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A systematic review of the cost-effectiveness of medication adherence-enhancing intervention for asthma

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Objective This systematic review aimed to evaluate the cost-effectiveness of medication adherence-improving interventions in patients with asthma. **Data source** Search engines including PubMed, Scopus and EBSCOhost were used to locate relevant studies from the inception of the databases to 19 October 2018. Drummond's checklist was used to appraise the quality of the economic evaluation. **Study selection** Economic studies evaluating the cost-effectiveness of medication adherence enhancing interventions for asthmatic patients were selected. Relevant information including study characteristics, quality assessment, health outcomes and costs of intervention were narratively summarized. The primary outcome of interest was cost-effectiveness (CE) values and the secondary outcomes were costs, medication adherence and clinical consequences. **Results** Twenty studies including 11 randomized controlled trials, 6 comparative studies and 3 modelled studies using Markov models were included in the review. Among these, 15 studies evaluated an educational intervention with 13 showing cost-effectiveness in improving health outcomes. The CE of an internet-based intervention showed similar results between groups, while 3 studies of simplified drug regimens and adding a technology-based training program achieved the desirable cost-effectiveness outcome. **Conclusion** Overall, our results would support that all of the identified medication adherence-enhancing interventions were cost-effective considering the increased adherence rate, improved clinical effectiveness and the reduced costs of asthma care. However, it was not possible to identify the most cost-effective intervention. More economic studies with sound methodological conduct will be needed to provide stronger evidence in deciding the best approach to improve medication adherence.

Keywords Cost-effectiveness analysis; medication adherence; patient compliance; asthma; systematic review

Introduction

Asthma is a common severe respiratory disease in adults and children affecting around three billion people worldwide (1). Globally, the asthma incidence rate is rising and the rate is expected to increase by 50% every 10 years, with most of the new cases in lower-income countries (2, 3). Asthma may impair the daily activities of patients throughout the year, and a severe exacerbation could lead to an extended hospital stay (4), thereby significantly impacting the patient's quality of life (5–7). At the same time, asthma also imposes a large financial burden on national healthcare expenses. For example, the annual cost of asthma was reported to be \$64 billion in the US in 2011, \$24.7 billion (1992 to 2002) in Europe, and \$9.8 billion in the UK (8).

Clinically, asthma is a controllable disease but currently has no permanent cure. For management options, multiple types of medications such as daily controllers (to control inflammation) and relievers (to provide quick relief from asthma symptoms) are available to control

the symptoms. When used appropriately, symptoms of asthma can be well managed with these medications. However, despite proven effectiveness, the overall medication adherence is still poor and reported as the cause of 24% of exacerbations and 60% of hospital stays (9), thus leading to high economic costs (10).

The reported medication adherence rate in asthma ranged from 30 to 70% in adults to less than 50% in children (11). The consequence of medication non-adherence includes worsening of asthma symptoms, decreasing quality of life and increasing healthcare expenses. For example, 30 to 50% of patients in the US were reported to be non-adherent to long-term medications and would have incurred avoidable healthcare costs of \$100 billion a year (12). In addition, drug non-adherence was shown to contribute to a yearly hospital admission rate of 42.4 per 1000 population, but regular use of inhaled corticosteroids showed a 34% drop in hospital stays (13). Undeniably, better adherence to medication will produce good clinical and financial results in asthmatic patients.

Factors and barriers associated with medication non-adherence have been fairly well studied (14). In practice, many approaches such as education programs, technology-aided intervention and simplified regimen may overcome the barriers associated with non-adherence. These interventions to improve adherence had displayed favourable clinical and health effects as well as reduced healthcare expenses (15–17). Evidence has also demonstrated that medication adherence interventions are cost-effective in reducing asthma burden and improving adherence (18). Another study projected that the decrease in hospital stays and improved medication adherence could save £475 per year for each asthmatic patient (19).

Over the years, there were several studies aimed at maximizing gains at the lowest possible costs for improving medication adherence (20–23). Conducting such studies reflects the need to capture the value of intervention in aiding decision making in resource allocation. Although several economic studies had been conducted, only a few systematic reviews were able to identify, summarize and discuss the conduct and reporting of the included studies. Furthermore, the most recent systematic review conducted in 2013, summarizing the cost-effectiveness of approaches to improve medication adherence in chronic disease patients, was based on randomized controlled trials (RCTs) only (24). Although not specifically focusing on asthma, two of the included studies in the review reported that medication adherence enhancing interventions were cost-valuable in asthmatic patients, while another study reported non-cost-effectiveness results. Therefore, our current review aimed to evaluate the cost-effectiveness of medication adherence enhancing intervention focusing on asthmatic patients, as evidence has shown that medication non-adherence rate among these patients is high. Besides providing information about choosing medication adherence interventions for asthmatic patients, evidence from this review may also aid decision-makers to select the best intervention to improve medication adherence.

Methods

A systematic review of published literature was performed adhering to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement (PRISMA) for transparent reporting of the outcomes and following guidelines for appraisal of economic evaluation (25).

Search Strategy

Databases including Pubmed, Scopus and EBSCOhost were searched from the inception of the search engines to 19 October 2018. The following keywords and medical subject headings (MeSH) terms were used: (“cost” OR “cost analysis” OR “cost-effectiveness” OR “cost-benefit” OR “cost-utility” OR “cost minimization” OR “cost analysis” OR “economic evaluation”) AND

("medication adherence" OR "patient compliance" OR "nonadherence" OR "noncompliance") AND ("intervention" OR "enhancement") AND ("asthma" OR "chronic lower respiratory disease").

Publications were limited to English language articles only. Citations and bibliographies of retrieved articles and relevant reviews were screened for any relevant articles.

Criteria of Inclusion for this Review

The selection of articles was based on the following set of inclusion and exclusion criteria:

- (1) Types of study: Economic evaluation and studies comparing the cost-effectiveness of medication adherence enhancing interventions for asthmatic patients.
- (2) Types of interventions: Any intervention or combination of interventions to improve medication adherence in asthmatic patients, including educational interventions, technology-assisted programs and/or simplification of the dosing regimen.
- (3) Types of outcome measures: Cost-effectiveness outcomes were the primary measure comparing the costs and consequences between interventions. Secondary outcomes included the costs, healthcare use, rate of adherence and health outcomes.

Only full-text original articles satisfying the aforementioned criteria were included, while case reports, conference abstracts, editorials, expert opinions, reviews and study protocols were excluded.

Study selection

The title and abstract of the identified articles were independently screened according to the inclusion and exclusion by two researchers (KSM and NAMT). Then, the eligibility of full-text publications was independently assessed. Reasons for exclusion for each article were recorded. Any differences of opinion or disagreement between the two researchers (KSM and NAMT) were resolved by discussion and consensus, followed by an independent opinion from the third researcher (LSC).

Data extraction

Two researchers (KSM and NAMT) independently extracted data from the included studies using a standardized data collection form. The third researcher (LSC) resolved any disagreement between the two researchers (KSM and NAMT) until consensus was reached. Extracted data included year and site of study, type of study, type of intervention, the perspective of economic evaluation, type of cost, pricing year, data source, and time horizon of the study. Extracted outcomes data included the intervention effects towards the medication adherence rate, healthcare utilization (such as emergency room visits, physician visits, hospital admissions, and ICU admissions), healthcare costs and health outcomes (e.g. asthma control and quality of life measures such as quality-adjusted-life-years (QALYs) and disability-adjusted-life-years (DALYs)).

Quality appraisal

The methodological quality of a published economic evaluation was critically appraised using the ten key questions from the Drummond checklist (26). An economic evaluation was graded as high-quality when the article satisfied 9 key questions and above in the checklist, 7–8 key questions suggested good-quality, 5–6 key questions meant fair-quality, and 4 or lesser key questions as poor-quality (27).

Results

Literature selection

The electronic search of selected databases produced 4945 articles. After removing 36 duplicate articles and 4654 articles based on their irrelevant titles, the screening yielded 255 articles for further review. Another 201 articles were removed after reading the abstracts, the eligibility of the remaining 54 full-text articles was assessed, with 43 disqualified for inclusion. The reasons included the study did not fulfil the criteria for outcome measures, being a study protocol, review article, or report. The manual search of the reference list of identified articles added another nine extra publications. Overall, the search identified 20 eligible articles for inclusion in the systematic review. Figure 1 summarizes the details of the selection process.

Study characteristics

Table 1 summarizes the characteristics of the included studies (including 11 RCTs, six observational studies and three model-based economic evaluations). All studies were published between 1986 and 2018, with two studies published in 1986 (28, 29) and the latest study in 2018 (23). Most of the studies were conducted in high-income countries ($N = 18$), including eight studies conducted in the US (22, 28, 30–35) followed by two studies each in the UK (20, 36) and Germany (21, 29). Only Colombia and Malaysia were from the upper-middle-income countries based on the World Bank country income group classification. None of the identified studies were conducted in the lower-income country group.

The three main intervention types were education programs, technology-aided and simplified regimens. Overall, 15 studies evaluated the cost-effectiveness of an educational program (21–23, 28–33, 35, 37–41), two studies assessed technology-based intervention (Internet and telephone) (36, 42) and another study compared the simplified twice-daily to once-daily dosing regimens (43). Two studies evaluated a combined education and technology-aided intervention (20, 34). Self-management was the most popular skill highlighted in the education programs with seven studies employing the strategy (21, 28, 31, 33, 38, 39, 42).

Eight articles explicitly reported the perspectives of the study, either from the society ($N = 1$) (39), the healthcare payers ($N = 3$) (35, 41, 43), or a combined perspective ($N = 4$) (21, 23, 37, 42). After the full-text review, the author classified the perspective of the remainder as based on society ($N = 6$) (29, 31–33, 38, 40) or healthcare provider ($N = 6$) (20, 22, 28, 30, 34, 36). None of the studies used the patient's perspective in economic evaluation.

The time horizon ranged from 6-months up to the lifetime duration. Most of the RCTs ($N = 14$) calculated the costs and consequences of interventions for a duration between 12 to 18 months (20, 22, 28–31, 33, 34, 36, 37, 39, 40, 42, 43) with the shortest at 6 months (32). The longest duration of RCTs or observational studies was three years in two studies (21, 38), while the three model-based studies projected the impact of interventions up to a lifetime (23, 41, 43).

Quality assessment

The key elements based on the Drummond checklist are tabulated in Table 2. In summary, most studies ($N = 9$) were considered as fair to good-quality (20, 22, 23, 28, 35, 36, 38, 39, 42), with a study conducted by Neri et al. fulfilling all the criteria (37).

Overall, only 40% of the studies ($N = 8$) adequately described the competing alternatives (20, 22, 32, 33, 36–38, 43). In contrast, only five studies (25%) (22, 29, 30, 33, 43) failed to adequately report the methods for data collection and assumptions to prove the effectiveness of an intervention. However, the lack of suitable statistical tests may lead to potential biases in nearly 25% of the studies ($N = 5$) (22, 29, 30, 33, 43).

All relevant and important costs and outcomes were identified in 18 studies (20–23, 28, 29, 31–35, 37–43) and measured accurately in a suitable physical unit in 17 studies (20–23, 28–33, 35–37, 40–43). Sixteen studies credibly identifying, justifying and adjusting (if any) the costs and consequences values that were appropriate to the questions posed using market value (20–23, 28–30, 34–39, 41–43).

For discounting, only four studies (out of seven with >12 months' study duration) had discounted the future costs and effects to reflect their present values (21, 23, 38, 41). Twelve studies reported the incremental costs and consequences between comparators (21–23, 28, 29, 33, 37, 39–43). Eight studies performed sensitivity analyses to address uncertainties associated with the assumptions and the change in the key costs and their units (21, 23, 36, 37, 39, 41–43).

Cost-effectiveness of medication adherence-enhancing interventions for patients with asthma

This section gives a brief outline of the study outcomes by the types of interventions (Table 3).

Educational program

A majority ($N = 15$) of the included studies evaluated the cost-effectiveness of educational interventions for asthmatic patients (21–23, 28–33, 35, 37–41). Among these, 13 studies claimed that their educational intervention was cost-effective. Six studies reported the cost-benefit ratio (21, 22, 29, 33, 37, 40) with the ratio ranging from 1:1.46 to 1: 5.6. In contrast, one study considered the intervention program as not cost-effective because of the extensive use of resources despite its improved adherence (30), while another study could not confirm the cost-effectiveness of the intervention due to lack of full economic data (32). For secondary outcomes, the overall clinical effectiveness was better in the educational intervention group in all studies. Nine studies (21–23, 28, 29, 31, 33, 35, 40) that report the outcomes of hospitalization showed a reduction in hospital stays except for the study by Neri et al. (37) that had a trend of an equal number of hospitalization days. Also, Deter (29) concluded that an educational program was a cost-effective strategy especially for children with a history of hospital admissions. There are six studies (22, 28, 31, 35, 37, 40) that reported a reduction in ED visits among those in the educational group while there are no significant differences in ED visits in the study by Taitel et al (33). Almost half of the studies ($N = 6$) reported a lower frequency of loss of productivity days or absenteeism (21, 22, 29, 35, 37, 40). Another five studies (23, 32, 39–41) reported asthma-related quality of life had significantly improved in the education intervention group while another study reported equivalence score in both groups (38). The education group also showed better asthma control by the improvement of the FEV₁ value, lung functions, asthma attacks, a better year, symptoms-free days, symptoms-free nights, or limited activity days (21, 22, 31, 35, 37–39). Meanwhile, only two studies showed improving medication adherence (30, 32) and one proclaimed equivalent adherence between groups (38). A total of seven studies compared the costs between the education intervention and its comparator (23, 30, 31, 37–39, 41), with the costs of intervention reported being lower in four studies (23, 31, 38, 39) and higher in the rest (30, 37, 41).

Technology-aided intervention

There were two studies that evaluated technology-aided strategies for asthmatic patients (36, 42). Both studies showed good health outcomes but did not report the rate of medication adherence.

Pinnock et al. added a telephone alternative compared to a face-to-face only review and usual care (36). The telephone choice contained a structured recall and choice of face-to-face or telephone review. Questionnaire surveys [including the mini-Asthma Quality-of-Life Questionnaire (mini-AQLQ) and Asthma Control Questionnaire (ACQ)] assessing asthma morbidity found equivalent results between the groups. However, a significant difference was reported for the score of enablement and competency of self-care between the groups. The cost incurred per patient for telephone alternative was the lowest (Singaporean Dollar (SD) 5.53) compared with the face-to-face-only (SD 5.68) and usual care (SD 6.45) groups and the difference was statistically significant between groups. The sensitivity analysis results based on a 95% confidence interval were robust with the range of cost-saving per patient reviewed between SD 2.58 and 2.83. The authors concluded that offering telephone reviews was cost-effective considering the increase in asthma review rates, patient enablement and confidence in self-care with a good score for asthma control.

Van Der Meer et al. compared the outcomes of an internet-based self-management program to usual-care (42). The Internet group had more productivity loss (114 h) than the control group (98 h). The gain in QALYs was higher in the Internet group using the EuroQol Classification system (EQ-5D) instrument but the visual analog score reported equal results between groups. There were trends of higher health care costs in the Internet group compared with the control group based on both societal and health care perspectives. The incremental cost-utility ratio was reported as \$26700 per QALY gained. Based on the CE plane, the likelihood of the Internet program being cost-effective or domination over the usual care were 30% and 10% respectively. From the cost-effectiveness acceptability curve (CEAC), the chances of an internet-based program being a cost-effective alternative based on the societal and healthcare payers' perspective were 62% and 82% respectively at the \$50000 threshold, and 74% and 86% respectively at the \$100000 threshold.

Simplified medication regimen

There was only one study that evaluated a simplified medication regimen from twice daily (BD) to once-daily (OD) dosing of inhaled corticosteroid in children (43). Besides better adherence, patients on OD dosing incurred a lower average cost of US\$1529.3 per patient and a higher QALY (0.8284) compared with US\$1709.1 and 0.8084 QALY for BD dosing. Asthma exacerbation caused the greatest changes in both the cost and outcomes as reported by the sensitivity analyses. OD dosing was still a dominant strategy based on the results of uncertainty analyses such as scatter plot, CEAC and WTP thresholds,

Mixed types of interventions

Two studies evaluated mixed types of medication adherence enhancing interventions for patients with asthma (20, 34). Both studies did not measure medication adherence, instead they assessed the clinical outcomes.

The first study implemented integrated outpatient care including self-monitoring and educational intervention for asthma (20). There was no significant difference in the mean FEV₁, GP consultations, days of hospitalization, months of restricted activity, and percentage of stable day and night asthma between integrated and usual care. In contrast, integrated care had lower bronchodilators and inhaled steroids prescribed. The annual net cost saving of integrated care for patients was £39.52 per patient, for GP was £2.41 per patient, and for the hospital was £3.06 per patient. The authors concluded that integrated care was cost-effective from the perspective of patients, GP and hospital provider.

The study by Levenson et al. explored a care program comprising scheduled monitoring, education, telephone services, adequate doses of anti-inflammatory drugs and psychiatric referral among 8 patients with severe asthma (34). No further hospital admission was reported in 3 patients after intervention, while six patients had no hospitalization for 4 years and longer. The program was considered cost-effective for malignant potentially fatal asthmatic patients with the total costs reduced from \$22999/person/year to \$1107/patient/year after the program introduction.

Discussion

Adherence to asthma medication has a great impact on disease control and many intervention strategies have been attempted over the years to improve the medication adherence rate with various degrees of success. Furthermore, due to the high prevalence of asthma among the population and increasing pressure on the finite healthcare budget, decision-makers will need cost-effectiveness analysis as an aid in choosing the best intervention strategy to maximize the health gains at the lowest cost. Our current review identified, summarized and discussed 20 articles on the cost-effectiveness of medication adherence-enhancing interventions for patients with asthma. Almost half of the studies ($N=9$) had fair-good quality (20, 22, 28, 35, 36, 38, 39, 42, 43), with four studies achieving high-quality levels (21, 23, 37, 41).

Most of the included education-based studies ($N=17$) claimed their interventions to be cost-effective (20–23, 28, 29, 32–41, 43). In contrast, the three remaining studies had different conclusions with one study declaring equivalent results (42), another reporting non-cost-effectiveness (30) and one study could not decide (31). Overall, most of the medication adherence interventions reported achieving better clinical outcomes. However, only four studies reported the results of medication adherence (30, 32, 38, 43), with three studies (30, 32, 43) reporting better adherence and one reporting equal rates (38). When considering costs, most interventions had higher implementation costs compared to alternatives. Nevertheless, most of the increased expenses were offset by improved drug adherence and clinical effectiveness, resulting in positive CE values and favourable benefit-to-cost ratios.

Based on the results from our present study, several recommendations for conducting future cost-effectiveness studies on adherence intervention could be suggested. First, several guidelines were developed for assessing the quality of the economic evaluation to improve methodological conduct and its reporting (26, 44). These guidelines should be used in designing and reporting the outcomes of future studies to reduce bias and assist in comparison. At the very least, to avoid the Hawthorne effect, the study should include active comparators for direct comparison to estimate the incremental impacts of interventions and report the ICER. Also, details of costs identified may potentially influence the final estimation of the cost-effectiveness results causing either under- or over-estimation. Cost evaluation is largely dependent on the perspective of the study. From the perspective of enhancing public health, a study should use a societal perspective to capture a broader range of costs associated with the societal benefits of introducing the interventions. Further, the chosen time horizon of the study is also important because the impact of implementing an intervention may take time to show an effect, and may largely depend on the natural history of the disease; which in our case is asthma. For example, a 6-month period may be inadequate to measure the difference in hospital admission and readmission, and a longer study duration would be necessary to assess the impact of the intervention on the morbidity and mortality of asthma. Furthermore, there was a tendency for the intervention cost to further drop leading to higher cost-savings following the prolonged effects of imposed strategies (42).

Patient factors can also impact the cost-effectiveness of adherence intervention significantly. In our case, the target population ranging from children to adults, asthma severity, and the income of the countries can also lead to different results. For example, the likelihood of the dominant strategy

of OD dosing could only translate specifically to those patients with mild asthma as the severity of the disease would impact the overall clinical results. Fundamentally, future studies should first identify the most affected populations or those that could achieve optimal advantages from the intervention.

Furthermore, most of the studies included in this review represented studies conducted in developed countries. Generalizing these outcomes to countries with limited resources might not be reliable and challenging. More data from developing countries where disease prevalence and the rate of medication non-adherence are higher, are necessary to confirm our findings. Furthermore, another often neglected factor to consider is the technological expertise which refers to technological skills and knowledge of health professionals of the study country itself (45). Most developed countries have a higher ranking in technological skills reflecting the much easier entry of technology-aided strategies with plenty of skilled health professionals and cheaper costs of implementation. Despite the reported cost-efficacy of digital-based intervention in the UK (36) and in the US (34), achieving similar CE outcomes might be unrealistic for developing countries.

Overall, our systematic review is a more focused and comprehensive outline of medication adherence-enhancing interventions for asthma sufferers compared to the 2013 study by Oberje et al. (24). The previous review could not claim that introducing medication adherence strategies in patients with chronic disease was worthwhile because of the differences with the sample, methods and interventions between each study. Also, the previous review included RCTs only and excluded model-based economic evaluations and observational studies. However, well-conducted observational studies are also able to assess health outcomes between complex interactions. Thus, the inclusion of studies other than RCTs reflects the advantage of our review over the previous review. In addition, our review also included 2 studies (30, 31) from the previous review as they met our inclusion criteria. Therefore, besides a focus on medication adherence in asthmatic patients, our review added more qualified studies and included more studies published after 2013, further strengthening the evidence of medication adherence-enhancing interventions.

Finally, our review has several limitations. First, we could only extract modest numbers of studies evaluating both the clinical and economic results. For the included studies, large variations in the quality and reporting of the study designs would impact the validity and reliability to generalize and answer the research question. Furthermore, the exclusion of non-English studies may cause important publications in other languages to be excluded. In addition, we did not include any grey literature but this may not have much impact on our conclusion as it is usually difficult to assess the quality of grey literature. Hence, despite these limits, interventions to improve adherence for asthma showed a general trend of producing good, cost-effective results in our current review.

Conclusion

In conclusion, we have provided updated information on the cost-effectiveness of medication adherence intervention in asthmatic patients. Overall, all the medication adherence-enhancing interventions identified in our review were cost-effective considering increased adherence rate and clinical effectiveness together with the reduction in the costs of asthma care. However, based on the information available from our review, it was not possible to identify the most cost-effective intervention. Hence, more well-conducted economic studies will add stronger evidence in deciding the best approach to improve medication adherence.

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Declaration of interest

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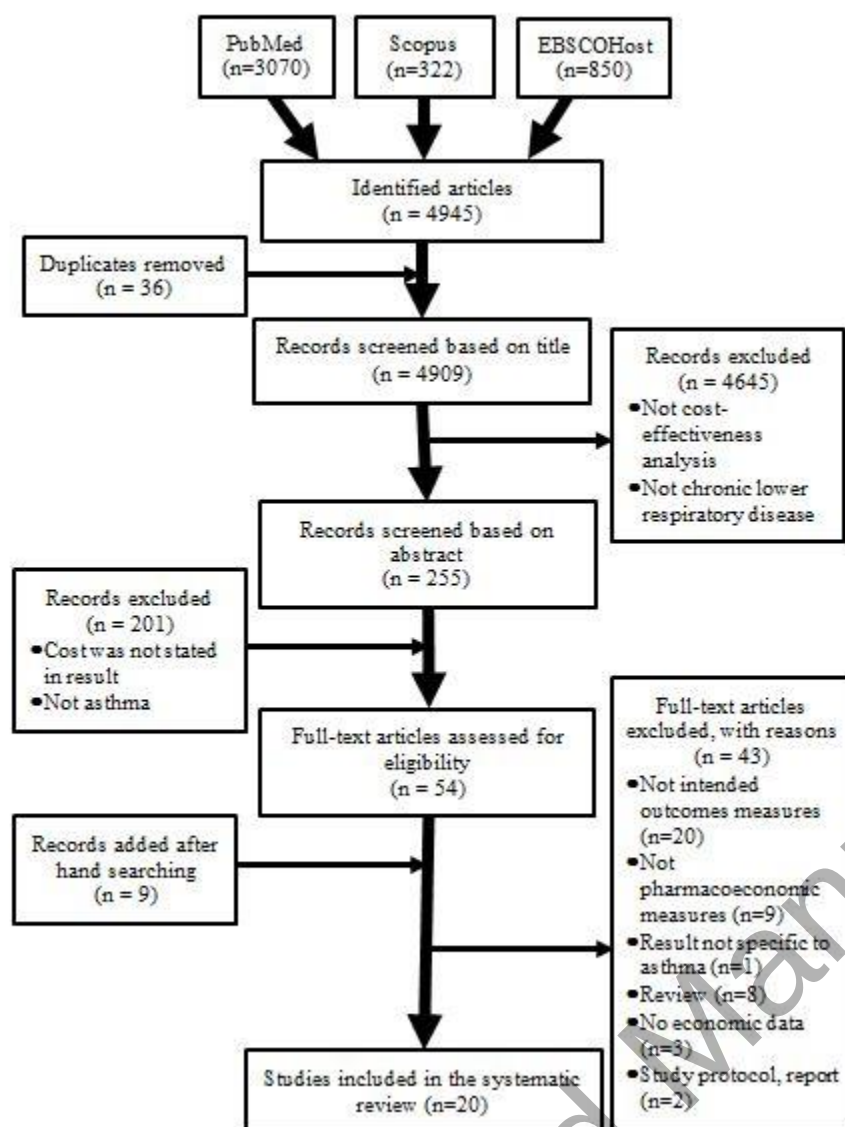


Figure 1. Flow Diagram for a systematic review of the cost-effectiveness of medication adherence enhancing interventions for asthma.

Table 1 Study Characteristics of Cost-Effectiveness of Medication Adherence-Enhancing Interventions for Asthma.

Author, Year, Country	Type of Study	Types of Intervention	Perspective ^a	Type of Cost	Collection of Data	Time Horizon
(Clark et al. 1986), USA	RCT	I = Usual care plus self-management education including six (5 separate classes and one combined class for parents and children) one-hour group training classes every month offered to asthmatic children and parents, introducing problem-solving skills by health educators. C = usual care one	Provider (NS)	DM: hospitalizations, ED visits, medication, health educators' time, educational materials.	1. Interviews. 2. Medical records	12-months
(Deter 1986), Germany	Observational follow-up study	I = "Psychosomatic coping group therapy" involving breathing and relaxation technique, open discussion, expressing feelings and defining group dynamics and patients' attitude C = usual care	Societal (NS)	DC: Hospitalizations, physician visits, treatment costs, travel costs. IC: working days lost.	1. Diary (severity grade, drug use). 2. Health insurance data	18-months
(Windsor et al. 1990), USA	RCT	I = Educational intervention consisted of 30-minutes individual sessions (use of PEF meter and inhaler, and guideline on asthma control) plus a 60-minutes group session involving 4-6 asthmatic patients and caregivers and 2 telephone reinforcement calls conducted by a specialized health educator. C = usual care consisted of a 10-minute regular discussion about the importance of adhering to medical regimes and two 15-minute follow-ups.	Provider (NS)	DC: human resource, program-related costs.	1. Questionnaire (10-item observational checklist documented inhaler use and skill, instruments adapted from literature) 2. Theophylline level assessment. 3. Self-report.	12-month
(Bolton et al. 1991), USA	RCT	I = "Self-management training program" of 3 one-hour group education sessions emphasizing the importance of medication compliance, providing control and preventive strategy during an asthma attack, explaining the rationale of medication uses and its efficacy, encouraging relaxation exercise and	Societal (NS)	DMC: Hospitalizations, physician's visits and ED visits. IC: days of limited activity	1. Patient recall through telephone interviews at baseline and every 4 months 2. Billing	12-months

		promoting smoking cessation, led by specially trained-registered nurses C = usual care			records 3. Patient attendance 4. Patient evaluations of the classes	
(Soondegaard et al. 1992), USA	RCT	I = An intensive educational intervention involving one-to-one and group education in hospital (at first month) plus home education at second and six months (education on the mechanism of asthma, lung structure, route of administration and timing of drug, and the use of PEF, the efficacy and ADR of drug the use of inhaler device by the physicians, pharmacists and nurses. C = less detailed instructions and no formal education.	Societal (NS)	DC: hospitalizations, human resources (salary and time), teaching materials, GP visits, medications. IC: sickness days.	1. Questionnaires (Psychosomatic discomfort scale and Asthma quality of life scale questionnaire) 2. Hospital data.	6-month
(Trautner et al. 1993), Germany	Comparative, observational study	I = Structured asthma treatment and teaching program (ATTP) involving self-management training (patient participated in the decision making of their asthma treatment plan) and 20-hours inpatient group education for 5 days provided by a trained nurse. C = before enrolment	Societal & payer	DC: hospitalizations, GP visits, medications, peak flow meter, educational material, nurse salary. IC: productivity loss	1. Questionnaire (asthma attack and physician visit). 2. Per diem price. 3. Medical examinations.	3 years
(Drummond et al. 1994), UK	RCT (Pragmatic controlled trial)	I = An integrated asthma care involving physician reviews and making necessary appointments to assess their asthma condition. Upon consultation, patients were provided with a PEF diary card and a questionnaire containing information such as advice, lung function, prescribed medication, medication adjustment and hospital admission. C = conventional outpatient care	Provider (NS)	DC: hospitalizations, physician consultation, program operation (staffing, material costs),	1. Patients interviews (self-efficacy scale, hospital anxiety and depression scale, living with asthma scale (social and physical function), number of prescriptions (bronchodilators, inhaled and oral steroids), and costs).	12-months

					2. Hospital administrative data	
(Taitel et al. 1995), USA	RCT, pre (one year before) and post (one year after) study	I = Seven weeks of 90-minute self-management training sessions plus behavioral control aspects. C = patient on the waiting list.	Societal (NS)	DC: GP visits, hospitalizations, ED visits, medications, laboratory tests, travel costs, others (related to introducing the program). IC: productivity losses	1. Diary (asthma attack and PEF). 2. Based on the outcomes of the previous study by Kotses et al.	12-month
(Neri et al. 1996), Italy	RCT	I = Complete program containing 5 lessons of one-hour duration twice weekly for 2 weeks and a reinforcing session after 3 months based on the educational booklet and 20-minutes educational video at 2nd, 3rd and 4th sessions plus monitoring and recording PEF value. C = Reduced education program through self-reading of an educational booklet on asthma) plus monitoring and recording PEF value.	Societal & payer	DC: medical examinations, spirometry tests, hospitalizations, medication, program costs (healthcare provider-related costs, videotapes, room and video recorder rental). IC: work lost days	1. Daily diary. 2. Spirometry tests (FEV1 and FVC). 3. Medical records	12-months
(Levenson et al. 1997), USA	Comparative, observational study	I = A treatment program encompassing a combination of routine physician visits, simplified medical regimen, psychiatric intervention and adequate doses of anti-inflammatory medications (if necessary). C = before enrolment	Provider (NS)	DC: hospitalizations, ED visits, ICU admissions,	1. Hospital data. 2. Medical records	18-months
(Kauppinen et al. 1999), Finland	RCT	I = Intensive patient education and supervision for self-management. Involved basic education package administered by respiratory nurses (knowledge on the use of inhaled drugs, PEF monitoring and concept of treatment) plus individual education every third month plus nurse and physiotherapist-led 2-hour group education of 2-3 people plus revision of	Societal (NS)	DC: hospitalizations, ED visits, outpatient visits, transportation costs, nurses and physiotherapist time, medication. IC: loss of	1. Spirometers tests. 2. Diary. 3. Questionnaires (Generic 15 D and St. George's Respiratory Questionnaire	3-year

		self-management by chest physician at 1-year follow-up. C = basic education package		working days	). 4. Hospital data. 5. Insurance database.	
(Gallefo ss et al. 2001), Southern Norway	RCT	I = Two (2 h each) group education sessions and 1-2 personal education led by nurse and physiotherapist focusing on self-management by providing a 19-pages booklet and self-management plan. C = outpatient consultation	Societal	DC: hospitalizations (based on the Norwegian diagnosis-related group), GP visits, pulmonary consultant visits, medication, education program, travel (for GP visits and educational program). IC: Absenteeism	1.St. George's Respiratory Questionnaire . 2. Spirometry tests.	12-months
(Tschopp et al. 2005), Switzerland and	Comparative, observational study	I = Educational intervention including a combination of a 30-minute one-to-one briefing by nurse and chest physician, educational brochure, call service when necessary, individualized notebook with an action plan and education seminar conducted by multidisciplinary collaboration. C = before enrolment.	Societal (NS)	DC: hospitalizations, outpatient visits, medication, program-related (development and production of a brochure, human resources). IC: work absenteeism.	1. Notebook. 2. Questionnaire (Quality of life and asthma severity). 3. GP and insurance company.	12-month
(Bunting et al. 2006), Asheville, North Carolina USA	Quasi-experimental, longitudinal pre-post study	I = One or two sessions of 60-90 min duration involving one-to-one educational intervention (led by asthma educator) and MTM of 30 min at every third month of consultation (led by a care manager, a pharmacist chose by the patient) C = three years before enrolment	Payer	DMC: physician visits, ED visits, hospitalizations, medications (and its copayment waiver), cognitive MTM services, educator IC: lost work hours due to	1. Questionnaire (e.g. Likert-scale AOMS questions) 2. Spirometry testing 3. Medical records, insurance and prescription claims and employer	5 years

				absenteeism and presenteeism.	records. 4. Self-report data.	
(Gordois et al. 2007), Australia	Model-based economic evaluation	I = Pharmacy asthma care program (PACP) led by community pharmacists to deliver education on asthma, medical therapy, risk factor, inhaler technique, goal setting and patient review aspects. The annual review scenario involved a pharmacist review visits every year while no annual review assumed that initial asthma improvements were maintained without subsequent pharmacist reviews. C = usual care.	Provider	DC: Hospitalizations, GP visits, ED visits, medication, pharmacist's time, program costs (spirometers, consumables, software, promotional materials, and training resources), training of pharmacists.	Questionnaire (healthcare utilization, AQL instrument, service delivery time)	6-months (modelled to 5-year)
(Pinnock et al. 2007), UK	Phase IV controlled pre and post-implementation study	I = telephone option consisting of structured recall group and face-to-face or telephone review. C = face-to-face only consisting of structured recall and face-to-face review or usual care.	Provider (NS)	Type of costs not stated	Questionnaires: mini-AQLQ, mini-Asthma Quality-of-Life Questionnaire) (physical/emotional impact of asthma); Asthma Control Questionnaire (clinical goal of asthma management); mPEI, Modified Patient Enablement Instrument (enablement); Asthma Bother Profile (patient confidence for self-management)	12-months
(Van Der Meer et al. 2011),	RCT	I = Internet-based self-management involving monitoring of asthma control and lung function every week, seeking treatment advice, a	Societal & provider	DC: Contacts with healthcare professionals, ED visits, hospitalization	1. Questionnaire (costs, EQ-5D and visual	12-month

Netherlands		tailored action plan, e-learning, group learning, and remote web communication led by a specially trained nurse. C = usual care.		s, medications, program-related (materials, personnel and patient travel costs). IC: productivity loss	analog score). 2. Pharmacy records.	
(Woods et al. 2012), USA	Comparative, observational study	I = A community asthma initiative model included case management and coordination of care, supervised home visits and referral to an integrated pest management exterminator (when indicated). C = usual care.	Provider (NS)	DC: hospitalizations, ED visits	1. Periodic interview related to an asthma action plan (asthma severity score). 2. Medical records. 3. Hospital data.	12-month
(Rodriguez-Martinez et al. 2016), Colombia	Model-based economic evaluation (Markov)	I = once daily (OD) dosing of inhaled corticosteroids (ICS) C = twice daily (BD) dosing of ICS.	Healthcare provider	DC: Hospitalizations, GP consultations, Pediatrician consultations, ED visits, medication, spirometry tests, others (radiology procedures, laboratory tests, ambulance services)	From a systematic review of the literature published.	12-months
(Yong et al. 2018), Malaysia	Model-based economic evaluation	I = Respiratory medication therapy adherence clinic (RMTAC) led by pharmacists involving health, adherence and inhaler skill assessment, monitoring services, educations, identification of asthma risk factors and issues on the asthma treatment. C = respiratory clinic including asthma medical treatment, assessment and monitoring services.	Provider & Payer	Maintenance, acute and hospitalizations events	1. Medical records. 2. Questionnaires (asthma control test, modified Morisky adherence scale). 3. Published data.	Lifetime

Footnote:..

AOMS: Asthma Outcomes Monitoring System, AQoL: Assessment of Quality-of-Life Instrument, ATTP: A Structured Treatment and Teaching Program, C: Control Group; Comparator, EQ-5D: EuroQoL Classification System, FEV1: Forced Expiratory Volume In One Second, FVC: Forced Vital Capacity, GP: General Practitioner, h: hour, I: Intervention Group, MTM: Medication Therapy Management, NA: Not Available, NS: Not Stated, PEF: Peak Expiratory Flow, RCT: Randomized Controlled Trial.

^a perspective (NS): perspective was not stated in the article, based on the author judgement.

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Table 2 Quality of Economic Evaluation for Medication Adherence-Enhancing Interventions for Asthma.

Study	Well-defined questions	Description of competing alternatives	Effectiveness established	All relevant costs and effects identified	Appropriate measurement	Credible valuation	Appropriate Adjustment	Incremental costs and effects	Allowance made for uncertainty	Overall presentation and discussion
Clark et al. 1986	✗	✗	✓	✓	✓	✓	NA	✓	✗	✓
Deter (1986)	✗	✗	✗	✓	✓	✓	✗	✓	✗	✗
Windsor et al. 1990	✗	✗	✗	✗	✓	✓	NA	✗	✗	✗
(Bolton et al. 1991)	✗	✗	✓	✓	✓	✗	NA	✗	✗	✗
(Soondergaard et al. 1992)	✗	✓	✓	✓	✓	✗	NA	✗	✗	✗
(Trautner et al. 1993)	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓
Drummond et al. 1994	✗	✓	✓	✓	✓	✓	NA	✗	✗	✓
(Taitel et al. 1995)	✗	✓	✗	✓	✓	✗	NA	✓	✗	✗
Neri et al. 1996	✓	✓	✓	✓	✓	✓	NA	✓	✓	✓
(Levenson et al. 1997)	✗	✗	✓	✓	✗	✓	✗	✗	✗	✗
(Kauppinen et al. 1999)	✗	✓	✓	✓	✗	✓	✓	✗	✗	✓
(Gallefoss et al. 2001)	✓	✗	✓	✓	✗	✓	NA	✓	✓	✓
Tschopp et al. 2005	✗	✗	✓	✓	✓	✗	NA	✓	✗	✗
Bunting et al. 2006	✓	✗	✓	✓	✓	✓	✗	✗	✗	✓
Gordois et al. 2007	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓
(Pinnock et al. 2007)	✗	✓	✓	✗	✓	✓	NA	✗	✓	✓
(Van Der Meer et al. 2011)	✗	✗	✓	✓	✓	✓	NA	✓	✗	✓
Woods et al. 2012	✓	✓	✗	✓	✓	✓	NA	✓	✓	✓
(Rodriguez-Martinez et al. 2016)	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓
Yong et al.	✗	✗	✓	✓	✓	✓	NA	✓	✗	✓

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Table 3 Cost-Effectiveness Outcomes of Medication Adherence-Enhancing Interventions for Asthma.

Study	Comparisons	Medication adherence and clinical outcomes	Cost	Cost and effectiveness outcomes
Clark et. al. 1986	Intervention vs control	Medication adherence: NA Zero baseline hospitalization regardless of baseline ER visits for both intervention and control group More than 5 baseline ER visits: Hospitalizations (Baseline to follow-up): -7.44 vs. 0.43, $p = 0.03$	\$1558	Total costs saving \$17481 equivalent to \$11.22 saved per dollar spent (Based on one or hospitalization in the baseline year) \$0.62 saved per dollar spent (regardless of baseline hospitalization)
Deter 1986	Intervention vs control	Medication adherence: NA Hospitalizations (days): -21.5 vs. 8.5 per patient, $p > 0.05$ GP visits (days): -6 vs. -5.5 Missed workdays: -30.4d vs. +17.7d, $p < 0.05$	Cost/patient: DM 1951	Benefit/patient: DM 11 026 Benefit-cost ratio: DM 5.6.
Windsor et.al. 1990	Intervention vs control	Medication adherence: +44% vs. +2%	Total cost/patient: \$ 32.03 vs. \$ 3.61	Average cost-effectiveness per improvement in adherence score: \$ 96.09 vs. \$ 243.68
Bolton et al. 1991	Intervention vs. control	Medication adherence: NA ER visits: 16 vs. 39, $p = 0.0005$ Physician visits: 46 vs. 58, $p = 0.16$ Number of Hospitalizations: 7 vs. 10, $p = 0.23$ Limited-activity days: 161 vs. 246, $p = 0.04$	\$2936 vs. \$4849, $p = 0.10$	\$628 saved/ \$85 spent (as a result of lower ER visits)
Soondergaard et al. 1992	Intervention vs control	Medication adherence (based on medication utilization): £275.9 vs. £198.8 QoL: +2%, $p = 0.0015$ Health status: +38.9%, $p < 0.05$ Missed workdays (days): 177 vs. 249	£ 16639 (£554.6/patient)	Saving due to the reduction of income loss: £4528 saved per loss of wages.

Trautner et.al. 1993	Pre (1 year before) vs post (3 years after)	Medication adherence: NA Hospitalizations/year (days): 10.1 vs. 4.9 (-5.2), $p = 0.023$ Physician visits/month: 3.3 vs. 1.0 visits (-2.3), $p < 0.0001$ Missed workdays/year: 41.5d vs. 23.1d (-18.4d), $p = 0.003$ Severe asthma attacks/year: 4.8 vs. 1.0 attacks (-3.8), $p < 0.0001$ Dose of MDI bronchodilator: 1.34 mg/day vs. 1.46 mg/day, $p = 0.03$	Direct cost: DM 2250 Indirect cost: DM 1000	Societal perspective Net cost-benefit: DM 12 850/ patient Benefit-cost ratio: DM 5/dollar spent on the program Payer perspective Net cost-benefit: 5900/patient Benefit-cost ratio: DM 2.7/dollar spent on the program
Drummond et al. 1994	Intervention vs control	Medication adherence: NA GP visits: 2.7 vs. 2.5 Number of hospitalizations: 0.15 vs. 0.11 Limited-activity day/month: 5.7d vs. 4.8d FEV1: 76% vs. 75%, PEF: similar in both groups (351 L/min) Bronchodilators prescribed: 10.1 vs. 10.6 Inhaled steroids prescribed: 6.4 vs. 6.5 Oral steroids used: similar in both groups (1.6) Nights waking/week: similar in both groups (2.4) Anxiety, Self-efficacy scale (0-3, where 0 = no confidence, 3 = full), living with asthma scale (1-4, where 1 = most restriction on activity, 4 = least), depression: similar in both groups (6.5, 2.0, 2.9, 3.6, respectively) % of well-controlled asthma: 68% vs. 60%, $p < 0.05$ Supported integrated care program: 75% vs. 62%, $p < 0.05$.	NA	Patient: £39.52 saved/patient GP: £2.41 saved/patient Hospital: £3.06 saved/patient.
Taitel et.al.	Pre (1 year before) vs	Hospitalizations: \$ 18 488 vs. \$ 1538,	Cost/patient:	Benefit/patient:

1995	post (1 year after)	$p = 0.017^*$ Physician visits: \$ 19 984 vs. 24 000, $p = 0.238$ ED visits: \$ 5199 vs. 3496, $p = 0.646$ Loss of earnings: \$ 11 593 vs. \$ 4 589, $p = 0.072^*$ Anti-asthmatics: \$ 25 555 vs. \$ 30 485, $p = 0.114$ Parenteral vaccinations: \$ 4051 vs. 1550, $p = 0.264$ Transport: \$ 4354 vs. \$ 3101, $p = 0.166$ Laboratory charges: \$ 1820 vs. \$ 2315, $p = 0.814$ Others: \$ 16 211 vs. \$ 9165, $p = 0.286$ <i>*statistically significant at $p < 0.10$</i>	\$208.33	\$502.19 (all) & \$475.29 (based on a decreased event of hospitalizations and loss of earnings only) Benefit-cost ratio: 2.28 (based on a decreased event of hospitalizations and loss of earnings only).
Neri et.al. 1996	Interventio n vs control	Medication adherence: NA Emergency clinical checkup (numbers): 0.72 vs. 2.18, $p < 0.05$ Equal days of hospitalizations: 0.12 days Missed workdays: 2.1d vs. 5.1d, $p > 0.05$ Asthma attacks (numbers): 4.72 vs. 7.91, $p > 0.05$	Cost/patient: \$713.20 vs \$669.80 Cost of medication used: \$528.6 vs. \$631.8, $p > 0.05$	Societal perspective Cost-benefit: \$1181.5 vs \$1028 Cost-benefit ratio: 1:2.66 vs. 1:2.53 Payer perspective Cost-benefit: \$ 636.3 vs \$ 632 Cost-benefit ratio: 1:1.89 vs. 1:1.94
Levens on et al. 1997	Pre vs post- interventio n	Eight cases in total No further hospitalizations: 3 people No hospitalizations for ≥ 4 years: 6 Lethal event and ICU admission: 0	Cost/year: \$22 999 (before intervention) vs. \$1107 (after intervention), $p < 0.02$	NA
Kauppi nen et. al. 1999	Interventio n vs control	Medication adherence: similar in both groups SGRQ (100 = maximum disability): 15.5*** vs. 16.8***, $p > 0.05$	£464 vs. £476	NA

		Sickness days: 104 vs. 273 15 D (1 = full HRQoL, 0 = death): 0.92** vs. 0.92**, $p > 0.05$ 3-year, FEV1: 89.2%* vs. 83.9%, $p < 0.05$ FEV%: 93.8%*** vs. 92.0%**, $p > 0.05$ PEF: 91.6%*** vs. 87.2%**, $p < 0.05$ FVC: 94.8% vs. 91.4%, $p > 0.05$ PD15: 1.57*** vs. 1.26*** dose steps statistically significant from baseline to 3-year, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$		
Gallefo ss et.al 2001	Intervention vs control	Medication adherence: NA No impact on daily life: 88% vs. 62%, $p = 0.02$, NNE: 3.9 SGRQ (100 units = maximum disability): 20.2 vs. 36.5, $p < 0.001$ FEV1: 3.4% vs. -2.7%, $p < 0.05$ Better year: 81% vs. 43%, $p = 0.002$, NNE: 2.6 Symptom free days: 81% vs. 36%, $p = 0.001$, NNE: 2.2 Symptom free nights: 94% vs. 60%, $p = 0.001$, NNE: 2.9	NOK 10 500 vs. NOK 16 000, $p = 0.510$	NOK -3400/10 units decrease in SGRQ NOK -4500/5% increase in FEV1 NOK -12200/ patient symptom free days.
Tschopp et. al. 2005	Baseline vs 12 months after the intervention	Medication adherence: NA Hospitalizations: 35% vs. 8% (-27%), $p = 0.001$ ED visits: 88% vs. 53% (-35%), $p = 0.001$ Missed workdays: 39% vs. 14% (-25%), $p = 0.002$ Night symptoms ($p < 0.001$) and whole asthma-associated quality of life ($p < 0.01$) were improved significantly.	€ 117 699	Net cost reduction: € 230 810 Cost-benefit ratio: 1:1.96
Bunting et al. 2006	3 years before vs. 5 years after enrolment	Medication adherence: NA ED visits per year: 9.9% vs. 1.3% (-8.6%) Hospitalizations per year: 4.0% vs. 1.9% (-2.1%)	Health care cost: \$341 vs. \$206 Medication cost: \$231 vs. \$1379	\$1955 saved/patient/year

		Missed workdays per year (days): 2.5 vs. 0.5 (-2) Unproductive hours per year: 66.5 vs. 16.8 (-49.7) 5-years severity score: 3.3 vs. 2.2 (-1.1), $p < 0.0008$; FEV1: 65% vs. 90% (+25%), $p = 0.028$ 4-week, awakening nights: 2.7 vs. 1.9 times, $p = 0.01$; Asthma episode: 2.8 vs. 2.1 times, $p = 0.0011$; Frequency of symptoms (numbers), all $p < 0.003$: - SOB: 2.6 vs. 1.9; - Wheezing: 2.5 vs. 1.7; - Chest pain: 2.1 vs. 1.6; - Coughing: 2.9 vs. 2.2; - due to allergy: 3.0 vs. 2.4; - due to exercise: 2.8 vs. 2.0 Attendance of asthma action plans: 63% vs. 99% (+36%)		
Gordois et.al 2007	Intervention vs control	Medication adherence: NA GP visits: 309 vs. 278 visits Hospitalizations: 6 vs. 11 ED visits: 7 vs. 9 visits, $p = \text{NS}$. QALY (at 5 years) = 3.443 vs. 3.312 (+0.131) AQoL: 0.763 vs. 0.761 (-0.04 = worse than death, 1 = perfect health). 6-month, Salbutamol mean daily dose: 238 mcg vs. 222 mcg.	At 6-months: \$A675 vs. \$A172 At 5-years: \$A2136 vs. \$A1514 (annual review), \$A1890 vs. \$A1514 (no annual review)	At 6-months (mainly from set up costs): \$A64 870/QALY gained At 5-years: - Annual review: \$A4753/QALY gained - No annual review: \$A2869/QALY gained
Pinnock et.al. 2007		Medication adherence: NA Mini-AQLQ: 5.29 vs. 5.31 vs. 5.27, $p > 0.05$ ACQ (1 = good control, 6 = responsive to change):	Cost per patient reviewed: SD£5.53 (telephone) vs. SD£5.68 (face to face) vs. SD£6.45 (usual care),	£ 2.58 - £ 2.83 saved per patient reviewed.

		1.2 vs. 1.33 vs. 1.24, $p > 0.05$ mPEI (0 = low enablement, 12 = high): 7.29(t) vs. 6.43 (f), $p = 0.03^*$, vs. 6.9 (UC), $p = 0.23^{**}$ ABPm (0 = no confidence, 5 = full): 3.99 (t) vs. 3.78 (f), $p = 0.007^*$ vs. 3.9 (UC), $p = 0.14^{**}$ Attendance of asthma review: 397 vs. 352 vs. 282 people *telephone vs. face-to-face **face-to-face vs. usual care	$p < 0.001$	
Van Der Meer et. al. 2011	Intervention vs control	Medication adherence: NA Workplace absenteeism (hours): 114 vs. 98 EuroQol tools (EQ-5D)* : 0.92 vs. 0.90 (+0.024), $p = 0.25$ Visual analog score*: 0.88 vs. 0.88 (+0.007), $p = 0.57$ *The QALYs value for usual care group vs internet group (difference of QALY based on non-parametric bootstrap estimation),	Health care perspective \$ 2555 vs. \$ 2518, $p = 0.94$ Societal perspective \$ 6,289 vs. \$ 5,647, $p = 0.63$	Health care perspective ICER (per QALY gained): \$ 1500 Societal perspective ICER (per QALY gained): \$ 26 700.
Woods et. al. 2012	Baseline vs 2-years follow-up	Medication adherence: NA Significant reduction ($p < 0.0001$) in ED visits (-68%), hospitalizations (-84.8%), limited-activity days (-42.6%), missed school days (-41%), missed workdays from caregiver (-49.7%).	Cost per child: \$ 2529	At 2-years' follow-up: \$3,827/child saved Return on investment: 1.46
Rodriguez-Martinez et al. 2016	Intervention vs control	Higher adherence rate for OD than BD dosing (+18.3%). QALY: 0.8284 vs. 0.8084 (US\$ +0.0199)	US\$1529.3 vs. US\$1709.1	Average CER (per QALY gained): US\$1846.2 vs. US\$2114.1
Yong et. al. 2018	Intervention vs control.	Medication adherence: NA Number of Hospitalizations: 16.6 vs. 22.22. QALY: 9.61 vs. 9.43 Life years: 27.88 vs. 27.76	\$ 16 370.35 vs. \$ 18 780.21	RMTAC plus usual care was a dominant alternative compared to usual care alone.

Footnote: \$: United States Dollar, \$A: Australian Dollar, £: Pound Sterling, €: Euro, ABPm: Asthma Bother Profile, ACQ: Asthma Control Questionnaire, AQoL: Assessment of Quality-of-Life Instrument, CER: Cost-effectiveness ratio, DM: Deutsche Mark; EQ-5D: EuroQoL Classification System, ED: Emergency

Department, ER: MDI: Metered-Dose Inhaler, mini-AQLQ: mini-Asthma Quality-of-Life Questionnaire, mPEI: modified Patient Enablement Instrument, NA: Not Available, NNE: Number Needed to Educate, NOK: Norwegian Krone, NS: Not Significant, OD: Once-Daily, PD15: Dose of Histamine Needed to Provoke 15% Drop in FEV1 (Expressed in Dose Step), QALY: Quality-Adjusted Life-Year, RMTAC: Respiratory Medication Adherence Clinic, SGRQ: St. George's Respiratory Questionnaire,.

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