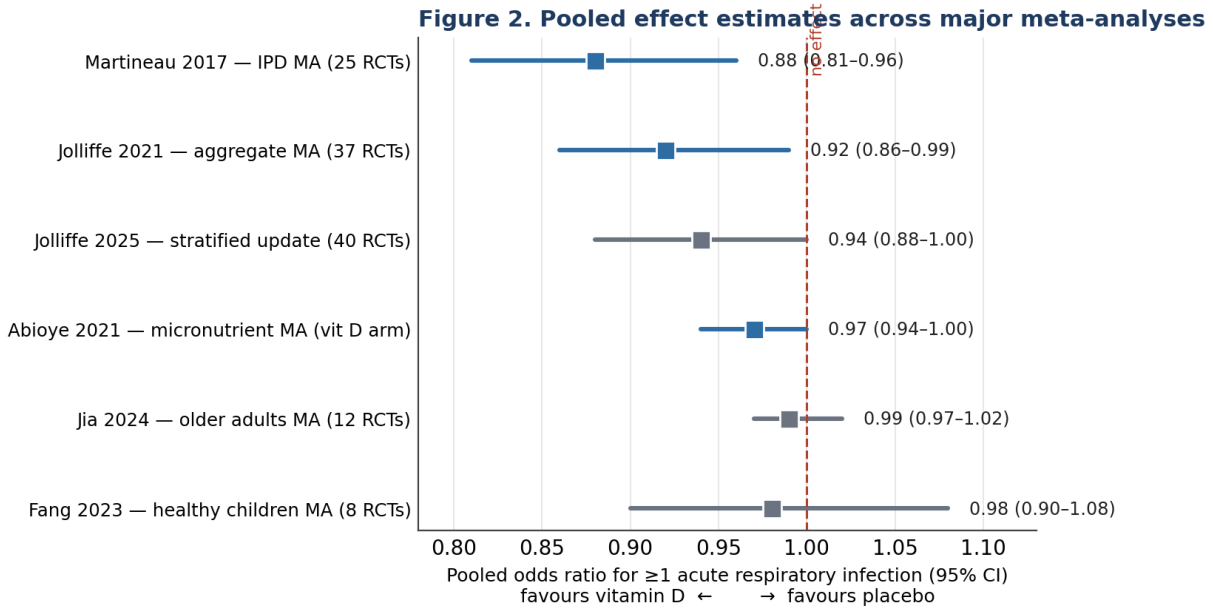


Figure 3: Pooled odds ratios for acute respiratory infection across major meta-analyses. Blue markers denote statistically significant estimates; grey markers denote non-significant estimates. The vertical dashed line marks no effect.

CONCLUSION

Vitamin D supplementation is safe and, at most, modestly protective against acute respiratory infection. The pooled randomized estimate has weakened from a clearly significant benefit in 2017 to a borderline, non-significant result in 2025 as large trials in replete and unselected populations have accumulated. The most coherent synthesis of trials, subgroup analyses, and mechanism is that supplementation helps chiefly by correcting genuine deficiency, and chiefly when given in regular physiological doses rather than large intermittent boluses. For practice, this argues for targeted detection and correction of Vitamin D deficiency rather than universal supplementation aimed at preventing respiratory infection-an interpretation that honors both the safety of the intervention and the limits of the evidence.

ABBREVIATIONS

25(OH)D: 25-Hydroxyvitamin D; **ARI:** Acute Respiratory Infection; **RCT:** Randomized Controlled Trial; **IPD:** Individual Participant Data; **URTI:** Upper Respiratory Tract Infection; **URI:** Upper Respiratory Infection; **aOR:** Adjusted Odds Ratio; **RR:** Risk Ratio; **CI:** 95% Confidence Interval; **OR:** Odds Ratio; **I^2:** Statistical Heterogeneity; **IU:** International Units; **D_3:** Cholecalciferol; **D_2:** Ergocalciferol; **LL-37:** Cathelicidin; **β-defensins:** Antimicrobial Peptides in Airway Epithelial Cells; **VITAL:** Vitamin D and OmegA-3 TriaL; **VIDARIS:** Vitamin D3 Supplementation on Upper Respiratory Tract Infections in Healthy Adults; **CORONAVIT:** Test-and-Treat Approach to Vitamin D Supplementation on Risk of All-Cause Acute Respiratory Tract Infection and COVID-19.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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