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TABLE OF CONTENTS

HEADER .................................................................................................................. 1
ABSTRACT ................................................................................................................ 1
BACKGROUND ......................................................................................................... 1
OBJECTIVES ........................................................................................................... 3
METHODS ............................................................................................................... 3
ACKNOWLEDGEMENTS .......................................................................................... 6
REFERENCES .......................................................................................................... 6
APPENDICES .......................................................................................................... 7
CONTRIBUTIONS OF AUTHORS ........................................................................ 9
DECLARATIONS OF INTEREST ........................................................................... 9
SOURCES OF SUPPORT ....................................................................................... 9
**Vitamin D for the management of asthma**

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**ABSTRACT**

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the efficacy of administration of vitamin D and its hydroxylated metabolites in reducing asthma exacerbations and improving asthma symptom control.

**BACKGROUND**

**Description of the condition**

Asthma is a chronic inflammatory condition of the airways, characterised by recurrent attacks of breathlessness, wheezing, cough and chest tightness, termed ‘exacerbations’. The prevalence of asthma varies widely between countries. In children, the prevalence of severe asthma symptoms ranges from 0% (India) to 20.3% (Costa Rica) (Lai 2009); in adults, the prevalence of doctor-diagnosed asthma ranges from 0.2% (China) to 21.0% (Australia) (To 2012). Exacerbations represent the major cause of morbidity and mortality in patients with asthma (Johnston 2006). Asthma exacerbations are classified as severe when they result in hospitalisation or death, and moderate when they prompt a need for a change in treatment, such as initiation of systemic corticosteroids, without causing death or hospitalisation (Reddel 2009). Common precipitants of asthma exacerbation include acute respiratory infections and exposure to allergens and particulates (Singh 2006).

**Description of the intervention**

Vitamin D is a pre-pro-hormone that has two parent forms: cholecalciferol (vitamin D₃) and ergocalciferol (vitamin D₂). Cholecalciferol is synthesised in human skin from its precursor molecule 7-dehydrocholesterol on exposure to ultraviolet B (UVB) radiation in sunlight; it may also be ingested, either in the diet (primarily from eating oily fish) or in vitamin D supplements. Ergocalciferol is the plant and fungal form of the vitamin, which may occasionally be ingested in the diet (primarily by eating fungi) or in vitamin D supplements. In situations where cutaneous exposure to UVB radiation of appropriate intensity is limited (e.g. during winter at latitudes above 34°N or below 34°S, or in settings where people do not regularly expose their skin to sunlight), dietary sources of...
vitamin D and/or vitamin D supplements may be required to meet the body's vitamin D requirement (Holick 2007). Following cutaneous synthesis or ingestion, both forms of parent vitamin D undergo metabolism to form 25-hydroxyvitamin D (25(OH)D), the major circulating vitamin D metabolite whose serum concentration indicates vitamin D status. 25-hydroxylation may occur in the liver and in extra-hepatic tissues, including leucocytes (Holick 2007). Serum 25(OH)D concentrations < 50 nmol/L are widely accepted to indicate vitamin D deficiency; concentrations < 25 nmol/L represent profound deficiency. Concentrations of 50-74 nmol/L may represent a milder state of inadequate vitamin D status, commonly termed ‘vitamin D insufficiency’. 25(OH)D undergoes a second hydroxylation step at the 1-alpha position to form the active vitamin D metabolite 1,25-dihydroxyvitamin D (1,25(OH)₂D) - the steroid hormone and active vitamin D metabolite which mediates the biological actions of vitamin D by binding the vitamin D receptor to regulate gene expression (Holick 2007). This 1-alpha hydroxylation step is catalysed by the enzyme CYP27B1, which is expressed in multiple tissues including the kidney, leucocytes and pulmonary epithelium; expression of CYP27B1 in leucocytes and pulmonary epithelium is up-regulated in response to infection and inflammation. This review will include studies which evaluate the effects of administration, by any route and at any dose, of vitamin D₂, vitamin D₃, 25(OH)D or 1,25(OH)₂D. Vitamin D₂, vitamin D₃ and 25(OH)D are usually administered orally; the ‘parent compounds’ vitamin D₂ and vitamin D₃ may also be given intramuscularly. Intramuscular administration of a bolus dose of vitamin D induces a slower increase and a lower peak in serum 25(OH)D than oral administration of the same dose (Romagnoli 2008), and consequently this route of administration is not widely employed in clinical trials of vitamin D supplementation. The functional in vivo half-life of 25(OH)D in the circulation is 1 to 2 months; accordingly, it takes at least 3 months to attain steady-state concentrations of 25(OH)D in response to daily administration of vitamin D (Heaney 2003). Because of the relatively long half-life of 25(OH)D, parent vitamin D and 25(OH)D may be administered intermittently as well as daily; weekly and monthly dosing regimens are often employed, and more widely spaced dosing regimens are also used. However, dosing less frequently than two monthly results in large non-physiological fluctuations in serum 25(OH)D concentration, which may cause undesirable effects (Vieth 2009; Martineau 2012; Hollis 2013). The influence of dosing interval on biological responses to administration of vitamin D is an area of active research in the field.

Why it is important to do this review

There is considerable interest in the potential of administration of vitamin D to reduce exacerbation risk and improve asthma symptom control. Two small trials of vitamin D supplementation in children with asthma treated with inhaled corticosteroids have reported reduced rates of exacerbation among participants randomised to the intervention arm (Majak 2011; Yadav 2014), and one small trial showed no effect of vitamin D supplementation on inflammatory markers or lung function (Bar-Yoseph 2014). One larger trial in adults has also reported a trend towards reduced exacerbation rate in the intervention arm (adjusted Hazard Ratio 0.63, 95% confidence interval (CI) 0.39 to 1.01) (Castro 2014). Other trials are either in progress or completed but as yet unpublished. Meta-analysis of these trials has the potential to increase statistical power to detect effects of administering vitamin D on exacerbation risk and symptom control both in study populations as a whole, and within subgroups who might be expected to derive particular benefit from this intervention (e.g. those with lower vitamin D status at enrolment).
OBJECTIVES
To evaluate the efficacy of administration of vitamin D and its hydroxylated metabolites in reducing asthma exacerbations and improving asthma symptom control.

METHODS

Criteria for considering studies for this review

Types of studies
We will review double-blind randomised placebo-controlled trials of at least twelve weeks' duration. We will include studies reported as full-text and unpublished data. Studies published as abstract only will also be included, but we will note that they are pending definitive evaluation as and when fuller reports are available.

Types of participants
We will include children and adults with a clinical diagnosis of asthma, based on the presence of characteristic symptoms and variable airflow obstruction. No restrictions regarding disease severity, baseline vitamin D status or duration of treatment with asthma medication will be imposed, in order to maximise generalisability.

Types of interventions
We will include studies in which vitamin D₃, vitamin D₂, 25(OH)D or 1,25(OH)₂D are administered at any dose.

Types of outcome measures

Primary outcomes
The primary outcome of this review is asthma exacerbation treated with systemic corticosteroids.

Secondary outcomes

Effectiveness
1. Asthma exacerbation requiring hospital admission;
2. Asthma exacerbation precipitating an emergency department visit;
3. Fatal asthma exacerbations;
4. Symptom control as judged by use of a validated instrument;
5. Time off school or work;
6. Beta₂ agonist use;
7. Asthma quality of life as judged by use of a validated instrument.

Physiological/biochemical
1. Peak expiratory flow monitoring;
2. Spirometric values (forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC));
3. Biomarkers of asthma control (exhaled nitric oxide, lower airway eosinophilia in induced sputum or bronchoalveolar lavage, other immunological parameters);
4. Airway reactivity.

Health economic
1. Costs from the perspective of healthcare providers.

Safety
1. Proportion of patients experiencing an adverse event attributed to administration of vitamin D or its metabolites;
2. Proportion of patients experiencing any severe adverse event, irrespective of causation;
3. Proportion of patients withdrawing from the trial.

Search methods for identification of studies

Electronic searches
We will identify trials from the Cochrane Airways Group’s Specialised Register (CAGR), which is maintained by the Trials Search Co-ordinator for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED, and PsycINFO, and handsearching of respiratory journals and meeting abstracts (please see Appendix 1 for further details). We will search all records in the CAGR using the search strategy in Appendix 2. We will also conduct searches of ClinicalTrials.gov (www.ClinicalTrials.gov), the WHO trials portal (www.who.int/ictrp/en/), the ISRCTN clinical trials register (http://www.controlled-trials.com/ISRCTN/), the Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au/) and the UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr/). We will search all databases from their inception to the present, and we will impose no restriction on language of publication.
Searching other resources

We will check reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers' websites for trial information. We will search for errata or retractions from included studies published in full-text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and report the date this was done within the review. We will contact a panel of international experts for additional references and information on trials in progress.

Data collection and analysis

Selection of studies

Two review authors (ARM, AT) will independently screen for inclusion the titles and abstracts of all the potentially relevant studies we identify as a result of the search, and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports/publication and two review authors (ARM, AT) will independently screen the full-text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person (CJG or AS). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which has been piloted on at least one study in the review. Two review authors (ARM, AT) will extract study characteristics from included studies. We will extract the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, body mass index, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (ARM, AT) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third person (CJG or AS). One review author (AT) will transfer data into the RevMan 2014 file. We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (ARM) will spot-check study characteristics for accuracy against the trial reports.

Assessment of risk of bias in included studies

Two review authors (TBA, AT) will independently assess the risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will resolve any disagreements by discussion or by involving another author (CJG or AS). We will assess the risk of bias according to the following domains.

1. Random sequence generation;
2. Allocation concealment;
3. Blinding of participants and personnel;
4. Blinding of outcome assessment;
5. Incomplete outcome data;
6. Selective outcome reporting;
7. Other biases, including study size

We will grade each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgment in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table. When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as odds ratios, since the rate of exacerbations may vary widely between studies, and the weights for each study using relative risk will be heavily dependent on the choice of outcome measure. We will analyse continuous data as
mean difference or standardised mean difference. We will enter
data presented as a scale with a consistent direction of effect.
We will undertake meta-analyses only where this is meaningful i.e.
if the treatments, participants and the underlying clinical question
are similar enough for pooling to make sense.
We will narratively describe skewed data reported as medians and
interquartile ranges.
Where multiple trial arms are reported in a single trial, we will
include only the relevant arms. If two comparisons (e.g. drug A
versus placebo and drug B versus placebo) are combined in the
same meta-analysis, we will halve the control group to avoid dou-
ble-counting.
For outcomes measured at different time points, we will include
the longest time point after randomisation.

Unit of analysis issues
Where data are expressed in unconventional units of analysis we
will convert them to conventional units, liaising with authors if
required.

Dealing with missing data
We will contact investigators or study sponsors in order to verify
key study characteristics and obtain missing numerical outcome
data where possible (e.g. when a study is identified as abstract
only). Where this is not possible, and the missing data are thought
to introduce serious bias, we will explore the impact of including
such studies in the overall assessment of results by a sensitivity
analysis.

Assessment of heterogeneity
We will use the I² statistic to measure heterogeneity among the
trials in each analysis. If we identify substantial heterogeneity (I² >
40%) we will report it and explore possible causes by pre-specified
subgroup analysis.

Assessment of reporting biases
If we are able to pool more than 10 trials, we will create and
examine a funnel plot to explore possible small study biases.

Data synthesis
We expect significant heterogeneity: accordingly, we will use a
random-effects model and perform a sensitivity analysis with a
fixed-effect model.
An intention-to-treat model will be used to analyse data when
possible. Continuous data will be analysed as a mean difference;
dichotomous data will be reported as odds ratios. Number needed
to treat for an additional beneficial outcome (NNTB) and number
needed to treat for an additional harmful outcome (NNTH) for
adverse events will be calculated where appropriate, to give an
indication for each dichotomous outcome, to reflect the number
of patients required to achieve a benefit or disbenefit with the
intervention.
Means and standard deviations (SDs) will be used when available.
We will approach authors where data are not reported. Values will
be extracted from graphs if authors do not respond.

'Summary of findings' table
We will create a 'Summary of findings' table using the follow-
ing outcomes: incidence of moderate/severe asthma exacerbation;
proportion of patients with one or more emergency department
attendance or hospitalisation for asthma; asthma symptom con-
trol; asthma quality of life; lung function; biomarkers of asthma
control; and incidence of severe adverse events attributed to ad-
ministration of vitamin D. We will use the five GRADE consid-
ERATIONS (study limitations, consistency of effect, imprecision, in-
directness and publication bias) to assess the quality of a body of
evidence as it relates to the studies which contribute data to the
meta-analyses for the pre-specified outcomes. We will use methods
and recommendations described in Section 8.5 and Chapter 12
of the Cochrane Handbook for Systematic Reviews of Interventions
(Higgins 2011) using GRADEpro software.
We will calculate NNTB from the control group event rate (unless
the population event rate is known) and odds ratios using the
Visual Rx NNT calculator (http://www.nntonline.net/visualrx/).
We will list trials in progress.
We will justify all decisions to down- or up-grade the quality of
studies using footnotes and we will make comments to aid readers'
understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity
We plan to carry out the following subgroup analyses.
1. Baseline vitamin D status (e.g. serum 25(OH)D < 50
nmol/L vs. ≥ 50 nmol/L). If data on baseline vitamin D status
are unavailable, we will investigate whether the effects of
administering vitamin D vary according to proxy measures of
vitamin D status (e.g. season of randomisation, latitude of
residence);
2. Age (e.g. children aged < 5 years versus 5 to 16 years versus
adults);
3. Severity of asthma and concomitant asthma treatment
being taken (e.g. taking versus not taking ICS, taking versus not
taking leukotriene receptor antagonists);
4. The dose (e.g. daily equivalent of < 400 IU versus 400 to
2000 IU versus > 2000 IU) and form of vitamin D administered
(e.g. cholecalciferol versus calcitriol);
5. The frequency of administration (e.g. daily versus
intermittent bolus doses);
6. Genetic variation in pathways of vitamin D metabolism,
transport and signalling (e.g. GC 2/2 versus 2/1 versus 1/1

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genotype for the Gc polymorphism of the vitamin D binding protein).

7. Body mass index (e.g., < 25 kg/m² versus ≥ 25 kg/m²). We will use the following outcome in subgroup analyses.
   1. Severe asthma exacerbation.
   We will use the formal test for subgroup interactions in RevMan 2014.

Sensitivity analysis
We plan to carry out the following sensitivity analysis:

Additional references

Bar Yoseph 2014

Brehm 2010

Brehm 2012

Castro 2014

Confino-Cohen 2014

Heaney 2003

Higgins 2011

Holick 2007

Holiss 2013

Johnston 2006

Lai 2009

Lan 2014

Majak 2011

Mann 2014
Mann EH, Chambers ES, Pfeffer PE, Hawrylowicz CM. Immunoregulatory mechanisms of vitamin D relevant to

ACKNOWLEDGEMENTS

The authors thank Emma Welsh, Elizabeth Stovold and Chris Cates of the Cochrane Airways Group, who provided advice on protocol content and search structure respectively. Chris Cates was the Editor for this review and commented critically on the review.

REFERENCES

**Martineau 2012**

**Moher 2009**

**Reddel 2009**

**RevMan 2014 [Computer program]**

**Romagnoli 2008**

**Singh 2006**

**To 2012**

**Vieth 2009**
Vieth R. How to optimize vitamin D supplementation to prevent cancer, based on cellular adaptation and hydroxylase enzymology. *Anticancer Research* 2009;29(9):3675–84.

**Xystrakis 2006**

**Yadav 2014**

* Indicates the major publication for the study

### APPENDICES

#### Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

<table>
<thead>
<tr>
<th>Database</th>
<th>Frequency of search</th>
</tr>
</thead>
<tbody>
<tr>
<td>CENTRAL (The Cochrane Library)</td>
<td>Monthly</td>
</tr>
<tr>
<td>MEDLINE (Ovid)</td>
<td>Weekly</td>
</tr>
<tr>
<td>EMBASE (Ovid)</td>
<td>Weekly</td>
</tr>
<tr>
<td>PsycINFO (Ovid)</td>
<td>Monthly</td>
</tr>
</tbody>
</table>

*Vitamin D for the management of asthma (Protocol)*
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Handsearches: core respiratory conference abstracts

<table>
<thead>
<tr>
<th>Conference</th>
<th>Years searched</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Academy of Allergy, Asthma and Immunology (AAAAI)</td>
<td>2001 onwards</td>
</tr>
<tr>
<td>American Thoracic Society (ATS)</td>
<td>2001 onwards</td>
</tr>
<tr>
<td>Asia Pacific Society of Respiratory (APSR)</td>
<td>2004 onwards</td>
</tr>
<tr>
<td>British Thoracic Society Winter Meeting (BTS)</td>
<td>2000 onwards</td>
</tr>
<tr>
<td>Chest Meeting</td>
<td>2003 onwards</td>
</tr>
<tr>
<td>International Primary Care Respiratory Group Congress (IPCRG)</td>
<td>2002 onwards</td>
</tr>
<tr>
<td>Thoracic Society of Australia and New Zealand (TSANZ)</td>
<td>1999 onwards</td>
</tr>
</tbody>
</table>

MEDLINE search strategy used to identify trials for the CAGR

**Asthma search**
1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency$)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
Filter to identify RCTs
1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11
The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Search strategy to retrieve trials from the CAGR
#1 AST:MISC1
#2 MeSH DESCRIPTOR Asthma Explode All
#3 asthma*:ti,ab
#4 #1 or #2 or #3
#5 MeSH DESCRIPTOR Vitamin D Explode All
#6 MeSH DESCRIPTOR Vitamin D Deficiency Explode All
#7 "vitamin d"
#8 #5 or #6 or #7
#9 #4 and #8
(in search line #1, MISC1 refers to the field in the record where the reference has been coded for condition, in this case, asthma)

CONTRIBUTIONS OF AUTHORS
CJG and AM wrote the protocol. AS, UN and AT commented on it.

DECLARATIONS OF INTEREST
No conflicts of interest to declare.

SOURCES OF SUPPORT
Internal sources

- Internal funds, UK.
  Chris Griffiths

External sources

- No sources of support supplied