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REVIEW

Complex interventions reduce use of urgent healthcare in adults with asthma: Systematic review with meta-regression

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Asthma;
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Summary
Introduction: Asthma accounts for considerable healthcare expenditure, a large proportion of which is attributable to use of expensive urgent healthcare. This review examines the characteristics of complex interventions that reduce urgent healthcare use in adults with asthma.
Method: Electronic searches of MEDLINE, EMBASE, PSYCINFO, CINAHL, the British Nursing Library and the Cochrane library, from inception to January 2013 were conducted. Studies were eligible for inclusion if they: i) included adults with asthma ii) assessed the efficacy of a complex intervention using randomised controlled trial design, and iii) included a measure of urgent healthcare utilisation at follow-up. Data on participants recruited, methods, characteristics of complex interventions and the effects of the intervention on urgent healthcare use were extracted.
Results: 33 independent studies were identified resulting in 39 comparisons altogether. Pooled effects indicated that interventions were associated with a reduction in urgent healthcare use

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(OR = 0.79, 95% CI = 0.67, 0.94). When study effects were grouped according to the components of the interventions used, significant effects were seen for interventions that included general education (OR = 0.77, 95% CI = 0.64, 0.91), skills training (OR = 0.64, 95% CI = 0.48, 0.86) and relapse prevention (OR = 0.75, 95% CI = 0.57, 0.98). In multivariate meta-regression analysis, only skills training remained significant.

Conclusions: Complex interventions reduced the use of urgent healthcare in adults with asthma by 21%. Those complex interventions including skills training, education and relapse prevention may be particularly effective in reducing the use of urgent healthcare in adults with asthma.

Contents

Background

There are over 300 million people living with asthma worldwide and this is expected to increase to 400 million by 2025 [1]. Asthma causes approximately 1 in every 250 deaths and is associated with poor quality of life and increased healthcare use [1–3].

Current UK government policy recommends that the use of urgent care should be reduced in people with long term conditions by introducing alternative care pathways in primary care settings [4]. The cost of healthcare use in asthma is significantly increased for patients who have poor asthma control [5,6]. Therefore, achieving good symptom control in order to reduce exacerbations is currently the main goal for asthma therapy [7].

Depression and anxiety are common comorbidities in adults with asthma [8] and are known to be significantly related to poor asthma control which is independent of asthma severity [9]. In a sample of 127 adults with asthma who also had anxiety about their physical symptoms, anxiety was a significant predictor of both asthma control and asthma related health-related quality of life [10]. Depression and anxiety in adults with asthma are also associated with decreased adherence to medication [11], increased healthcare use [12], and mortality [13].

Results from reviews of individual interventions are mixed in their effectiveness in reducing the use of urgent healthcare in adults with asthma. Yorke and colleagues (2007) [14] conducted a systematic review of psychological interventions to improve health and behavioural outcomes for adults with asthma. They found that cognitive behavioural interventions improved quality of life and that relaxation therapy was successful in reducing the use of 'as needed' medication. The observed benefits to health outcomes were mixed however; two studies included healthcare use (hospitalisation, emergency room visits and GP visits) as an outcome, both of which reported no significant reduction in use of healthcare [15,16]. Tapp and colleagues (2007) [17] conducted a systematic review which shows that educational interventions can significantly reduce future hospital admissions for adults who attend the emergency department with acute asthma exacerbations. However, there was no significant effect on emergency department attendance found between the intervention and control groups. A recent review of complex interventions (interventions which involve multiple components) showed that they were successful in reducing urgent

care use by 32% in patients with chronic obstructive pulmonary disease (COPD) [18]. The effects of such complex interventions and the components associated with a reduction in urgent care in asthma patients remain unclear.

We have conducted a systematic review of the literature with meta-regression to identify the characteristics of complex interventions that reduce the use of urgent healthcare among adults with asthma. The identification of such characteristics would facilitate the design of optimal interventions with the potential to reduce the use of urgent healthcare and thus result in considerable savings in healthcare expenditure.

Method

Studies were eligible for inclusion in the review if they met the following criteria.

i. Included adults with asthma (aged 16 years or over).
ii. Assessed the efficacy/effectiveness of a complex intervention. For the purpose of this review, complex interventions involved multiple components and/or multiple professionals, and could be delivered on an individual or group basis, or using technology such as telephone or computer. Interventions could include education, rehabilitation, psychological therapy, social intervention (social support, support group), organisational intervention (such as collaborative care or case management), and drug trials which targeted a psychological problem, e.g. anxiety or depression. Simple interventions, such as the introduction of a new treatment targeting the underlying long-term condition, compared to treatment as usual were not included in this review.
iii. Assessed urgent healthcare use as an outcome, e.g. emergency department visits, urgent hospitalisation[1] or unscheduled GP visits.
iv. Used randomised controlled trial design.

Studies were not excluded by date or language of publication, sample size or follow up period. See online appendix (Pages 2—3) for full PICO criteria. Unpublished studies and those published in abstract form only, were not included in this review.

Electronic search strategies were developed in-team, in consultation with librarians with experience of performing systematic reviews (RM). Search strategies were peer reviewed by experts from within the University (LG) and modified accordingly. Search strategies included terms relevant to prospective studies and also asthma, with further limiting to randomised controlled trials of complex interventions in asthma using hand searching (see pages 4—17 in online appendix for details of search strategies used). We were not able to develop sensitive and reliable strategies to identify studies investigating use of urgent healthcare specifically, so searches were developed to identify all healthcare utilisation, and further restriction to relevant papers was achieved by hand searching potentially eligible papers.

Searches were conducted in MEDLINE, EMBASE, PSYCHINFO, CINAHL, The British Nursing Index (using the OVID search interface) and the Cochrane Library, from inception of each database. Electronic searches were completed on 25th January 2013. Electronic searches were further supplemented by hand searches of reference list of papers meeting PICO criteria and relevant reviews identified through searching electronic databases. All titles and abstracts of papers were screened by two out of three researchers (AB, RA, AK) to identify studies which potentially met the inclusion criteria, disagreements were resolved through discussion. Full text reports of studies that were potentially relevant to this review were again screened by two out of three researchers (AB, RA, AK) to determine eligibility. To avoid double counting studies, findings for any population which was presented in multiple publications were included only once in this review. See Fig. 1 for a summary of the study selection process.

Data extraction

Standardised electronic data extraction sheets were developed by the team and modified after piloting on the first 5 papers. Data were extracted for characteristics of the participants, the characteristics of the intervention, the methodological characteristics of the study and the effects of the intervention on the use of urgent healthcare.

The characteristics of the complex interventions were coded according to the following 11 key characteristics, that were generated a priori [19]: general education, general discussion, skills training, exercise, behaviour therapy, relapse prevention, problem solving, cognitive behavioural therapy, social support, relaxation and biofeedback. Intervention components not fitting the description required for the above categories or not described in sufficient detail were recorded as "miscellaneous" [19].

Primary data extraction was performed by two researchers (AB, AK), with discussion between researchers and another member of the team (CD) where there was uncertainty in any aspect of data interpretation or extraction.

Risk of bias in individual studies

The methodological quality of each included trial was assessed using a component approach [20] to assess whether:

i) the allocation sequence was adequately generated (e.g. random number lists, computer generation, tossing a coin etc.)
ii) adequate methods were used to conceal treatment allocation
iii) knowledge of the allocated intervention was adequately prevented

[1] Since we anticipated differing thresholds for hospital admissions between countries and over time, for the purposes of this review hospitalisations were only considered urgent if they were described as such in the published paper, if hospitalizations were described as being the result of an acute exacerbation of underlying LTC or if researchers confirmed that hospitalizations were urgent.

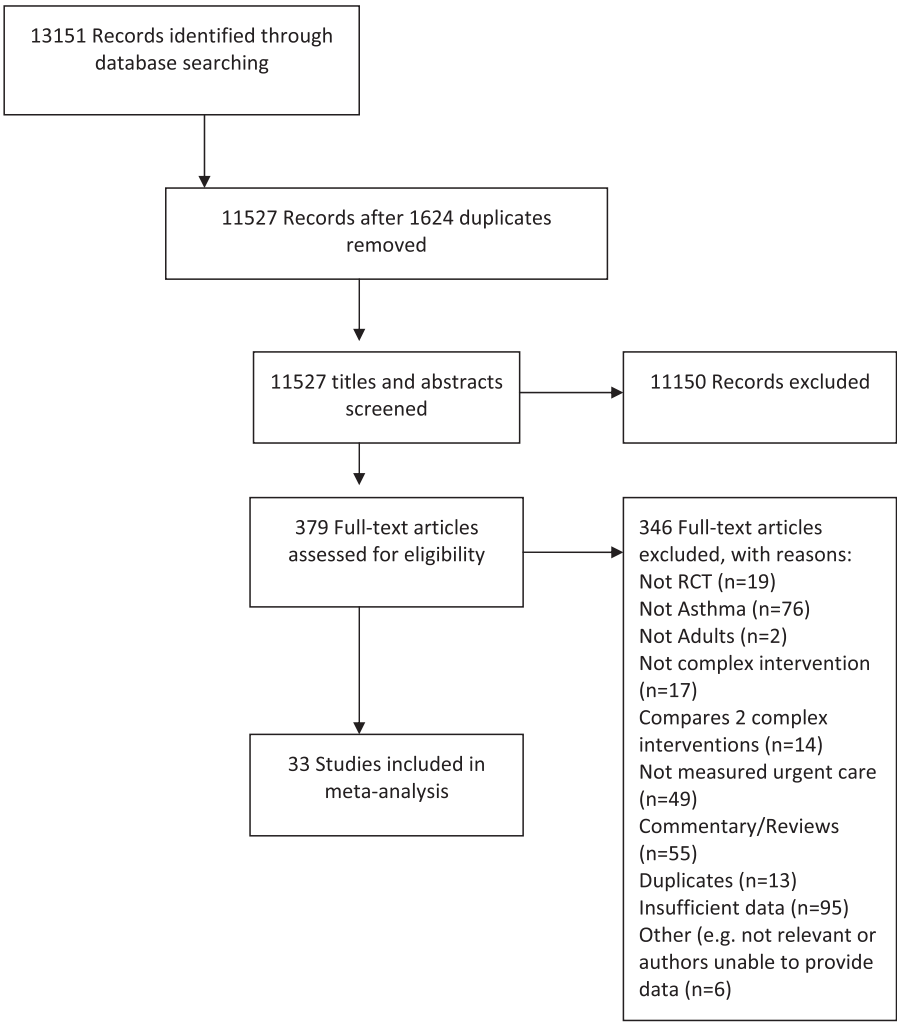

Figure 1 Review flow chart.

iv) incomplete outcome data was adequately dealt with
v) reports of the study were free from suggestion of selective outcome reporting
vi) the study was apparently free of other problems that could put it at risk of bias

Each study was given a rating of either low risk, high risk or unclear for each of the components above as recommended by the Cochrane Handbook [20].

For the meta-analysis, a binary measure of quality was used determined by whether concealment of treatment allocation was used or not [21]. Quality for each study was assessed by two out of three researchers (AB, AK, RA) and any uncertainties were resolved through discussion within the team.

Statistical analysis

Odds ratios (OR) and 95% confidence intervals (95% CIs) were calculated for each study where the number of subjects using urgent healthcare and the total number of subjects in each trial arm were presented. ORs <1 indicated that the intervention reduced the use of urgent healthcare [20]. Where data were presented in alternative formats, for example where summary test results or where continuous data were presented, appropriate transformations were made [22].

Where follow-up data were collected at multiple time points, ORs were calculated for the data collected nearest to 1 year to maximise consistency across studies. Where studies included more than 1 measure of urgent healthcare, effects for each measure were averaged. Where studies included more than 1 intervention compared with a TAU group, the data for each intervention group were entered as separate records and the sample size for the control group was halved for each comparison [20]. Effects of interventions were combined across independent studies using random effects models, weighted using the inverse of the variance [23]. Heterogeneity among studies was assessed using Cochrane Q and the I^2 statistic. Publication bias was assessed using funnel plots and Eggers' regression method [24,25].

Differences in effect across the methodological characteristics of the trials including, i) the features of the study

population, ii) the methods of delivering the intervention and iii) the methods of the trial, were assessed using the analog to Analysis of Variance for categorical variables [22] and univariate meta-regression for continuous variables.

To identify which intervention components were independently associated with reductions in urgent care, intervention components were entered into a random effects multivariate meta-regression [26,27]. Effects for interventions are presented in text, tables and forest plot.

Meta analyses were performed using Comprehensive Meta-analysis (version 2.2.048, Nov 7th 2008) and Stata (version 12, StataCorp LP, Texas, US).

Results

Details of studies included

Thirty-three independent studies met criteria for inclusion in this review of which 6 contributed results for 2 different interventions, resulting in 39 comparisons altogether. The 33 studies included 4246 patients with asthma. Sample sizes varied from 22 to 608 subjects, with an average of 129 participants. Seventeen studies assessed attendance at the emergency department, 2 assessed urgent hospitalisation, 3 assessed both, 6 assessed ED and another type of urgent care (such as emergency visits to primary or secondary care, non-specified urgent doctor visits, ambulance calls etc) and 5 assessed one of these other types only. Eight studies obtained urgent care data from patient records, 12 from self-reports, 5 used a combination of sources and for 8 studies the sources of urgent care data were unclear. Length of follow-up varied from 6 weeks to 36 months (mean = 10.8 months). See Table 1 for details of the methodological characteristics of the studies included.

Details of patient populations

Two studies recruited females only and the remainder included both sexes. Mean ages varied from 18.4 to 72.8 years. Patients were recruited from secondary care in 24 of the studies, primary care in 7 and from a combination in 1 study. See Table 1 in online appendix for characteristics of study populations.

Details of the intervention

The mean number of treatment components included within each intervention was 3.2 (range 1—9). The average number of treatment sessions (stated in 28 studies) was 4.4 (range 1—24); in 5 studies the exact number of additional health practitioner contacts associated with the interventions were unclear, most frequently because the number of contacts was flexible.

Treatment was delivered in hospital or doctor's clinic in 12 studies, at home or in the community in 10, and in a combination of these in 8. Treatment was delivered through face to face contact in 20 studies, telephone in 5 and a combination in 8. The intervention was delivered by a non-mental health practitioner in 27 studies, was non-practitioner delivered in 1 and unclear in 5. None was delivered by a mental health practitioner. Treatment was delivered by a multidisciplinary team in 10 studies and a unidisciplinary team in 18. Twenty-five of the studies used a structured management plan, 28 included scheduled follow-up, 8 included enhanced inter-professional communications, and in 6 this constituted collaborative care. See Table 2 in online appendix for details of interventions.

Reports of the risk of bias varied; 14 studies reported details of allocation concealment, of which 8 described adequate methods and were considered to be of high methodological quality. See Table 3 in online appendix for details of study quality.

Effects sizes for 39 comparisons are presented in the forest plot in Fig. 2. Overall the combined effect indicates that interventions were associated with a reduction in the use of urgent care (OR = 0.79, 95% CI = 0.67, 0.94). A moderate degree of heterogeneity was seen across studies (Q = 58.1 df = 38, p = 0.020, I^2 = 34.6%).

Effect sizes of the interventions did not vary significantly with the mean age of patients, gender mix, duration of illness, where the patients were recruited from, how or where treatments were delivered, who delivered treatment, number of treatment sessions or whether there was a structured management plan or scheduled follow up. The effect sizes were not significantly associated with type of unscheduled care, source of this data, or length of follow up. Among the minority of studies that reported details of treatment allocation concealment, those using adequate methods to conceal allocation showed similar effects to the 5 studies that did not (OR = 0.85 vs. 0.86, respectively). See Table 3 in online appendix for variation in effect across methodological characteristics.

When studies were grouped according to the components of interventions used, significant effects on the use or urgent care were seen for interventions that included general education (OR = 0.77), skills training (OR = 0.64), and relapse prevention (OR = 0.75) (Table 2). No studies had used exercise or CBT. On multivariate meta-regression, skills training remained significant (regression coefficient = −0.81, 95% CI −1.45, −0.17, p = 0.014), but behaviour therapy became significant (regression coefficient = 1.42, 95% CI 0.25, 2.58, p = 0.019) suggesting a worse outcome. However, only 2 comparisons involved behaviour therapy (Wilson (a) and (b)), which both also included skills training and social support. This suggests that behaviour therapy does not result in a significant additional improvement when skills training is also provided.

Publication bias

Although the funnel plot appears asymmetrical, with a relative absence of small studies in which interventions are associated with increased use of urgent care (Fig. 3), Egger's regression method did not confirm a statistically significant association between Log OR and standard error of Log OR [Egger's intercept = −0.37, (95% CI -1.21—0.48), p = 0.38].

Table 1 Impact of methodological characteristics on effect sizes.

	Number of studies	Number of comparisons	OR (95% CI)	*P*	Comparison across groups[a]
Number of patients recruited					
Mean age of subjects	29	33			−0.01 (−0.03,0.01) $p = 0.35$
Percentage male	31	36			−0.004 (−0.016,0.007) $p = 0.4$
Duration of treatment	21	26			−0.008 (−0.054,0.037) $p = 0.71$
Patient recruitment					
Primary care	7	8	1.13 (0.79,1.61)	0.51	
Secondary care	24	28	0.72 (0.59,0.88)	0.002	$Q = 4.2$, df $= 2$, $p = 0.12$
Combined	1	2	0.76 (0.46,1.26)	0.29	
Where delivered					
Hospital/clinic	12	14	0.69 (0.53,0.89)	0.004	
Home/community	10	13	0.82 (0.64,1.04)	0.097	$Q = 0.6$, df $= 2$, $p = 0.73$
Combined	8	8	0.77 (0.41,1.43)	0.41	
Mode of delivery					
Face-to-face	20	24	0.73 (0.57,0.93)	0.010	
Telephone	5	5	0.99 (0.79,1.22)	0.90	$Q = 1.7$, df $= 2$, $p = 0.43$
Combined	8	10	0.82 (0.58,1.16)	0.27	
Number of intervention sessions	28	33			−0.009 (−0.061,0.042) $p = 0.71$
Number of different components	31	37			−0.021 (−0.112,0.069) $p = 0.64$
Delivered by					
Non-mental health professional	27	33	0.83 (0.69,0.99)	0.034	
Multidisciplinary team	10	12	0.79 (0.62,1.01)	0.060	
Unidisciplinary team	18	22	0.87 (0.71,1.08)	0.21	$Q = 0.3$, df $= 1$, $p = 0.59$
Structured management plan	25	31	0.82 (0.69,0.98)	0.031	
No structured management plan	8	8	0.61 (0.36,1.02)	0.057	$Q = 1.0$, df $= 1$, $p = 0.33$
Scheduled follow-up	28	34	0.82 (0.69,0.98)	0.027	
No scheduled follow-up	4	4	0.65 (0.32,1.28)	0.21	$Q = 0.6$, df $= 1$, $p = 0.45$
Enhanced inter-professional communication	8	10	0.89 (0.68,1.16)	0.39	
No Enhanced inter-professional communication	24	28	0.77 (0.63,0.95)	0.015	$Q = 0.4$, df $= 1$, $p = 0.51$
Did intervention constitute collaborative care					
Yes	6	8	0.76 (0.55,1.04)	0.086	$Q = 0.1$, df $= 1$, $p = 0.82$
No	27	30	0.80 (0.66,0.97)	0.024	
Methodological characteristic					
Type of unscheduled care					
Emergency Department	17	19	0.82 (0.67,1.01)	0.060	
Urgent hospital admissions	2	2	1.16 (0.12,11.0)	0.90	$Q = 4.5$, df $= 3$, $p = 0.21$
ED/other	9	11	0.60 (0.40,0.89)	0.011	
Others	5	7	1.09 (0.73,1.63)	0.67	
Source of urgent care data					
Records	8	12	0.73 (0.58,0.91)	0.006	$Q = 3.0$, df $= 2$, $p = 0.22$
Self-report	12	14	0.91 (0.68,1.21)	0.52	
Combined	5	5	0.97 (0.75,1.25)	0.81	
Length of follow-up	33	39			−0.019 (−0.069,0.031) $p = 0.45$
Higher study quality	8	11	0.85 (0.70,1.03)	0.096	
Lower study quality	5	5	0.86 (0.55,1.33)	0.50	$Q = 0.001$, df $= 1$, $p = 0.97$

[a] Comparison across groups by meta-regression for continuous variables, mean age, percentage male, duration of illness, number of intervention sessions, number of components and length of follow up. Statistic quoted are regression coefficient (95%CI) and *p*. For categorical variables comparison across groups was done by CMA group comparison using options 'do not assume common variance within groups', and random effect.

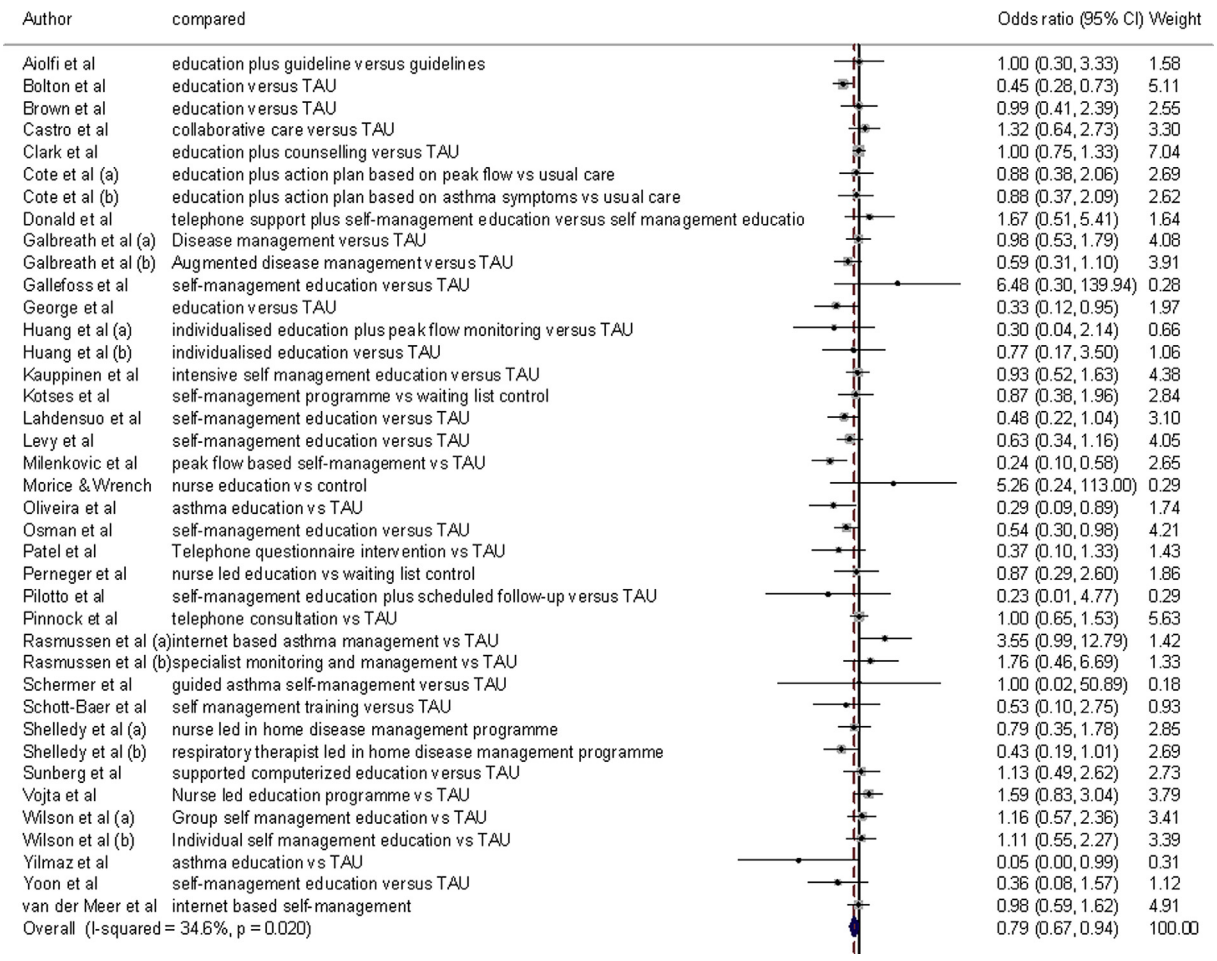

Figure 2 Effect sizes and 95% confidence intervals for complex interventions to reduce urgent healthcare use in adults with asthma.

Discussion

We conducted a systematic review and meta-analysis of complex intervention studies in people with asthma in order to identify the characteristics that were associated with a reduction in the use of urgent healthcare. We identified 33 studies with 39 separate comparisons of complex interventions in which use of urgent healthcare was an outcome. Overall we found that complex interventions reduced use of urgent healthcare by 21% (OR = 0.79, 95% CI 0.67, 0.94), though the effects of individual studies were moderately heterogeneous. We found that education, skills training and relapse prevention reduced urgent care use by 24%, 37% and 27% respectively. No studies used exercise or cognitive behavioural therapy. Observed effects did not vary significantly with other methodological characteristics and there was no significant evidence of publication bias.

Our review has a number of strengths. First, we conducted extensive searches of key electronic databases and asked experts in the area about potentially relevant studies to ensure we identified as many studies as possible. Second, our electronic searches were broad and only narrowed to the relevant papers using rigorous hand-searching. Third we did not limit the types of urgent healthcare included a priori though we were rigorous in the exclusion of studies for which it was not absolutely clear that the use of healthcare was urgent. We did not limit our review by the date or language of publication, sample size or duration of follow-up. Finally, the detection of between-study variance can be interpreted as a positive finding since it indicates that the heterogeneity was identified and then appropriately accounted for with a random-effects model for meta-analysis [28].

Our study has some weaknesses. First pooled effects across a wide range of complex interventions of varying intensities, delivered in varying settings by different professionals tells us little about which interventions might be most effective. Our intention had always been to explore the extent to which methodological characteristics influenced this heterogeneity, to identify intervention components associated with reduced urgent care. Second, we focused entirely on reduction in use of urgent care rather than medical outcomes, such as health status, morbidity or health-related quality of life, which means we cannot determine whether the reductions in the use of urgent healthcare were due to a reduction in need due to improved health, or simply by substitution of urgent with

Table 2 Random effect ORs and 95% CIs by type of treatment.

Variable	OR	95% CI	*P* value	Q on 1df *p*	Meta-regression coefficient (95% CI) *P*
General education: Yes ($n = 32$)	0.77	0.64, 0.91	0.003	$Q = 1.3$	−0.24 (−0.73, 0.26)
No ($n = 7$)	0.98	0.57, 1.67	0.94	$p = 0.26$	$P = 0.34$
General discussion: Yes ($n = 7$)	0.87	0.64, 1.17	0.34	$Q = 0.2$	0.11 (−0.34, 0.55)
No ($n = 32$)	0.77	0.64, 0.94	0.010	$p = 0.67$	$P = 0.62$
Skills: Yes ($n = 20$)	0.64	0.48, 0.86	0.003	$Q = 7.8$	−0.35 (−0.68, −0.02)
No ($n = 19$)	0.94	0.80, 1.09	0.41	$p = 0.005$	$P = 0.038$
Behaviour therapy: Yes ($n = 2$)	1.14	0.69, 1.88	0.62	$Q = 1.7$	0.38 (−0.31, 1.08)
No ($n = 37$)	0.77	0.65, 0.92	0.004	$p = 0.19$	$P = 0.27$
Relapse prevention: Yes ($n = 23$)	0.75	0.57, 0.98	0.036	$Q = 2.7$	−0.15 (−0.50, 0.20)
No ($n = 16$)	0.90	0.76, 1.07	0.23	$p = 0.098$	$P = 0.39$
Problem solving: Yes ($n = 6$)	0.84	0.59, 1.20	0.35	$Q = 0.3$	0.08 (−0.36, 0.51)
No ($n = 33$)	0.78	0.64, 0.95	0.012	$p = 0.56$	$P = 0.72$
Increased social support:					
Yes ($n = 2$)	1.14	0.69, 1.88	0.62	$Q = 1.7$	0.38 (−0.31, 1.08)
No ($n = 37$)	0.77	0.65, 0.92	0.004	$p = 0.19$	$P = 0.27$
Relaxation therapy: Yes ($n = 6$)	0.75	0.51, 1.10	0.14	$Q = 1.4$	−0.09 (−0.54, 0.36)
No ($n = 33$)	0.81	0.67, 0.97	0.023	$p = 0.24$	$P = 0.70$
Miscellaneous: Yes ($n = 26$)	0.79	0.63, 1.00	0.048	$Q = 0.01$	0.02 (−0.35, 0.39)
No ($n = 13$)	0.79	0.61, 1.01	0.061	$p = 0.93$	$P = 0.91$
Number of components $P = 0.67$					−0.02 (−0.11, 0.07)

scheduled healthcare, delivered as part of the intervention.

We interpret our findings to indicate that complex interventions for people with asthma can reduce the use of urgent healthcare by up to 21%. In particular those interventions that include education, skills training and relapse prevention are effective. However, the only intervention to remain significant in the multivariable meta-regression was skills training.

Guidelines for the management of asthma recommend that patients are trained to use their inhaler; the technique should be demonstrated to patients by health care professionals using placebo devices, and regularly monitored throughout the course of their healthcare [7,29,30].

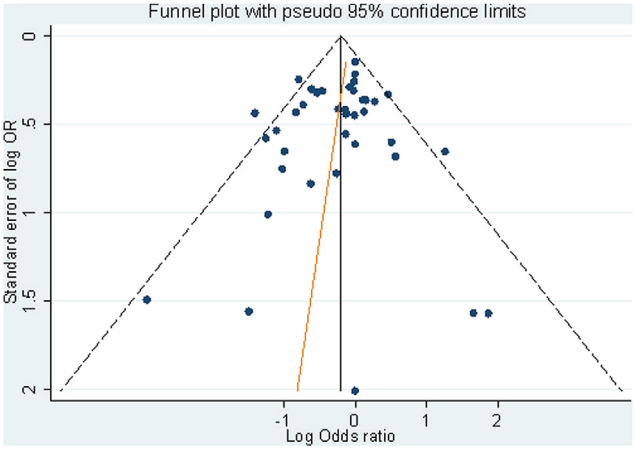

Figure 3 Funnel plot for included studies.

However, many patients do not receive adequate training on how to use inhalers for asthma and the percentage of errors recorded in inhaler use is high with up to 44% of patients reported as making errors [31,32]. Poor inhaler technique is associated with poor asthma control, increased risk of exacerbations, and increased use of urgent healthcare [31]. Our current findings suggest that improved skills training which is focussed on the use of inhalers would help to ensure that patients receive the optimum preventative medication and could have a central role in the reduction of urgent healthcare use for adults with asthma.

Overall the findings of our review show a significant effect of complex interventions for adults with asthma but this effect is smaller than those in a recent systematic review of complex interventions for people with COPD [18]. Dickens and colleagues found that complex interventions reduced the use of urgent care by up to 32% compared with 21% in the current study. Dickens and colleagues found that relaxation and general education were particularly beneficial interventions for patients with COPD [18], whereas we have found that skills training and relapse prevention were the most beneficial interventions for adults with asthma. Interventions such as these are relatively easy to implement but the size of the effects are relatively small. An important question therefore, is whether the size of the effect could be increased by the integration of treatments for anxiety and/or depression.

Anxiety and depression are common in people with asthma, both in the community [33–35] and in clinic-samples [36]. They carry a negative prognostic value and are associated with worse health outcomes for people with

asthma, including: poor medication adherence [11]; poor health-related quality of life [37], increased use of both scheduled and urgent healthcare [12,38,39]. Current NICE guidelines recommend the active treatment of depression in patients with long term conditions, beginning with non-pharmacological approaches but also including antidepressants if indicated [40].

Dickens and colleagues (2012) have recently shown that depression is a significant predictor of the use of urgent healthcare in people with long term medical illnesses, including asthma [12]. It was surprising therefore that none of the complex interventions eligible for inclusion in the present review included a specific psychological treatment and/or antidepressant therapy. The potential impact of targeted psychological and pharmacological interventions which aim to improve symptoms of depression and anxiety in adults with asthma on the use of urgent healthcare of requires evaluation. If effective such psychological interventions could be implemented within holistic packages of integrated care for adults with asthma that should also include skills training, education and relapse prevention.

Author contributions

Blakemore: ran the searches, screened titles and abstracts to identify eligible papers, extracted data, conducted quality review and assisted with meta-analysis. Interpreted the findings, drafted the paper and tables, co-ordinated with co-authors to collate comments and wrote the final draft of the paper.

Dickens: planned and designed the review and meta-analysis, drew up the inclusion and exclusion criteria, supervised the development of search strategies, supervised the identification of eligible papers, supervised data extraction and meta-analysis, interpreted findings, contributed to the paper, commented on each draft of the paper and approved the final version of the paper.

Anderson: assisted with screening titles and abstracts to identify relevant papers, assisted in data extraction, the drafting of the paper and tables and approved the final version of the paper.

Tomenson: assisted in the design of the study, conducted the meta-analysis, assisted in the drafting of the paper and tables, commented on each draft of the paper and approved the final version of the paper.

Woodcock: made important intellectual contribution to the interpretation of the findings and to the drafting of the paper. Approved the final version of the paper.

Guthrie: assisted in the planning and design of this review and meta-analysis, assisted in the development of inclusion and exclusion criteria and search strategies. Interpreted the findings and contributed important intellectual content to the paper commenting on each draft of the paper and approved the final version of the paper.

Disclosure of potential conflicts of interest, activities, relationships and affiliations

None of the authors have conflicts of interests or financial interests to declare.

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Role of the sponsor

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Disclaimer

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2014.11.002.

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