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Systematic Review with Meta Analysis

Vitamin D supplementation for the prevention of childhood acute respiratory infections: a systematic review of randomised controlled trials

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Abstract

Results from recent trials assessing the effect of vitamin D supplementation on the prevention of childhood acute respiratory infections (ARI) have been inconsistent. In the present study, we determined whether vitamin D supplementation prevents ARI in healthy children and repeated infections in children with previous ARI. We conducted a systematic literature search using MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. The search included only randomised controlled clinical trials (RCT) comparing vitamin D supplementation with either placebo or no intervention in children younger than 18 years of age. We identified seven RCT and found that the summary estimates were not statistically significantly associated with a reduction in the risk of ARI (relative risk (RR) 0·79, 95 % CI 0·55, 1·13), all-cause mortality (RR 1·18, 95 % CI 0·71, 1·94), or the rate of hospital admission due to respiratory infection in healthy children (RR 0·95, 95 % CI 0·72, 1·26). However, in children previously diagnosed with asthma, vitamin D supplementation resulted in a 74 % reduction in the risk of asthma exacerbation (RR 0·26, 95 % CI 0·11, 0·59; test of heterogeneity, $I^2 = 0{\cdot}0\,\%$). Our findings indicate a lack of evidence supporting the routine use of vitamin D supplementation for the prevention of ARI in healthy children; however, they suggest that such supplementation may benefit children previously diagnosed with asthma. Due to the heterogeneity of the included studies and possible publication biases related to this field, these results should be interpreted with caution.

Key words: Vitamin D: Acute respiratory infections: Randomised controlled trials

Acute respiratory infections (ARI) are the most important global cause of morbidity and mortality in young children. In 2010, an estimated 11·9 million episodes of severe ARI and 3·0 million episodes of very severe ARI in young children resulted in hospital admissions globally[1]. Of the 7·6 million children worldwide who died within the first 5 years of life, almost two-thirds died of infectious diseases, among which pneumonia was the leading cause for a total of 1·396 million deaths[2].

Although vitamin D is widely recognised for its importance in Ca metabolism and bone health, researchers have spent several years focusing on its growing number of possible non-calcaemic health effects[3]. One of the more promising areas of study is the relationship between vitamin D status and respiratory infection. Recent research has indicated that vitamin D may play a role in protecting against ARI by increasing the body's production of naturally acting antibiotics[4]. In some observational studies, low plasma levels of calcidiol,

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; ARI, acute respiratory infections; RCT, randomised controlled trial.

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the accepted marker of vitamin D status, have been observed to be associated with both an increased risk and a greater severity of infection, particularly the infection of the respiratory tract[5–7]. Although the exact mechanisms by which vitamin D may improve immune responses to infection remain unknown, vitamin D supplementation trials on the prevention and adjunct therapy for infection are ongoing. Given its influence on the immune system and inflammatory cascades, vitamin D may play an important role in both the prevention and treatment of infection[8].

Several recent trials investigating the effect of vitamin D supplementation on the prevention of childhood ARI have reported inconsistent results. Therefore, we conducted a study to determine whether vitamin D supplementation prevents ARI in healthy children and repeated episodes of ARI in children previously diagnosed with either asthma or pneumonia.

Materials and methods

Search strategy and selection criteria

We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify studies published before 14 March 2014 that evaluated vitamin D supplementation for the prevention of childhood ARI. We used several search terms, including trials ('randomized controlled trial', 'controlled clinical trial', 'random allocation', 'double-blind method', 'single-blind method', 'placebo', 'randomly', 'clinical trial*' and 'trial*'), vitamin D ('vitamin D', 'vitamin', 'cholecalciferol', 'hydroxycholecalciferol', 'calcifediol', 'ergocalciferol', 'calcidiol', 'vitamin D/blood/25-hydroxyvitamin D', '1,25-dihydroxyvitamin D', '1-α-hydroxyvitamin D', '1-α-hydroxyvitamin D', 'calcitriol', 'alfacalcidol', and 'paricalcitol'), and ARI ('pneumonia', 'respiratory infection*', 'respiratory tract infection*', 'lower respiratory tract infection*', 'LRTI', and 'lower respiratory infection*'). Additional search strategies included hand searches of journals not indexed by the aforementioned electronic sources, Web-based searches, and screening of the reference lists of retrieved studies for additional relevant articles.

The inclusion criteria were as follows: (1) randomised controlled trials (RCT) exploring the effect of vitamin D supplementation on the prevention of ARI, primarily focused on individuals younger than 18 years of age; (2) studies reporting the dosages, modes and durations of vitamin D supplementation; (3) studies reporting the definitions of ARI and the methods used to diagnose ARI or to determine the primary outcomes associated with ARI; (4) studies reporting either the prevalence or the relative risk (RR) estimates, along with either corresponding 95 % CI or raw data enabling the calculation of 95 % CI.

We collected data only from complete published papers, and excluded data from meetings, literature reviews, letters and news articles. We also excluded studies that contained overlapping data. When there were multiple publications involving the same population, the study containing the largest sample size was included. When a study reported results from different subpopulations, we treated the results for each subpopulation independently. We excluded trials that did not include a control group, observational studies and animal studies. We also excluded trials reporting a follow-up rate of <50 % or not reporting a follow-up rate. Trials in which vitamin D was used in combination with other interventions were not included in the final analysis.

Both the titles and the abstracts of all identified studies were screened independently by two researchers (L. X. and Z. Y.). Studies that appeared to be relevant were selected, and full-text versions were subsequently assessed by the same two reviewers. Disagreements were resolved by either consensus or the involvement of a third reviewer (M. W.). Fig. 1 depicts a flow chart for the selection of the articles.

Data collection and methodological quality assessment

We developed and modified a data abstraction form following a training exercise for investigators. We extracted the following data from the eligible studies: (1) general characteristics (title, first author, journal and year of publication); (2) methodology (type of study, country of origin, sequence generation, allocation concealment, masking or blinding, incomplete outcome data, selective reporting and other sources of bias, follow-up duration, and loss to follow-up); (3) characteristics of participants (recruitment site, enrolment periods, mean age and proportion of male participants); (4) trial and control groups (number of eligible trial groups, vitamin D doses and routes of administration, trial duration, frequency, and details of comparison); (5) primary outcomes. We contacted the authors of the included studies to obtain additional information regarding data items that required clarification.

The methodological quality of sequence generation, allocation concealment, blinding, missing outcome data, selective reporting, and other biases was subsequently assessed using the Cochrane Collaboration's risk of bias method. Each domain was rated as low, high or unclear regarding the risk of bias, and the overall risk of bias was rated as low (low risk of bias for all domains), high (high risk of bias for one or more domains) or unclear (unclear risk of bias for one or more domains)[9].

Discrepancies were resolved either through discussion with other team members (S. X., K. L. and H. D.) or contact with the original investigators, all of whom received data extraction sheets with requests for correction.

Outcomes

The primary outcome measures of the present study were the prevention of ARI (including influenza, pneumonia and asthma) in healthy children, asthma exacerbation in children with previous ARI, and recurrent pneumonia in children with a prior history of pneumonia. The secondary outcomes of the present study were the prevention of influenza and pneumonia in healthy children, all-cause mortality, the rate of hospital admission due to ARI, and changes in mean serum vitamin D levels.

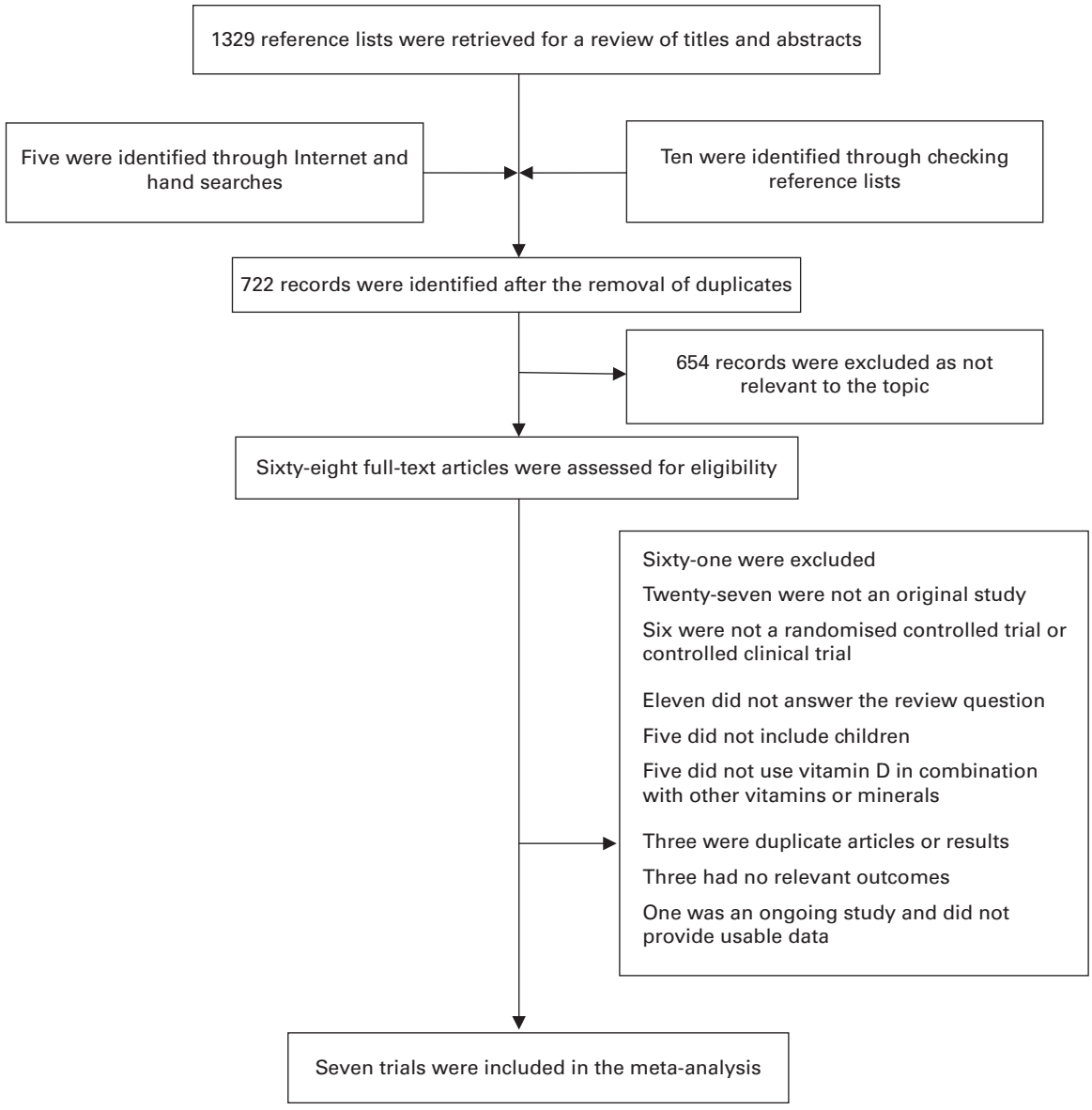

Fig. 1. Flow chart for the selection of studies for the present meta-analysis.

Statistical analysis

For binary outcomes, we calculated risk ratios (RR); for continuous outcomes, we calculated weighted mean differences. A random-effects model was used to estimate the pooled RR and weighted mean differences to account for the heterogeneity of the estimates, and to provide more conservative estimates compared with those generated using the fixed-effects model[10]. The heterogeneity of the outcome measures among the studies was assessed using the χ^2 test-based Q statistic[11]. A significant Q statistic ($P<0{\cdot}10$) indicated heterogeneity in the outcome measures between the studies. We quantified statistical heterogeneity with the I^2 statistic, and used 'small', 'moderate' and 'large' heterogeneity to correspond to I^2 values of 25, 50 and 75 %, respectively[12,13]. We did not conduct subgroup analyses or meta-regression analyses because of the small number of included RCT. We performed sensitivity analyses to establish the robustness of the primary outcomes. To establish the robustness of the primary outcomes via sensitivity analyses, we utilised a fixed-effects model and excluded studies containing small sample sizes. Publication bias was investigated using a funnel plot, in which the standard error of log RR of each study was plotted against its RR, and plot asymmetry was subsequently assessed using Egger's linear regression test[14]. If the regression line did not pass through the origin, asymmetry was assigned; the intercept α provided a measure of asymmetry. The larger the deviation of α from zero, the more pronounced the asymmetry. The analyses were performed using Stata (version 11.0). All P values were two-sided. A P value of $<0{\cdot}05$ was considered to be statistically significant.

Results

Characteristics of the eligible studies

Fig. 1 shows the study profile. A total of 1329 papers were identified via the database search, and fifteen papers were identified via reference lists and hand searches. Following screening, 1276 papers were excluded, and the sixty-eight remaining full-text articles were assessed for eligibility. We excluded an ongoing trial that did not provide any usable data[15]. A total of seven RCT were ultimately included in the meta-analysis (Table 1) [16–22]. Most of the trials (*n* 6/7) were conducted in Asian countries, and all study participants were younger than 18 years of age (Table 1). Of these included trials, six provided data regarding the incidence of ARI; four provided data regarding all-cause mortality; two provided data regarding the incidence of pneumonia; two provided data regarding the incidence of repeated episodes of pneumonia; two reported data regarding the rate of hospital admission; and one reported data regarding the incidences of influenza A and influenza-like illnesses.

The risk of bias was assessed using a risk-of-bias graph (Fig. 2). All of the RCT exhibited adequate sequence generation, and most of the RCT exhibited good allocation concealment, reporting of blinding methods, and incomplete outcome data; however, the extent of selective reporting in three of the seven studies was unclear.

Effect of vitamin D supplementation on the primary outcomes

Overall effects. Data regarding ARI were reported by four trials. We did not observe a statistically significant decrease in the incidence of ARI (RR 0·79, 95 % CI 0·55, 1·13). There was evidence of significant heterogeneity between the studies ($I^2 = 73{\cdot}6\,\%$, $P = 0{\cdot}010$; Fig. 3).

Data regarding all-cause mortality were reported by four trials. We did not observe any statistically significantly association between the summary estimates for the vitamin D supplementation group and a reduction in the risk of all-cause mortality (RR 1·02, 95 % CI 0·92, 1·13). There was no significant heterogeneity observed between the studies ($I^2 = 0\,\%$, $P = 0{\cdot}920$; Fig. 3).

Data regarding pneumonia were reported by three trials. We did not observe any statistically significantly association between the summary estimates for the vitamin D supplementation group and a reduction in the risk of pneumonia (RR 1·06, 95 % CI 0·90, 1·25). There was no significant heterogeneity was observed between the studies ($I^2 = 0\,\%$, $P = 0{\cdot}952$; Fig. 3). Data regarding pneumonia recurrence were reported by two trials. Interestingly, pooled analyses demonstrated that vitamin D supplementation significantly increased the risk of pneumonia recurrence (RR 1·17, 95 % CI 1·00, 1·38). There was evidence of significant heterogeneity between the studies ($I^2 = 95{\cdot}1\,\%$, $P < 0{\cdot}001$) (Fig. 3).

Table 1. Characteristics of clinical trials included in the meta-analysis*

	Participants							
		Age (years)						
Study, year, location	*n*	Mean	SD	Health status	Follow-up	Adherence (100 %)	Dose of vitamin D_3†	Outcomes measured
Urashima, 2010, Japan	430	10·2	2·2	Healthy school children	4 months	77·67	1200 IU/d	Incidence of FLU (A and B), ILI, PNE, ARI, asthma exacerbation and admission to hospital
Manaseki-Holland, 2010, Afghanistan	453	13·19	9·14	Children with pneumonia	3 months	91·61	Single bolus dose of 100 000 IU	Incidence of repeated episodes of PNE during the 90 d post-treatment period, and all-cause mortality
Kumar, 2011, India	2079	< 0·5		Low-birth weight infants	6 months	72	1400 IU/week	Incidence of pneumonia, or all-cause hospital admission or death
Majak, 2011, Poland	48	11·5	3·3	Children with newly diagnosed asthma	6 months	100	500 IU/d	Incidence of asthma exacerbation triggered by ARI
Manaseki-Holland, 2012, Afghanistan	3046	< 1		Healthy infants	18 months	85·88	3-Monthly bolus dose of 100 000 IU	Incidence of PNE, repeated episodes of PNE, rate of hospital admission and all-cause mortality
Camargo, 2012, Mongolia	247	9·97	0·95	Healthy school children	7 weeks	98·79	300 IU/d	Rate of ARI
Choudhary, 2012, India	200	1·16	0·98	Children with severe pneumonia	5 d	84·50	1000 IU for < 1 year and 2000 IU for > 1 year	All-cause mortality

FLU, influenza; ILI, influenza-like illness; PNE, pneumonia; ARI, acute respiratory infection.
* The quality of each included trial was evaluated using the modified Jadad score.
† 1 μg vitamin D = 40 IU.

Data regarding asthma exacerbations triggered by respiratory infections among children with newly diagnosed asthma were reported by two trials. The summarised results indicated that treatment with vitamin D significantly reduces the risk of asthma exacerbation (RR 0·28, 95 % CI 0·12, 0·64). No significant heterogeneity was observed between the studies ($I^2 = 0{\cdot}0\,\%$, $P = 0{\cdot}355$) (Fig. 3). Data regarding the rate of hospital admission due to respiratory infections were reported by two trials. The summary estimates for the vitamin D supplementation group were not statistically significantly associated with a reduction in the risk of hospital admission (RR 0·95, 95 % CI 0·71, 1·25). No significant heterogeneity was observed between the studies ($I^2 = 0\,\%$, $P = 0{\cdot}358$; Fig. 3).

Data regarding influenza A were reported by only one study. Influenza A occurred in eighteen (10·8 %) of the 167 children in the vitamin D supplementation group compared with thirty-one (18·6 %) of the 167 children in the placebo group (RR 0·58, 95 % CI 0·34, 0·99; Fig. 3).

Fig. 4 shows the changes in plasma 25-hydroxyvitamin D (25(OH)D) levels for both the intervention and control groups over a period of 3 months for the three trials from which such data were available. The plasma levels

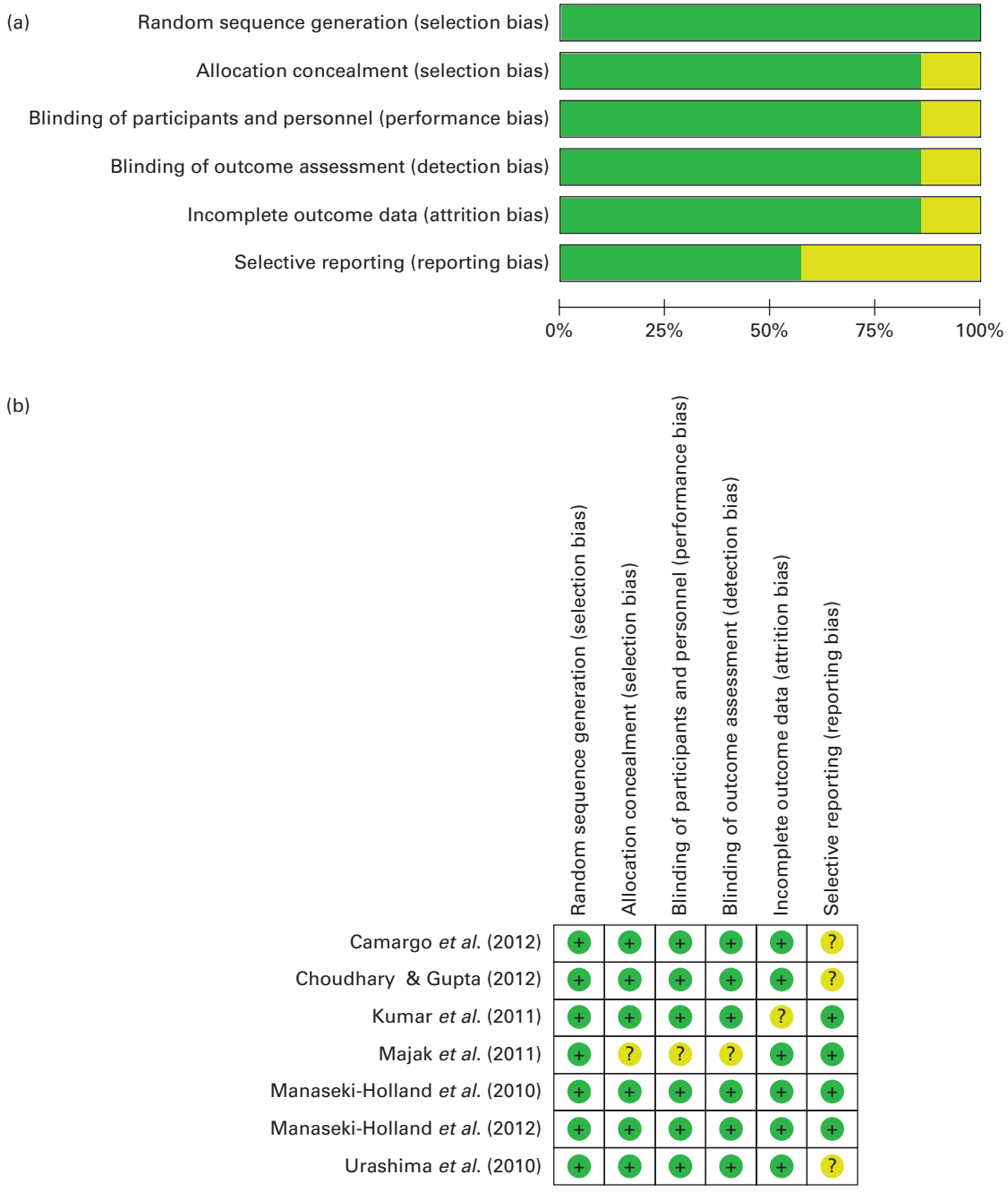

Fig. 2. (a) Risk-of-bias graph and (b) risk-of-bias-summary graph. ■, Low risk of bias; ■, unclear risk of bias; ■, high risk of bias. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn).

of 25(OH)D in the vitamin D supplementation group were significantly higher than those in either the control or placebo group after 3 months (weighted mean difference = 9·06, 95 % CI 5·43, 12·70). There was evidence of significant heterogeneity between the studies ($I^2 = 87·9\,\%$, $P<0·001$).

Sensitivity analyses

The sensitivity analyses of ARI are included in Table 2. Using a fixed-effects model and excluding trials containing fewer than thirty participants per group yielded results similar to those of the primary analysis. The other sensitivity analyses demonstrated that the effect size was significantly reduced (RR 0·76, 95 % CI 0·54, 1·07 *v.* RR 1·02, 95 % CI 0·92, 1·13).

Evaluation of publication bias

We assessed funnel plot asymmetry using Egger's linear regression test. There was no evidence of publication bias regarding either ARI (intercept $\alpha = -2·12$, 95 % CI −9·09, 4·66) or all-cause mortality (intercept $\alpha = 0·37$, 95 % CI −1·39, 2·13). We also generated funnel plots and visually examined these plots for signs of asymmetry. We generated two funnel plots to assess the publication bias of the RR of both ARI and all-cause mortality. For all-cause mortality, the asymmetry observed in the funnel plots was minimal; in contrast, the asymmetry was significant for ARI, which may indicate either the absence of trials with negative results or publication bias (Fig. 5). We did not complete funnel plots for the other outcomes, as only a few studies contributed to the outcome measures.

Discussion

We included and examined seven RCT to assess the effect of vitamin D supplementation on the prevention of ARI in children. Our findings revealed that vitamin D supplementation

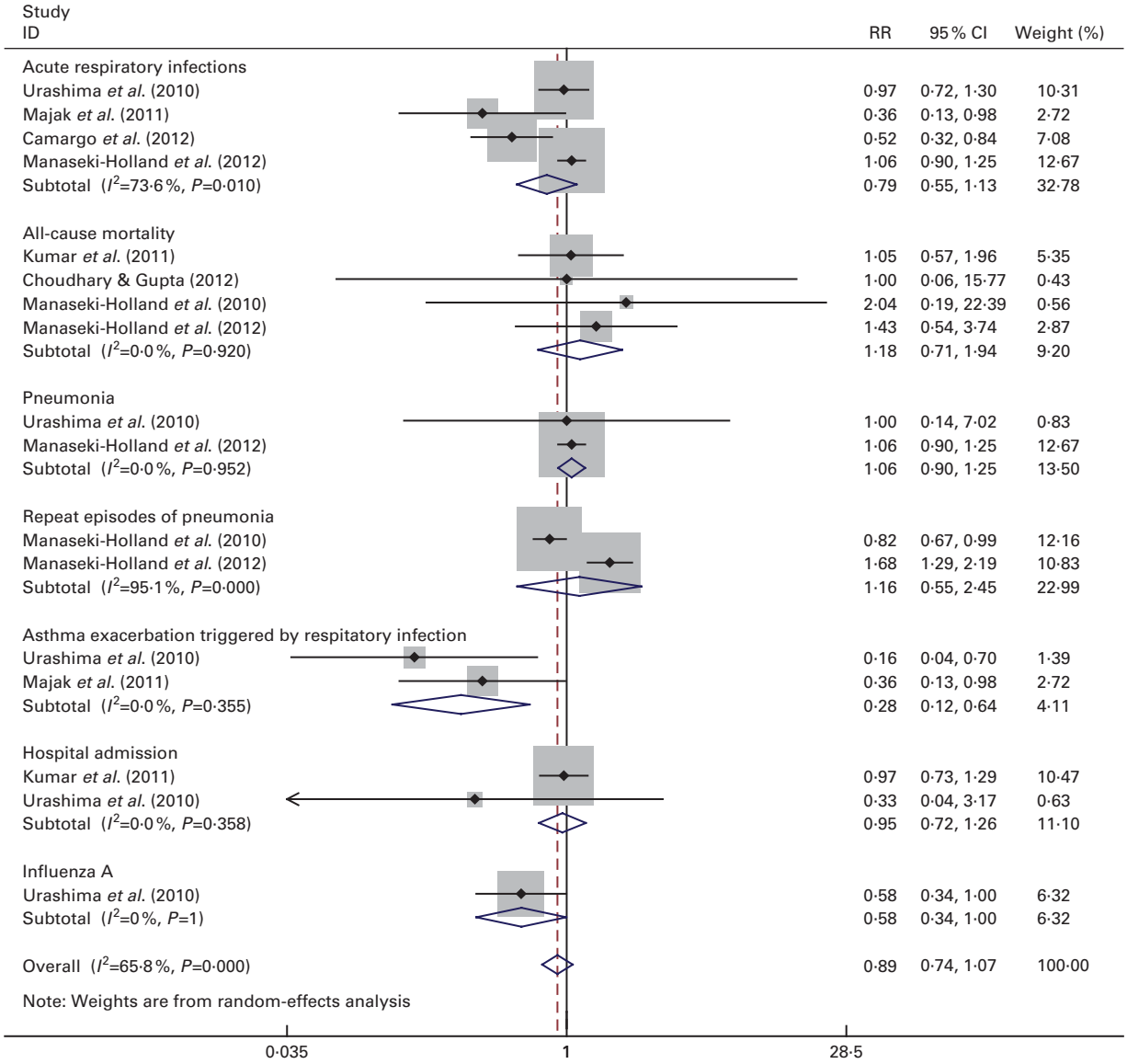

Fig. 3. Effects of vitamin D supplementation on the primary outcomes. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn).

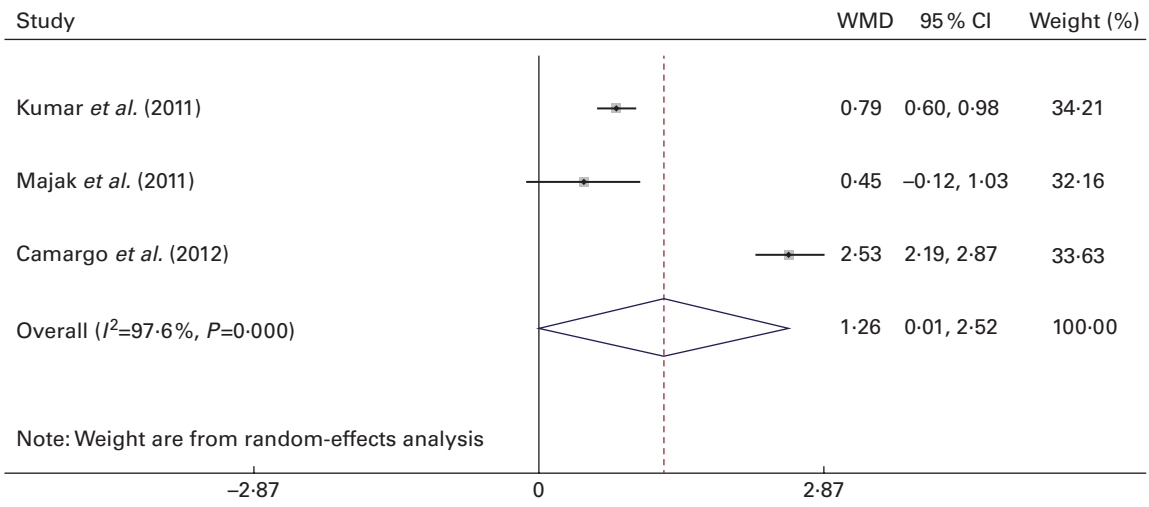

Fig. 4. Effects of vitamin D supplementation on plasma 25-hydroxyvitamin D levels more than 3 months later ($z = 1{\cdot}98$, $P = 0{\cdot}048$). To convert nmol/l to ng/ml for 25-hydroxyvitamin D concentrations, divide by 2·496. WMD, weighted mean difference. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn).

did not significantly reduce the risk of ARI, all-cause mortality, or the rate of hospital admission in healthy children. Due to the small number of included studies, there was a lack of evidence supporting the routine use of vitamin D supplementation for ARI prevention in healthy children. However, in children previously diagnosed with asthma, vitamin D supplementation may reduce the risk of asthma exacerbation triggered by a respiratory infection. Based on the primary analysis, the I^2 value was >50 %, primarily because the primary analysis consisted of a very heterogeneous mixture of endpoints. These results should be interpreted with caution due to the small number of included trials and the significant heterogeneity between them.

The observed lack of an effect of vitamin D supplementation on the prevention of ARI in the present study may have resulted from differences in the dosing regimens used in the included trials. Bergman *et al.*[23] reported that the protective effect of vitamin D was larger in studies using once-daily dosing compared with bolus dosing; all studies using bolus dosing reported a null effect. Unfortunately, we did not perform subgroup analyses based on dosing regimens due to the small number of included trials. In all observational studies, the relationship between inadequate vitamin D status and susceptibility to an ARI was significant. For example, Jolliffe *et al.*[24] revealed evidence of a relationship between inadequate vitamin D status and susceptibility to an ARI based on observational studies involving large numbers of participants of all age groups in diverse geographical settings with wide distributions of serum 25(OH)D concentrations. Quraishi *et al.*[25] also observed a nearly linear relationship between vitamin D status and the cumulative frequency of childhood community-acquired pneumonia. Additional trials regarding vitamin D supplementation for the prevention of ARI should be conducted in populations with a high prevalence of vitamin D deficiency at baseline, using doses sufficient to induce sustained elevations in serum 25(OH)D concentrations and studies powered to detect clinically important subgroup effects[24].

Regarding pneumonia, one of the two studies (Urashima *et al.*[16]) had no discernible impact on the results. Thus, the present meta-analysis merely presented the results obtained by Manaseki-Holland *et al.*[18] in 2012, providing no further insight into the matter. Regarding pneumonia recurrence, heterogeneity was too large to meaningfully pool estimates ($I^2 = 95\,\%$). Both included RCT were conducted by Semira Manaseki-Holland and utilised the same study population, inclusion criteria, and definitions of outcomes[17,18]. We believe that there was no clinical heterogeneity or methodological heterogeneity, and that statistical heterogeneity primarily accounted for the high level of heterogeneity observed between these studies. Additionally, Manaseki-Holland *et al.*[17,18] used a single dose of 100 000 units of oral vitamin D_3 in their trials; the results of other studies indicated that a daily dose schedule exerts superior therapeutic

Table 2. Sensitivity analyses of acute respiratory infections after vitamin D supplementation
(Risk ratios and 95 % confidence intervals)

	Number of trials	Total number of participants	Risk ratio	95 % CI	*P*
Fixed-effects model	6	8673	0·89	0·67, 1·19	0·43
Using trim-and-fill analysis	6	8673	0·89	0·67, 1·18	0·43
Excluding a trial with fewer than thirty participants per group	5	8625	0·94	0·71, 1·26	0·70
Excluding two trials regarding asthma exacerbation	4	8291	0·97	0·67, 1·39	0·86
Excluding two trials regarding repeated episodes of pneumonia	4	4190	0·76	0·54, 1·07	0·12

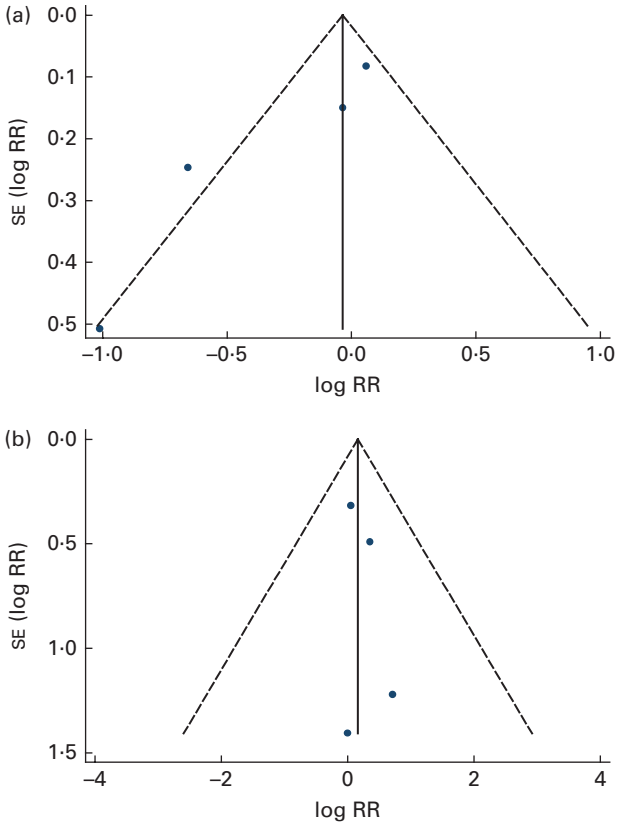

Fig. 5. Funnel plots for (a) acute respiratory infections and (b) all-cause mortality. RR, risk ratio. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn).

effects to large bolus doses, and that vitamin D exerts immunosuppressive effects at higher doses[23,26–28]. The administration of large intermittent bolus doses of vitamin D results in both a steep and a rapid increase in circulating 25(OH)D levels, followed by a slow decline. Such peaks and troughs may have potentially deleterious effects on the immune response; concentrations of 25(OH)D >56 ng/ml have been linked to impaired immunity, which may indicate that vitamin D suppresses adaptive responses to infection and boosts innate responses[29]. Given these conflicting results, as well as the small number of included studies, more rigorously designed clinical trials are necessary to ascertain the actual effects of vitamin D supplementation on the prevention of pneumonia recurrence in children.

Based on the results of recent cross-sectional and basic scientific studies[19], we speculate that vitamin D supplementation may prevent the development of asthma. However, no meta-analysis of intervention trials regarding the prevention of asthma attacks using vitamin D supplements has been conducted; therefore, this hypothesis has not been tested. We determined that vitamin D supplementation may reduce the risk of asthma exacerbation triggered by ARI in children with asthma. Due to the small number of included studies and their small sample sizes, this result should be interpreted with caution; however, our preliminary analysis supports the implementation of full-scale RCT. As reported, vitamin D supplementation simultaneously enhances the effectiveness of the antimicrobial response of the innate immune system and diminishes the natural consequences of inflammation, which appear to exert an adverse effect on asthma pathogenesis[30]. A study conducted by Damera *et al.*[31] demonstrated that vitamin D activity decreased the growth of airway smooth muscle cells stimulated by platelet-derived growth factor *in vitro*, and their result was not contradicted by our findings.

Each of the trials included in the present study was randomised, double-blinded and placebo-controlled. These criteria eliminated the possibility of reverse causation and minimised both recall and selection bias. The risk of bias was very low as a result of the use of a modified Jadad scale. However, the observational studies were characterised by a larger number of confounding factors; the incidence of ARI may have been influenced by recall bias, which may have exaggerated the effects of vitamin D supplementation.

The present meta-analysis has limitations. First, the serum concentrations of 25(OH)D were reported by only three trials; therefore, we do not know whether the baseline serum concentrations of 25(OH)D modified the effects of vitamin D supplementation. Second, we did not perform either subgroup analyses or meta-regression analyses investigating the influence of the characteristics of the trials on the observed effects of vitamin D because of the small number of trials included in the meta-analysis.

Conclusion

In summary, the present meta-analysis did not reveal sufficient evidence to support a beneficial effect of vitamin D supplementation on the prevention of ARI, the reduction of all-cause mortality, or the rate of hospital admission due to respiratory infections in healthy children. Among children previously diagnosed with asthma, vitamin D supplementation appears to significantly reduce the risk of asthma exacerbation triggered by a respiratory infection. However, these results should be interpreted with caution due to the small number of included trials and the significant heterogeneity observed between them.

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The authors' responsibilities were as follows: L. X. and Z. H. reviewed the literature and selected the eligible studies; C. X., Z. Y. and S. X. extracted the data; M. W. and H. D. performed the statistical analysis; L. X., Z. H. and K. L. wrote the manuscript. All authors reviewed and approved the final manuscript.

The authors declare that they have no conflicts of interest.

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