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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
BACKGROUND	1
OBJECTIVES	3
METHODS	3
ACKNOWLEDGEMENTS	6
REFERENCES	6
APPENDICES	9
CONTRIBUTIONS OF AUTHORS	11
DECLARATIONS OF INTEREST	11
SOURCES OF SUPPORT	11

[Intervention Protocol]

Interventions for autumn exacerbations of asthma in children

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ABSTRACT

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

To assess the effects of pharmacotherapy and behavioural interventions enacted in the lead-up to the school return during autumn which are designed to reduce asthma exacerbations in school-aged children during this period.

BACKGROUND

Description of the condition

Asthma is a chronic disease of the airways characterised by recurrent episodes of wheezing, breathlessness and cough, together with variable expiratory airflow limitation. Symptoms are frequently associated with airway inflammation and bronchial hyperresponsiveness (GINA 2016). Asthma can affect people of all ages, although childhood onset is common. Asthma is diagnosed clinically based upon evaluation of symptoms and response to pharmacotherapy. There is no specific diagnostic test, although spirometric measurement of reversible airflow limitation and indirect or direct tests of airway hyperresponsiveness can be useful (GINA 2016).

Currently, the number of people with asthma globally is estimated to be approximately 300 million; this number is predicted to be closer to 400 million by 2025 (WHO 2007). Asthma is the most common chronic disease among children (Asher 2014). The

ISAAC study in 2002 to 2003 found the highest prevalence of childhood wheeze in Latin and North America, and in English-speaking countries in Australasia and Europe (Asher 2006). Currently, more than a million children (one in eleven) in the UK are believed to be living with asthma (Asthma UK 2016).

Symptom exacerbations can be triggered by a number of environmental challenges including pollutants (Lierl 2003; Schildcrout 2006), physical activity (Randolph 2013), and respiratory infections or allergens (Brandt 2015; Ito 2015; Murray 2006; Olenec 2010). People whose airway inflammation is not adequately controlled are more vulnerable to exacerbations than those on adequate therapy with good treatment adherence. Poorly controlled day-to-day asthma symptoms can limit activities, including schooling, and impair sleep quality and overall quality of life (Kiotseridis 2013; Teyhan 2015; van Maanen 2013). However, it is asthma exacerbations - acute or subacute progressive worsening of symptoms (NAEPP 2007) - which pose the greatest danger to people with asthma. Asthma exacerbations are also associated with reduced school or work attendance and are the most important

contributor to the economic and social costs of asthma (Bahadori 2009; Hoskins 2000; Ismaila 2013).

A seasonal peak in exacerbation rates has been consistently demonstrated in the autumn across multiple Northern Hemisphere countries (Fleming 2000; Gergen 2002). More specifically, exacerbation rates peak in September following the summer school holiday and in line with the start of the autumn term (Johnston 2006). Equivalent peaks during February have been reported in Southern Hemisphere countries (Lincoln 2006; Lister 2001). The autumn peak in asthma exacerbations is temporally linked to children returning to school and most pronounced in school-aged children (Corne 2002). Hospitalisations and emergency department visits attributable to asthma demonstrate an initial peak in school-aged children; however this is followed within days by increased hospitalisations in preschool children and a more blunted peak in adults up to the age of 50 years (Sears 2008). There is evidence that viral infections, particularly rhinovirus, may contribute to this seasonality (Johnston 1996; Johnston 2005; Thumerelle 2003); but also that sub-optimal asthma treatment may be a contributing factor (Johnston 2005). Not only do viral infections trigger asthma exacerbations but there is also evidence that asthmatic individuals are more susceptible to rhinovirus infection than those without asthma (Baraldo 2012; Wark 2005). Individuals at particular risk of asthma exacerbation have been identified as those with more severe disease, greater degree of atopy, and recent exacerbations (Teach 2015b).

Description of the intervention

A number of interventions including asthma education programmes, action plans, self-monitoring, and self-initiation of oral corticosteroid treatment have been shown to reduce both symptom exacerbations and need for unscheduled acute care in children with asthma (Bhagal 2006; Guevara 2003; Vuillermin 2011). Given that the seasonality of asthma exacerbations in school-aged children is predictable and repeatable, it is reasonable to assume that management strategies which anticipate increased risk in the autumn might reduce exacerbation frequency during this period. Whilst the exact aetiology of the seasonal peak in asthma exacerbations is not fully understood, any change in management aimed at improving asthma control in anticipation of the autumn school return, if successful, could offer protection against the increased risk recognised to be associated with this event. Therapies that have demonstrated to reduce the seasonal excess of exacerbations in the autumn, in addition to the annual number of exacerbations, include year-round treatment with the anti-IgE monoclonal antibody, omalizumab (Busse 2011); or with high-dose inhaled corticosteroids (Szeffer 2008). Omalizumab is, however, an expensive treatment, whilst high-dose inhaled corticosteroids are associated with adverse effects upon growth and bone health (Sharek 2000; Wong 2000).

Given the pragmatic difficulties associated with minimising viral or allergen exposure, two main potential strategies remain which might reduce autumn asthma exacerbations whilst minimising treatment costs and adverse effects. The first strategy would be to add on, or increase, asthma pharmacotherapy before the autumn period; and the second strategy would be to focus upon treatment adherence and achieving symptom control before and during the autumn. It is anticipated that the greatest benefit from an intervention targeting seasonal exacerbations would be gained by school-aged children since the autumn peak in exacerbations is most pronounced in this age group. Similarly, greater benefit might be demonstrable in those at increased risk of exacerbation due to poor treatment adherence, disease severity, allergic phenotype or recent exacerbation.

Add-on therapies include those aimed at reducing airway inflammation, such as corticosteroid preparations, macrolide antibiotics or leukotriene receptor antagonists. Alternatively, agents such as biologics which more specifically target the interaction between the immune response and viral infection might be selected (Durrani 2012; Gill 2010). Important considerations with respect to choice of intervention include onset of action and ease of administration, in addition to cost and adverse effect profile.

Strategies to improve treatment adherence require adherence status to be assessed, and barriers leading to non-adherence to be identified and addressed. The success of adherence interventions can be increased by a number of strategies, including providing biofeedback (Feldman 2012), and increasing motivation via motivational interviewing techniques (Borrelli 2007). Nevertheless it is difficult to achieve sustained adherence (Jonasson 2000). Targeting adherence interventions to periods of increased exacerbation risk might increase their overall success.

How the intervention might work

Since the greatest peak in exacerbation rates is observed amongst school-aged children this potentially implicates some aspect of the school environment in the aetiology of the seasonal peak. Upon return to school in the autumn children are exposed to allergens and respiratory infections by close contact with their classmates (Cai 2011; Krop 2014). Moreover, it has been suggested that changes in routine during the summer holidays and lower perceived risk of cold weather or respiratory infection might be associated with both intentional reduction in preventer medication and potentially poorer adherence (Johnston 2005; Sears 2008). During the autumn months mould spores, which can act as a trigger for allergic asthma, are more abundant than at other times of the year (de Ana 2006). However, the sequential periods of peak risk demonstrated by school-aged children, younger children and adults suggest a transmissible agent is responsible. In support of this are findings from virological studies that demonstrate increased viral isolations during autumn, notably rhinovirus, from children with asthma compared to those without, with the highest rates of

isolation measured in those admitted to hospital with an asthma exacerbation (Johnston 2005; Thumerelle 2003).

There is also evidence that baseline asthma control and treatment adherence might predict those most at risk. A higher rate of exacerbation has been reported in people prescribed bronchodilator therapy alone than in those prescribed an inhaled steroid or other preventer medication (Johnston 2005; Murray 2006). Furthermore, school-aged children with mild asthma but poor control, as evidenced by an exacerbation during the run-in period of 4 to 9 months, experienced a significant reduction in exacerbation frequency within a trial of seasonal omalizumab treatment (Teach 2015a). Exacerbation rate could not be significantly reduced in those with mild asthma but without a recent admission (Teach 2015a). Potentially any intervention based upon reinforcing or increasing adherence to regular treatment, monitoring symptoms to assess control or a seasonal enhancement of treatment might reduce ongoing airway inflammation and the likelihood of viral infection triggering an exacerbation.

Why it is important to do this review

Although the asthma epidemic observed in the 1980s and 1990s appears to have stabilised, a study from the Northern Hemisphere demonstrates that emergency care contacts due to asthma remain significantly higher in September than in other months (Larsen 2016). The recent trial of seasonal omalizumab administration demonstrated a significant reduction in exacerbation frequency amongst children with either severe asthma or poorly controlled mild to moderate disease (Teach 2015a). However, it is important to identify whether a similar effect can be achieved with less invasive and less expensive medications, particularly since in countries such as the UK, omalizumab can only be prescribed to people meeting strict severity criteria. It is estimated that up to 25% of annual hospitalisations for asthma occur in September (Johnston 2006). Moreover, acute exacerbations are the principal driver of the economic and social costs of asthma (Bahadori 2009; Hoskins 2000; Ismaila 2013). Therefore, interventions based upon an anticipatory change in asthma management, if successful, could substantially reduce both the overall exacerbation rate and the strain placed upon health services by multiple exacerbations during a relatively short period of time.

OBJECTIVES

To assess the effects of pharmacotherapy and behavioural interventions enacted in the lead-up to the school return during autumn which are designed to reduce asthma exacerbations in school-aged children during this period.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), quasi randomised controlled trials and observational studies. We will include studies reported as full-text, those published as abstract only, and unpublished data.

Types of participants

We will include studies which present data relating to school-aged children, 5 to 18 years old, with asthma. This is in recognition of the absence of a significant autumn peak in exacerbations in adults. We will also exclude studies of children below the age of 5 given the likely different aetiology and responses to treatment in preschool children; notably the high prevalence of wheezing in response to viral infection unresponsive to conventional inhaled or oral steroid asthma treatment.

Types of interventions

We will include studies comparing interventions aimed specifically at reducing autumn exacerbations with usual care where there is no systematic change in management in preparation for school return. Eligible interventions will include pharmacotherapy trials and behavioural or educational-based initiatives. Observational studies may have no usual care comparison group.

Types of outcome measures

Primary outcomes

For controlled trials the primary outcome, depending upon what is reported, will be number of participants experiencing one or more asthma exacerbation during the autumn period (the first three-month period following the autumn school return) or during the intervention period if this includes the autumn months. An exacerbation will be defined as increased asthma symptoms requiring treatment with oral steroids or hospitalisation.

In observational studies, where there may be no usual care comparison group, we will assess the relative number of participants experiencing asthma exacerbations during the autumn months (standardised as the first three months following the autumn school return) compared to the remainder of the year.

Secondary outcomes

1. Number of participants experiencing exacerbations of asthma requiring hospitalisation.
2. Number of participants experiencing exacerbations of asthma requiring paediatric intensive care (PICU) admission.
3. Number of asthma-related deaths.
4. Asthma control, measured by standardised tool (e.g. Childhood Asthma Control Test (cACT) or Asthma Control Test (ACT)).
5. Asthma-related quality of life measured by standardised tool (e.g. Paediatric Asthma Quality of Life Questionnaire (PAQLQ) or Asthma Quality of Life Questionnaire (AQLQ)).
6. Days of schooling (or employment for those beyond school age) missed.
7. Adverse events (including serious adverse events).

Secondary outcomes will only be considered in controlled trials. For each outcome data will be collected throughout the autumn period or the intervention period (as for the primary outcome) in both the intervention group and the standard therapy group. The number of young people requiring hospitalisation, PICU admission and number of asthma-related deaths as well as average questionnaire score, number of days education/employment missed or adverse events will be recorded.

Reporting the primary outcome is not required as an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We will identify trials from the Cochrane Airways Group's Register of controlled clinical trials (CAGR), which is maintained by the Information Specialist for the Group. The Register contains trial reports identified through systematic searches of multiple bibliographic databases 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 a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO trials portal (www.who.int/ictrp/en/). 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.

Data collection and analysis

Selection of studies

Two review authors (KP, KH) will independently screen titles and abstracts for inclusion of all the potential 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 (KP, KH) 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 review author (DK). 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. Three review authors (KP, KH, DK) will extract study characteristics from included studies in duplicate. 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: number, mean age, age range, gender, 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 (KP, DK) will independently extract outcome data from the included studies. We will note in the 'Characteristics of included studies' table if outcome data was not reported in a usable way. We will resolve disagreements by consensus or by involving a third review author (KH). One review author (KP) will transfer data into the Review Manager file ([RevMan 2014](#)). We will double-check that data is entered correctly by comparing the data presented in the systematic review with the study reports.

A second review author (DK) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (KP, KH) 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 review author (DK). 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 bias.

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 judgments 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 and 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, such as when the treatments, participants and 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 double-counting.

Unit of analysis issues

Asthma exacerbations will be considered a dichotomous outcome using participants as the unit of analysis. The odds of exacerbation in the intervention group during the intervention will be compared to the odds of exacerbation in individuals receiving standard therapy. For large-scale behavioural interventions (e.g. those that involve contacting young people in late summer to remind them of the need for treatment adherence), the unit of allocation may be primary care practice level rather than at the level of the individual. Where this is the case, results will only be included if the original trial accounted for clustering or if it is possible to adjust for this by calculating a design effect.

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 I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity ($I^2 > 50\%$) 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 and publication biases.

Data synthesis

We will use a Mantel-Haenszel random-effects model using Review Manager software (RevMan 2014) for all outcomes as we expect variation in effects due to differences in study populations and methods (Mantel 1959). We will perform a sensitivity analysis with a fixed-effect model when we encounter significant heterogeneity.

'Summary of findings' table

We will create a 'Summary of findings' table using the following outcomes: exacerbation occurrence (requiring oral steroids or hospitalisation); hospitalisation; PICU admission; asthma-related deaths; asthma control; asthma-related quality of life; days off school/employment missed; and adverse events. We will use the

five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness 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 GDT software. We will justify all decisions to down- or up-grade the quality of studies using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We recognise that intervention type or disease or severity might affect effect size and therefore plan to carry out the following subgroup analyses for all outcomes:

1. An analysis separating studies based upon pharmacological interventions from those based upon non-pharmacological interventions.

2. Analyses considering separately those with mild to moderate disease (intermittent bronchodilator only; or low/moderate inhaled steroids with or without a single add-on therapy) and those with severe asthma (high-dose inhaled steroids; or two or more add on therapies).

(High inhaled steroid dose beclomethasone equivalents daily: 5 to 12 years \geq 800 mcg, older than 12 years \geq 2000 mcg).

We will use the identical primary and secondary outcomes in subgroup analyses as in the main analysis.

We will use the formal test for subgroup interactions in Review Manager 5 to determine statistical significance of subgroup anal-

yses (RevMan 2014).

Sensitivity analysis

We plan to carry out the following sensitivity analyses:

1. An analysis including only studies without missing data.
2. An analysis excluding cluster randomised trials (in case any benefit in cluster randomised trials arises due to the 'herd' effect of an intervention).

We will also re-run analyses and compare results after sequential exclusion of each study from any meta-analysis.

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Christian Osadnik was the Editor for this protocol and commented critically on the document.

REFERENCES

Additional references

Asher 2006

Asher MI, Montefort S, Bjorksten B, Lai CKW, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet (London, England)* 2006;**368**(9537):733–43.

Asher 2014

Asher I, Pearce N. Global burden of asthma among children. *The International Journal of Tuberculosis and Lung Disease: the Official Journal of the International Union against Tuberculosis and Lung Disease* 2014;**18**(11):1269–78.

Asthma UK 2016

Asthma UK. Asthma facts and statistics. <https://www.asthma.org.uk/about/media/facts-and-statistics/> (accessed 1 September 2016).

Bahadori 2009

Bahadori K, Doyle-Waters MM, Marra C, Lynd L, Alasaly K, Swiston J, et al. Economic burden of asthma: a systematic review. *BMC Pulmonary Medicine* 2009;**9**:24. [PUBMED: 19454036]

Baraldo 2012

Baraldo S, Contoli M, Bazzan E, Turato G, Padovani A, Marku B, et al. Deficient antiviral immune responses in childhood: distinct roles of atopy and asthma. *The Journal of Allergy and Clinical Immunology* 2012;**130**(6):1307–14.

Bhogal 2006

Bhogal S, Zemek R, Ducharme FM. Written action plans for asthma in children. *Cochrane Database of Systematic Reviews* 2006, Issue 3. [DOI: 10.1002/14651858.CD005306.pub2]

Borrelli 2007

Borrelli B, Riekert K, Weinstein A, Rathier L. Brief motivational interviewing as a clinical strategy to promote

- asthma medication adherence. *Journal of Allergy and Clinical Immunology* 2007;**120**(5):1023–30.
- Brandt 2015**
Brandt EB, Biagini Myers JM, Acciani TH, Ryan PH, Sivaprasad U, Ruff B, et al. Exposure to allergen and diesel exhaust particles potentiates secondary allergen-specific memory responses, promoting asthma susceptibility. *The Journal of Allergy and Clinical Immunology* 2015;**136**(2): 295–303.e7.
- Busse 2011**
Busse W, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *The New England Journal of Medicine* 2011;**364**(11):1005–15.
- Cai 2011**
Cai G-H, Hashim JH, Hashim Z, Ali F, Bloom E, Larsson L, et al. Fungal DNA, allergens, mycotoxins and associations with asthmatic symptoms among pupils in schools from Johor Bahru, Malaysia. *Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Clinical Immunology* 2011;**22**(3):290–7.
- Corne 2002**
Corne JM, Marshall C, Smith S, Schreiber J, Sanderson G, Holgate ST, et al. Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. *Lancet* 2002;**359**(9309):831–4. [PUBMED: 11897281]
- de Ana 2006**
de Ana SG, Torres-Rodriguez JM, Ramirez EA, Garcia SM, Belmonte-Soler J. Seasonal distribution of *Alternaria*, *Aspergillus*, *Cladosporium* and *Penicillium* species isolated in homes of fungal allergic patients. *Journal of Investigational Allergology & Clinical Immunology* 2006;**16**(6):357–63. [PUBMED: 17153883]
- Durrani 2012**
Durrani SR, Montville DJ, Pratt AS, Sahu S, DeVries MK, Rajamanickam V, et al. Innate immune responses to rhinovirus are reduced by the high-affinity IgE receptor in allergic asthmatic children. *The Journal of Allergy and Clinical Immunology* 2012;**130**(2):489–95.
- Feldman 2012**
Feldman J, Kutner H, Matte L, Lupkin M, Steinberg D, Sidora-Arcoleo K, et al. Prediction of peak flow values followed by feedback improves perception of lung function and adherence to inhaled corticosteroids in children with asthma. *Thorax* 2012;**67**(12):1040–5.
- Fleming 2000**
Fleming DM, Cross KW, Sunderland R, Ross AM. Comparison of the seasonal patterns of asthma identified in general practitioner episodes, hospital admissions, and deaths. *Thorax* 2000;**55**(8):662–5. [PUBMED: 10899242]
- Gergen 2002**
Gergen PJ, Mitchell H, Lynn H. Understanding the seasonal pattern of childhood asthma: results from the National Cooperative Inner-City Asthma Study (NCICAS). *Journal of Pediatrics* 2002;**141**(5):631–6. [PUBMED: 12410190]
- Gill 2010**
Gill MA, Bajwa G, George TA, Dong CC, Dougherty II, Jiang N, et al. Counterregulation between the FcεpsilonRI pathway and antiviral responses in human plasmacytoid dendritic cells. *Journal of Immunology* 2010;**184**(11): 5999–6006.
- GINA 2016**
Global Initiative for Asthma. Global strategy of asthma management and prevention. <http://ginasthma.org/2016-gina-report-global-strategy-for-asthma-management-and-prevention/> 2016.
- GRADEpro GDT [Computer program]**
Brozek J, Oxman A, Schünemann H. GRADEpro GDT. Hamilton (ON): GRADE Working Group, McMaster University, 2014.
- Guevara 2003**
Guevara JB, Wolf FM, Grum CM, Clark NM. Effects of educational interventions for self management of asthma in children and adolescents: systematic review and meta-analysis. *BMJ (Clinical Research ed.)* 2003;**326**(7402): 1308–9. [PUBMED: 12805167]
- Higgins 2011**
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
- Hoskins 2000**
Hoskins G, McCowan C, Neville RG, Thomas GE, Smith B, Silverman S. Risk factors and costs associated with an asthma attack. *Thorax* 2000;**55**(1):19–24. [PUBMED: 10607797]
- Ismaila 2013**
Ismaila AS, Sayani AP, Marin M, Su Z. Clinical, economic, and humanistic burden of asthma in Canada: a systematic review. *BMC Pulmonary Medicine* 2013;**13**:70. [PUBMED: 24304726]
- Ito 2015**
Ito K, Weinberger KR, Robinson GS, Sheffield PE, Lall R, Mathes R, et al. The associations between daily spring pollen counts, over-the-counter allergy medication sales, and asthma syndrome emergency department visits in New York City, 2002–2012. *Environmental Health: a Global Access Science Source* 2015;**14**:71.
- Johnston 1996**
Johnston SL, Pattemore PK, Sanderson G, Smith S, Campbell MJ, Josephs LK, et al. The relationship between upper respiratory infections and hospital admissions for asthma: a time-trend analysis. *American Journal of Respiratory and Critical Care Medicine* 1996;**154**(3 Pt 1): 654–60. [PUBMED: 8810601]
- Johnston 2005**
Johnston NW, Johnston SL, Duncan JM, Greene JM, Kebabdzic T, Keith PK, et al. The September epidemic of asthma exacerbations in children: a search for etiology. *Journal of Allergy and Clinical Immunology* 2005;**115**(1): 132–8. [PUBMED: 15637559]

Johnston 2006

Johnston NW, Sears MR. Asthma exacerbations. 1: epidemiology. *Thorax* 2006;**61**(8):722–8. [PUBMED: 16877691]

Jonasson 2000

Jonasson G, Carlsen K-H, Mowinckel P. Asthma drug adherence in a long term clinical trial. *Archives of Disease in Childhood* 2000;**83**(4):330–3.

Kiotseridis 2013

Kiotseridis H, Cilio CM, Bjermer L, Aurivillius M, Jacobsson H, Dahl A, et al. Quality of life in children and adolescents with respiratory allergy, assessed with a generic and disease-specific instrument. *The Clinical Respiratory Journal* 2013;**7**(2):168–75.

Krop 2014

Krop EJM, Jacobs JH, Sander I, Raulf-Heimsoth M, Heederik DJJ. Allergens and beta-glucans in Dutch homes and schools: characterizing airborne levels. *PloS one* 2014;**9**(2):e88871.

Larsen 2016

Larsen K, Zhu J, Feldman LY, Simatovic J, Dell S, Gershon AS, et al. The annual September peak in asthma exacerbation rates. Still a reality?. *Annals of the American Thoracic Society* 2016;**13**(2):231–9. [PUBMED: 26636481]

Lierl 2003

Lierl MB, Hornung RW. Relationship of outdoor air quality to pediatric asthma exacerbations. *Annals of Allergy, Asthma & Immunology: official publication of the American College of Allergy, Asthma, & Immunology* 2003;**90**(1):28–33.

Lincoln 2006

Lincoln D, Morgan G, Sheppard V, Jalaludin B, Corbett S, Beard J. Childhood asthma and return to school in Sydney, Australia. *Public Health* 2006;**120**(9):854–62. [PUBMED: 16904142]

Lister 2001

Lister S, Sheppard V, Morgan G, Corbett S, Kaldor J, Henry R. February asthma outbreaks in NSW: a case control study. *Australian and New Zealand Journal of Public Health* 2001;**25**(6):514–9. [PUBMED: 11824986]

Mantel 1959

Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *Journal of the National Cancer Institute* 1959;**22**(4):719–48.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009;**6**(7): e1000097. [DOI: 10.1371/journal.pmed.1000097]

Murray 2006

Murray CS, Poletti G, Kebabdzic T, Morris J, Woodcock A, Johnston SL, et al. Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. *Thorax* 2006;**61**(5):376–82. [PUBMED: 16384881]

NAEPP 2007

National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *The Journal of Allergy and Clinical Immunology* 2007;**120**(5 Suppl):S94–138.

Olenec 2010

Olenec JP, Kim WK, Lee W-M, Vang F, Pappas TE, Salazar LEP, et al. Weekly monitoring of children with asthma for infections and illness during common cold seasons. *The Journal of Allergy and Clinical Immunology* 2010;**125**(5): 1001–6.e1.

Randolph 2013

Randolph C. Pediatric exercise-induced bronchoconstriction: contemporary developments in epidemiology, pathogenesis, presentation, diagnosis, and therapy. *Current Allergy and Asthma Reports* 2013;**13**(6): 662–71.

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Schildcrout 2006

Schildcrout JS, Sheppard L, Lumley T, Slaughter JC, Koenig JQ, Shapiro GG. Ambient air pollution and asthma exacerbations in children: an eight-city analysis. *American Journal of Epidemiology* 2006;**164**(6):505–17.

Sears 2008

Sears MR. Epidemiology of asthma exacerbations. *Journal of Allergy and Clinical Immunology* 2008;**122**(4):662–8; quiz 669–70. [PUBMED: 19014756]

Sharek 2000

Sharek PJ, Bergman DA. The effect of inhaled steroids on the linear growth of children with asthma: a meta-analysis. *Pediatrics* 2000;**106**(1):E8.

Szeffler 2008

Szeffler SJ, Mitchell H, Sorkness CA, Gergen PJ, O'Connor GT, Morgan WJ, et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. *Lancet* 2008;**372**(9643):1065–72.

Teach 2015a

Teach SJ, Gill MA, Togias A, Sorkness CA, Arbes SJ Jr, Calatroni A, et al. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *Journal of Allergy and Clinical Immunology* 2015;**136**(6):1476–85. [PUBMED: 26518090]

Teach 2015b

Teach SJ, Gergen PJ, Szeffler SJ, Mitchell HE, Calatroni A, Wildfire J, et al. Seasonal risk factors for asthma exacerbations among inner-city children. *The Journal of Allergy and Clinical Immunology* 2015;**135**(6):1465–73.e5.

Teyhan 2015

Teyhan A, Galobardes B, Henderson J. Child Allergic Symptoms and Well-Being at School: Findings from ALSPAC, a UK Cohort Study. *PLoS one* 2015;**10**(8): e0135271.

Thumerelle 2003

Thumerelle C, Deschildre A, Bouquillon C, Santos C, Sarder A, Scalbert M, et al. Role of viruses and atypical bacteria in exacerbations of asthma in hospitalized children: a prospective study in the Nord-Pas de Calais region (France). *Pediatric Pulmonology* 2003;**35**(2):75–82. [PUBMED: 12526066]

van Maanen 2013

van Maanen A, Wijga AH, Gehring U, Postma DS, Smit HA, Oort FJ, et al. Sleep in children with asthma: results of the PIAMA study. *The European Respiratory Journal* 2013; **41**(4):832–7.

Vuillermin 2011

Vuillermin PJ, Robertson CF, South M. The role of parent-initiated oral corticosteroids in preschool wheeze and

school-aged asthma. *Current Opinion in Allergy and Clinical Immunology* 2011;**11**(3):187–91. [PUBMED: 21464710]

Wark 2005

Wark PAB, Johnston SL, Bucchieri F, Powell R, Puddicombe S, Laza-Stanca V, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. *The Journal of Experimental Medicine* 2005;**201**(6):937–47.

WHO 2007

Bousquet J, Khaltayev N (editors). Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach. *Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach*. WHO Press Geneva Centers for Disease Control and Prevention, 2007.

Wong 2000

Wong CA, Walsh LJ, Smith CJ, Wisniewski AF, Lewis SA, Hubbard R, et al. Inhaled corticosteroid use and bone-mineral density in patients with asthma. *Lancet* 2000;**355**(9213):1399–403.

* Indicates the major publication for the study

APPENDICES**Appendix I. Sources and search methods for the Cochrane Airways Group's Specialised Register (CAGR)****Handsearches: core respiratory conference abstracts**

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respiriology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards

(Continued)

Thoracic Society of Australia and New Zealand (TSANZ)

1999 onwards

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.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomized 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 identify relevant 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 Seasons

#6 seasonal*:ti

#7 (season* NEAR (symptom* or vari* or exacerbat* or peak*)):ti,ab

#8 ((Autumn or Fall or summer or September or February) NEAR (symptom* or vari* or exacerbat* or peak*)):ti,ab

#9 MeSH DESCRIPTOR Schools Explode All

#10 (school* NEAR (holiday* or vacation* or return* or resume* or term* or year* or start*)):ti,ab

#11 #5 or #6 or #7 or #8 or #9 or #10

#12 #4 AND #11

[Note: in search line #1, MISC1 denotes the field in the record where the reference has been coded for condition, in this case, asthma]

CONTRIBUTIONS OF AUTHORS

KCP drafted the protocol.

KCP, KMH and DK reviewed the protocol before submission.

KCP will identify studies for inclusion, extract data from the included studies, perform the analyses and draft the final review.

KH and DK will select which studies to include in the review, extract data from the included studies and draft the final review.

DECLARATIONS OF INTEREST

KCP: none known

KMH: none known

DK: none known

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