Vitamin D supplementation to prevent acute respiratory infections: individual participant data meta-analysis

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Declared competing interests of authors: Susanna Esposito reports grants and personal fees from GlaxoSmithKline (GSK) plc (GSK House, Middlesex, UK), grants and personal fees from Pfizer Inc. (New York, NY, USA), grants and personal fees from Sanofi Pasteur MSD [Sanofi Pasteur (Lyon France) and Merck Sharp & Dohme Corp. (MSD, Kenilworth, NJ, USA)], grants from DuPage Medical Group (DMG, Downers Grove, IL, USA), personal fees from Valeas S.p.A. (Milan, Italy), and grants and personal fees from Vifor Pharma (Bern, Switzerland), outside the submitted work. Emma Goodall reports personal fees from GSK outside the submitted work. Wim Janssens reports grants from Instituut voor Innovatie door Wetenschap en Technologie (IWT)–Vlaanderen and from Laboratoires SMB (Brussels, Belgium) during the conduct of the study. David Mauger reports funding from the National Heart, Lung, and Blood Institute, MA, USA. Rachel Neale reports grants from the National Institutes of Health and the Medical Research Council during the conduct of the study. Judy R Rees reports that a use patent is held by Dartmouth College and Dr John A Baron for calcium as a chemopreventive agent. Dr Baron is not an author on this paper but is the principal investigator of the parent study from which the study by Rees (Rees JR, Hendricks K, Barry EL, Peacock JL, Mott LA, Sandler RS, *et al.* Vitamin D_3 supplementation and upper respiratory tract infections in a randomized, controlled trial. *Clin Infect Dis* 2013;**57**:1384–92) was conducted. The patent was previously licensed by Pfizer (with royalties), but has not been licensed for about 5 years. Judy R Rees is not involved in the patent and the patent does not involve vitamin D.

Published January 2019
DOI: 10.3310/hta23020

Scientific summary

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Health Technology Assessment 2019; Vol. 23: No. 2
DOI: 10.3310/hta23020

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Background

Acute respiratory infections (ARIs) are a major cause of global morbidity and mortality. Observational studies report consistent independent associations between low serum concentrations of 25-hydroxyvitamin D [25(OH)D], the major circulating vitamin D metabolite, and susceptibility to ARI. The observation that 25(OH)D supports induction of antimicrobial peptides in response to both viral and bacterial stimuli suggests a potential mechanism by which vitamin D-inducible protection against these outcomes may be mediated. Vitamin D metabolites have also been reported to induce other innate antimicrobial effector mechanisms, including autophagy and synthesis of reactive nitrogen intermediates and reactive oxygen intermediates.

These epidemiological and in vitro data have prompted numerous randomised controlled trials (RCTs) to determine whether or not vitamin D supplementation can decrease the risk of ARI. A total of five aggregate data meta-analyses incorporating data from up to 15 primary trials have been conducted to date, of which two report statistically significant protective effects and three report no statistically significant effects. All but one of these aggregate data meta-analyses reported significant heterogeneity of effect between primary trials.

Such heterogeneity of effect may have arisen as a result of intertrial variation in participant characteristics and in dosing regimens, either of which may modify the effects of vitamin D supplementation on immunity to respiratory pathogens. Subgroup analyses within primary trials of vitamin D supplementation for diverse indications show that participants with lower baseline vitamin D status may derive greater clinical benefit from supplementation than those with higher baseline status. Administration of large boluses of vitamin D has been associated with reduced efficacy for non-classical effects of vitamin D and, in some cases, increased risk of adverse outcomes. Although study-level factors are amenable to exploration via aggregate data meta-analysis of published data, potential effect modifiers operating at an individual level, such as baseline vitamin D status, can only be explored using individual participant data (IPD) meta-analysis. This is because subgroups are not consistently disaggregated in trial reports, and consistent adjustments for potential confounders cannot be applied. In order to determine the overall effect of vitamin D supplementation on the risk of ARI and to identify factors that might modify the effects of this intervention on the risk of ARI, we undertook a meta-analysis of IPD from RCTs that had investigated these outcomes.

Main objectives

1. To determine the overall effect of vitamin D supplementation on the risk of ARI and serious adverse events.
2. To determine whether or not the following factors modify the effect of vitamin D supplementation on the risk of ARI:

    i. baseline vitamin D status
    ii. vitamin D dosing regimen
    iii. size of vitamin D dose
    iv. age
    v. body mass index
    vi. presence versus absence of respiratory comorbidity [e.g. asthma, chronic obstructive pulmonary disease (COPD)]
    vii. influenza vaccination status.

Methods

Data sources

Two investigators searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, ClinicalTrials.gov and the International Standard Randomised Controlled Trials Number (ISRCTN) registry for eligible studies from database inception until December 2015.

Study selection (eligibility criteria)

Randomised, double-blind, placebo-controlled trials of supplementation with vitamin D_3 or vitamin D_2 of any duration were eligible for inclusion in the ARI analysis if they had been approved by a Research Ethics Committee and if data on incidence of ARI were collected prospectively and prespecified as an efficacy outcome. Studies reporting results of long-term follow-up of primary RCTs were excluded.

Data management

Individual participant data were requested from the principal investigator for each eligible trial, and the terms of collaboration were specified in a data transfer agreement, signed by representatives of the data provider and the recipient (Queen Mary University of London). Data relating to study characteristics were extracted for the following variables: setting, eligibility criteria, details of intervention and control regimens, study duration and case definitions for ARI. IPD were extracted for the following variables, when available: baseline data were requested for age, sex, cluster identification (cluster randomised trials only), influenza vaccination status, history of asthma, history of COPD, weight, height (adults and children able to stand) or length (infants), serum 25(OH)D concentration, study allocation (vitamin D vs. placebo) and details of any stratification or minimisation variables. Follow-up data were requested for the total number of ARIs, upper respiratory infections (URIs) and lower respiratory infections (LRIs) experienced during the trial, time from first dose of study medication to first ARI/URI/LRI if applicable, total number of courses of antibiotics taken for ARI during the trial, total number of days off work or school as a result of ARI symptoms during the trial, serum 25(OH)D concentration at final follow-up, duration of follow-up, number and nature of serious adverse events, number of adverse reactions (incident hypercalcaemia or renal stones) and end-trial status (completed vs. withdrew vs. lost to follow-up vs. died).

Data were de-identified at source prior to transfer via e-mail. On receipt, three investigators assessed data integrity by performing internal consistency checks and by attempting to replicate the results of the analysis for ARI incidence when this was published in the trial report. Study authors were contacted to provide missing data and to resolve queries arising from these integrity checks. Once queries had been resolved, clean data were uploaded to the main study database.

Assessment of validity

The Cochrane Collaboration Risk of Bias tool was used to assess the following variables: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; completeness of outcome data; evidence of selective outcome reporting; and other potential threats to validity.

Data synthesis

Initially, all studies were reanalysed separately; the original authors were asked to confirm the accuracy of this reanalysis when it had been performed previously, and any discrepancies were resolved. Then we performed both one-step and two-step IPD meta-analysis using a random-effects model adjusted for age, sex and study duration to obtain the pooled intervention effect on (1) the proportion of participants experiencing at least one ARI, (2) ARI rate and (3) time to first ARI with a 95% confidence interval (CI). The number needed to treat (NNT) for an additional beneficial outcome was calculated in which meta-analysis of dichotomous outcomes revealed a statistically significant beneficial effect of allocation to vitamin D compared with placebo.

In order to explore the causes of heterogeneity and identify factors modifying the effects of vitamin D supplementation on ARI risk, we also performed prespecified subgroup analyses by extending the one-step meta-analysis framework to include treatment–covariate interaction terms. Subgroups were defined

according to baseline vitamin D status [serum 25(OH)D concentration of < 25 nmol/l vs. ≥ 25 nmol/l], vitamin D dosing regimen [daily or weekly administration without bolus dosing vs. administration of a regimen including at least one bolus dose of ≥ 30,000 IU (international units) of vitamin D], dose size (daily equivalent < 800 IU vs. 800–1999 IU vs. ≥ 2000 IU), age (≤ 1 year vs. 1.1–15.9 years vs. 16–65 years vs. > 65 years), body mass index (< 25 kg/m^2 vs. ≥ 25 kg/m^2) and presence versus absence of asthma, COPD and previous influenza vaccination. Interaction analyses were adjusted for potential confounders (age, sex and study duration) in order to ensure that reported subgroup effects were independent. In order to minimise the chance of type I error arising from multiple analyses, significance was inferred only when *p*-values for treatment–covariate interaction terms were < 0.05.

Results

We identified 25 RCTs (total 11,321 participants, aged from 0 to 95 years) that were eligible for the ARI analysis. These trials were conducted in 15 different countries on four continents and enrolled participants of both sexes from birth to 95 years of age. The mean baseline 25(OH)D concentration ranged from 18.9 to 88.9 nmol/l. All studies administered oral vitamin D_3 to participants in the intervention arm: this was given as monthly to once every 3 months bolus doses in seven studies, as weekly doses in three studies, as a daily dose in 12 studies and as a combination of bolus and daily doses in three studies. Study duration ranged from 7 weeks to 1.5 years. Incidence of ARI was a primary or coprimary outcome for 14 studies and a secondary outcome for 11 studies.

Individual participant data were obtained for 10,933 out of 11,321 (96.6%) participants in these studies. In the one-step IPD meta-analysis, vitamin D supplementation resulted in a statistically significant reduction in the proportion of participants experiencing at least one ARI [adjusted Odds Ratio (aOR) 0.88, 95% CI 0.81 to 0.96; $p = 0.003$, p for heterogeneity < 0.001; 10,933 participants in 25 studies]. The number needed to benefit was 33 (95% CI 20 to 101). Statistically significant protective effects of vitamin D were also seen for one-step analyses of ARI rate [adjusted incidence rate ratio (aIRR) 0.96, 95% CI 0.92 to 0.997; $p = 0.04$; p for heterogeneity < 0.001; 10,703 participants in 25 studies] but not for analysis of time to first ARI [adjusted hazard ratio (aHR) 0.95, 95% CI 0.89 to 1.01; $p = 0.09$; p for heterogeneity < 0.001; 9108 participants in 18 studies]. Two-step analyses showed consistent effects for the proportion of participants experiencing at least one ARI (aOR 0.80, 95% CI 0.69 to 0.93; $p = 0.004$; p for heterogeneity = 0.001; 10,899 participants in 24 studies), ARI rate (aIRR 0.91, 95% CI 0.84 to 0.98; $p = 0.018$; p for heterogeneity < 0.001; 10,703 participants in 25 studies) and time to first ARI (aHR 0.92, 95% CI 0.85 to 1.00; $p = 0.051$; p for heterogeneity = 0.14; 9108 participants in 18 studies). Vitamin D did not influence the proportion of participants experiencing at least one serious adverse event (aOR 0.98, 95% CI 0.80 to 1.20; $p = 0.83$). This evidence was assessed as being of high quality.

Subgroup analyses revealed a strong protective effect of vitamin D supplementation among individuals with baseline circulating 25(OH)D concentration of < 25 nmol/l (aOR 0.58, 95% CI 0.40 to 0.82; NNT 8, 95% CI 5 to 21; 538 participants in 14 studies; within subgroup, $p = 0.002$), and no statistically significant effect among those with baseline 25(OH)D concentration of ≥ 25 nmol/l (aOR 0.89, 95% CI 0.77 to 1.04; 3634 participants in 19 studies; within subgroup, $p = 0.15$; for interaction, $p = 0.01$). Stronger protective effects of vitamin D against ARIs were also seen in trials in which vitamin D was administered using a daily or weekly regimen without additional bolus doses (aOR 0.81, 95% CI 0.72 to 0.91; NNT 20, 95% CI 13 to 43; 5133 participants in 15 studies; within subgroup, $p < 0.001$); no such protective effect was seen among participants in trials in which at least one bolus dose of vitamin D was administered (aOR 0.97, 95% CI 0.86 to 1.10; 5800 participants in 10 studies; within subgroup, $p = 0.67$; p for interaction = 0.05). For both of these subgroup analyses, broadly consistent effects were observed for event rate analysis and survival analysis. The *p*-values for interaction were > 0.05 for all other potential effect modifiers investigated.

We then proceeded to stratify the subgroup analyses according to dosing frequency, in order to provide a cleaner look at results of subgroup analyses under the assumption that administration of bolus doses was ineffective.The results of this exploratory analysis suggested that daily or weekly administration of vitamin D induced an even greater degree of protection against ARI among participants with baseline circulating 25(OH)D concentrations of < 25 nmol/l than in the unstratified analysis (aOR 0.30, 95% CI 0.17 to 0.53; NNT 4, 95% CI 3 to 7; 234 participants in six studies; within subgroup, $p < 0.001$). Moreover, administration of daily or weekly vitamin D also protected against ARI among participants with higher baseline 25(OH)D concentrations (aOR 0.75, 95% CI 0.60 to 0.95; NNT 15, 95% CI 9 to 86; 1603 participants in six studies; within subgroup, $p = 0.02$). The *p*-value for interaction for this subgroup analysis was 0.006, indicating that protective effects of daily or weekly vitamin D supplementation were significantly greater in the subgroup of participants with profound vitamin D deficiency. No other statistically significant interaction was seen; notably, bolus dose vitamin D supplementation did not offer any protection against ARI even when administered to those with circulating 25(OH)D concentrations of < 25 nmol/l (aOR 0.82, 95% CI 0.51 to 1.33; 304 participants in eight studies; within subgroup, $p = 0.43$).

Limitations

Our power to detect effects of vitamin D supplementation was limited for some subgroups [e.g. individuals with baseline 25(OH)D concentration of < 25 nmol/l receiving bolus-dosing regimens]. Null and borderline significant results for analyses of these outcomes may have arisen as a consequence of type II error. Data relating to adherence to study medication were not available for all subjects. However, the inclusion of non-adherent participants would bias results of our intention-to-treat analysis towards the null; thus, we conclude that effects of vitamin D in those who are fully adherent to supplementation will be no less than those reported for the study population overall. Finally, we caution that study definitions of ARI were diverse, and virological, microbiological and/or radiological confirmation was obtained for a minority of events. ARI is often a clinical diagnosis in practice, however, and as all studies were double-blind and placebo-controlled, differences in incidence of events between study arms cannot be attributed to observation bias.

Conclusions

Implications for health care

Our synthesis of the current evidence suggests that vitamin D supplementation can prevent ARIs, broadly defined. We identified that the greatest potential benefit is for those individuals who are very deficient in vitamin D. Those receiving daily or weekly supplementation without additional bolus doses also experienced particular benefit. Our results add to the body of evidence supporting the introduction of public health measures, such as food fortification, to improve vitamin D status in settings in which profound vitamin D deficiency is common.

Recommendations for research

1. Incorporation of additional IPD from ongoing trials in the field has the potential to increase statistical power for subgroup analyses; this IPD meta-analysis should therefore be updated when a significant new body of data has accumulated.
2. Given the major impact of ARIs on economic productivity and health-care use, our findings are likely to influence the economic case for the introduction of vitamin D fortification of foods in the UK. Economic models of the cost-effectiveness of vitamin D fortification in the UK should therefore be updated to take account of the previously unappreciated protective effects of vitamin D against ARIs.

Study registration

This study is registered as PROSPERO CRD42014013953.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.236

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 13/03/25. The contractual start date was in October 2014. The draft report began editorial review in January 2017 and was accepted for publication in October 2017. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

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