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REVIEWS

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Evaluating adherence and inhaler monitoring among adolescent asthmatic patients: a systematic review and meta-analysis of interventions

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Abstract

Introduction Inadequate care for asthma has been linked to higher hospital admissions and morbidity. Researchers have developed several strategies to improve treatment adherence in this specific group. We aimed to investigate the impact of several interventions on the adherence of asthmatic patients to controller inhalers.

Data sources We searched four databases (the Cochrane Library, PubMed, Embase, and Web of Science) for studies published between 1998 and 2022.

Study selections We considered studies that assessed adherence as the main finding of an intervention for asthma patients. Data were extracted and analyzed.

Results The analysis included a total of 40 studies. A diverse range of interventions was identified, including educational sessions on asthma, reminders via text messages, and technology-based feedback systems. The overall efficacy of interventions compared to the control group resulted in a small effect size, but it was statistically significant, with an estimated SMD of 0.44 (95% CI 0.24 to 0.63, $P < 0.001$). Electronic monitoring achieved a significantly higher effect size [SMD 0.8, 95% CI 0.46 to 1.14, $P < 0.001$) compared to pharmacy refill and self-report methods [(SMD 0.09, 95% CI −0.18–0.37, $P = 0.51$), and (SMD 0.25, 95% CI −0.03, 0.54, $P = 0.08$), respectively].

Conclusions Adherence promotion interventions have been proven effective among patients with asthma. Electronic monitoring modalities have demonstrated superiority and effectiveness in improving patient adherence to asthma inhalers. Additional longitudinal research studies can be conducted to evaluate the cost-effectiveness and identify a more accurate measure of intervention efficiency for prolonged follow-up time.

Keywords Asthma, Inhaled treatment, Adherence, Monitoring, Interventions

Background

Asthma is an inflammatory airway disease that can cause major health problems, morbidity, and disability. Around 18% of people worldwide have asthma. The symptoms of asthma are dyspnea, coughing, tightness, and wheezing [1]. The main objectives of asthma therapeutic strategies are to control symptoms, minimize attacks and exacerbations, keep normal daily activities, reduce medication side effects, and prevent disease progression later in life [2]. Asthma control is highly dependent on adherence

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to asthma medications, which is defined as the extent to which patients adhere to the recommended instructions provided by healthcare professionals [3]. Currently, asthma treatment encompasses both acute exacerbation (short-term relief medications) and preventive therapy (long-term control medications). The primary preventive medications include individual or combination use of inhaled corticosteroids (ICs) and β2-agonist (long-acting) [3, 4]. Improving asthmatic patients' commitment to long-term preventive medication has resulted in better asthma control and lower morbidity [5–7]. However, generally, average adherence rates remain suboptimal. Sub-optimal adherence has been associated with deterioration in lung function, recurrent exacerbations, emergency room admissions, oral steroids overuse, reduced productivity, and lower quality of life [8].

Asthma exacerbations and poor control have significantly increased the burden on the healthcare system and associated costs. Furthermore, they are considered significant factors contributing to mortality among asthma patients [9]. The optimal adherence contributing to adequate asthma control is estimated to be higher than 80% [10]. However, concerning children, the average adherence falls below the effective level, at approximately 50%, and among adults, it is even lower, at less than 30% [7]. Additionally, factors such as high costs, difficulty in remembering multiple-dose regimens, and unpleasant taste of medication may also contribute to poor adherence to inhaled medications [11]. These low adherence rates highlight the crucial need for effective strategies to enhance adherence and reduce disease burden [12, 13]. The decline in asthma adherence rates may be due to confusion and misinformation about treatment regimens. Numerous studies have evaluated various interventions aimed at improving the outcomes of asthmatic patients [13, 14]. These investigated interventions included inhaler reminders, parental education, electronic monitoring, phone calls, and text messages, transitioning to once-daily instead of twice-daily controlled medications, and various in-person approaches. The adherence outcomes included measures of self-reported adherence scales or pharmacist refills of asthma medications. Although studies reported promising outcomes in improving adherence, it is still unclear which modality is more effective in promoting medication adherence. Therefore, the primary objectives of this systematic review are as follows:

1) To evaluate and compare the influence of various interventions on patient's adherence to asthma controller inhalers,
2) To categorize these interventions and explore the difference in effect sizes between interventions,
3) To assess the risk of bias (RoB) associated with the implemented interventions.

Methods

The primary protocol of this study followed the established guidelines outlined by the preferred reporting items for systematic reviews and meta-analyses (PRISMA).

Search strategy of literature sources

We conducted an electronic search through PubMed, Google Scholar, Cochrane Library, and Web of Science (WOS) from 1998 to August 2022. Furthermore, we manually searched for the references list in the included studies to identify additional publications. We formulated a comprehensive literature search strategy, incorporating MeSH term combinations such as asthma, intervention, adherence, compliance, and monitoring. We cited and gathered all the retrieved articles into an EndNote file to avoid duplication and exclusion. We eliminated articles that we deemed irrelevant based on their objective, title, abstract, or full-text content.

Eligibility criterion for inclusion and study selection

The retrieved publications were included based on the specified eligibility criteria as follows:

(1) Quantitatively assessing the effect of an interventional strategy on adherence to asthma controller medications (e.g., ICS); (2), being well-designed randomized controlled trials (RCTs), and non-RCTs;

3) Adequately describing mean adherence outcomes and standard deviation (SD) data, necessary for estimating the overall effect size of the interventions.

Studies not meeting these criteria were excluded. We excluded publications from the analysis if they did not meet the following specified criteria: (1) their primary objective was not the quantitative assessment of an intervention's impact on adherence, (2) they were case reports, review articles, abstracts, dissertation and editorials; and (3) they had missing data or insufficient information for estimating the overall effect size, such as studies with dichotomous outcomes.

Two authors independently completed a screening process, initially evaluating the titles and abstracts of the articles that were obtained to determine their eligibility. Subsequently, they examined the studies' full texts. The search strategy and the selection of studies are outlined in Fig. 1. Additionally, a thorough review was performed to identify and address any potential duplication. In cases where disagreements arose regarding study quality or eligibility for inclusion in the analysis, these were resolved through discussion and consensus.

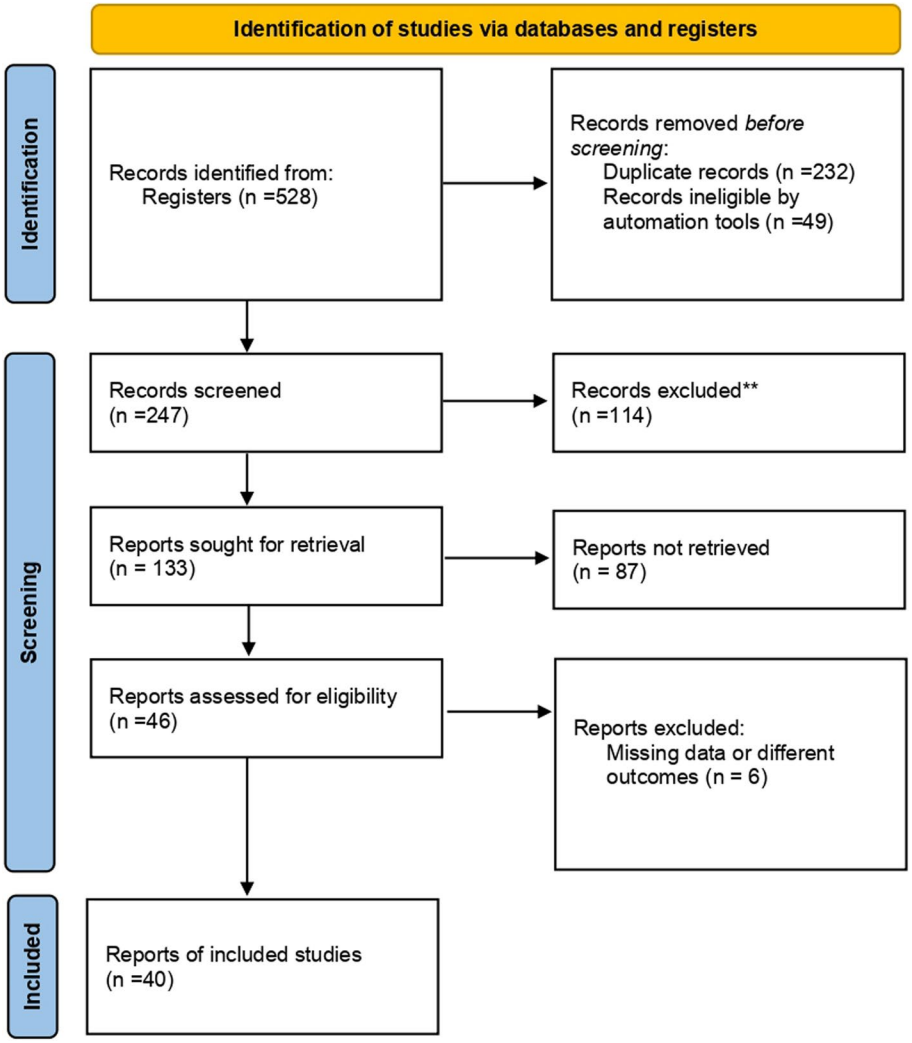

Fig. 1 Flow diagram of the studies search and inclusion for analysis

Extraction of data

A pre-designed structured form was utilized to extract and collect data, encompassing the following items: The first author's name, region, timeframe, year of publication, age range, study design, number of subjects, demographic information, details of the applied intervention protocol, and findings related to adherence. Data extraction was conducted directly from the selected studies, and there was no contact with authors to obtain missing data. The extracted outcomes included continuous variables related to adherence to asthma ICS medications. Various types of adherence measurements were considered, including pharmacy refill data, electronic monitoring, and self-reports. In our assessment of the intervention's impact on adherence magnitude, we excluded dichotomous variables of adherence that reported the percentage of participants with adherence higher than the threshold.

Quality and RoB assessment

Following the extraction of data, the investigators in this study assessed the quality of the chosen studies utilizing the validated Cochrane Collaboration tool [15]. Every study that met the criteria was given a bias rating, which was classified as low, medium, or high-risk bias, depending on the evaluation. This systematic approach ensured a thorough evaluation of the studies' quality and potential biases.

Bias risk assessment relied on factors such as the allocation concealment technique employed, blinding of the outcome assessment, the handling of missing data, the presence of attrition bias, and the potential for bias due to selective reporting. Any detected inconsistencies or

disagreements were resolved by re-investigating the original article.

Evidence quality assessment

We used the GRADE Pro software (http://www.gradepro.org/) to evaluate the overall quality of evidence for primary outcomes [16]. RoB, indirectness, inconsistency, and imprecision were among the factors that evaluated the evidence quality; these factors were categorized as "very low," "low," "moderate," or "high."

Statistical analysis

We generated pooled estimates of intervention effect sizes and graphs using the Reviewer Manager (RevMan) software, version 5.3 (The Cochrane Collaboration, Denmark). The summary statistic employed was the standardized mean difference (SMD) along with its confidence intervals (95% CIs). A positive SMD estimate indicates a favorable adherence outcome in the interventional arm compared to the control.

The random or fixed-effect model was employed for the analysis [17], and the chi-square test was utilized to evaluate for heterogeneity. The estimated I^2 index was used to quantify the extent of heterogeneity, ranging from 0 to 100% [14]. An I^2 index value of 0% denoted no heterogeneity, while estimates of 25%, 50%, and 75% were indicative of low, moderate, and high levels of heterogeneity, respectively.

When the I^2 exceeded 50%, we employed the random-effect model; conversely, if it was lower than 50%, we opted for the fixed-effect model [18]. Subgroup analysis was conducted for each type of adherence measurement, utilizing the stratification based on the original calculation per each outcome category. A P value below 0.05 among subgroups indicated statistical significance for discrepancies. For quantitative bias estimation, we utilized Egger's regression test, considering bias to be present if $P \leq 0.05$). Additionally, we examined funnel plots, plotting the logarithm of odds ratios against the standard errors, in order to evaluate qualitative bias.

Results

Study and intervention characteristics

After eliminating duplicates, a comprehensive database search yielded 528 records. Following the application of the pre-specified inclusion and exclusion criteria, 46 studies were deemed eligible for full-text review and evaluation. Ultimately, 42 publications adequately met the specified criteria and were included in the final qualitative and quantitative analysis. Among the selected publications, two studies were excluded from the quantitative analysis due to the variability in the reported outcomes, such as dichotomous adherence measure, the absence of mean adherence values, and SD in the study groups. The selected studies collectively encompassed a total of 16,609 asthma patients [19–58].

Out of the 40 eligible studies for the analysis, a clear majority of them ($n=36$) were designed as randomized controlled trials (RCTs). The sample sizes of the analyzed trials ranged between 8 and 8517 asthmatic patients initially. The key characteristics of these research studies are presented in Table 1. The average age of the participating patients in most studies ranged from 6 to 12 years old.

Efficacy of interventions

The interventions in the selected studies encompassed educational sessions focused on asthma, text message reminders, and technology-based feedback. Asthma inhaler adherence was assessed using three primary methods: pharmacy refill ($n=15$), electronic monitoring ($n=19$), and self-report ($n=6$). The overall efficacy of interventions versus the control group resulted in a statistically significant but small effect size (SMD 0.44, 95% CI 0.24 to 0.63, $P<0.001$), accompanied by a high level of heterogeneity among the studies ($I^2=96\%$). This high heterogeneity suggests the presence of potential moderators affecting the impact of interventions, which we aimed to analyze (Fig. 2). To further explore these potential moderators, we performed a subgroup analysis based on the type of adherence measurement. A significant difference was observed amongst the subgroups (df: 2, $P=0.006$). In studies utilizing pharmacy refill data, the pooled effect size was non-significant with an SMD of 0.09 (95% CI −0.18 to 0.37, $P=0.51$). However, for studies involving self-report interventions, a significant difference with an SMD of 0.25 was observed (95% CI −0.03 to 0.54, $P=0.08$). However, it is important to note that we observed a high level of heterogeneity when utilizing pharmacy refill data ($I^2=97\%$) and moderate heterogeneity with self-report adherence measures ($I^2=73\%$). In contrast, electronic monitoring achieved a higher pooled effect size compared to pharmacy refill and self-report, and this difference was statistically significant, with an SMD of 0.80 (95% CI 0.46 to 1.14, $P<0.001$). Nonetheless, it is worth mentioning that the heterogeneity level remained significantly high for studies utilizing electronic monitoring ($I^2=91\%$). We conducted a sensitivity analysis by excluding the study of William (2010), in which the intervention involved physicians only instead of patients. As a result, the overall effect size increased to SMD = 0.46 (95% CI 0.31 to 0.61), and the level of heterogeneity (I^2) decreased to 90%.

Table 1 Included studies' main characteristics

Study ID	Study design	No. of patients	Intervention description	Outcomes
Van ES et al. 2001 [19]	RCT	86	Sessions with asthma nurses individually or in groups for social support and motivation	Non-significant difference between groups ($P > 0.05$)
Chan et al. 2003 [20]	RCT	10	Internet-based monitoring and asthma education	Non-significant comparable adherence rates in two study arms
Farber and Oliveria, 2004 [21]	RCT	50	Asthma education of basics and self-control plan	Interventional arm showed a significantly higher adherence rate ($P = 0.004$)
Hederos et al. 2005 [22]	RCT	60	Parent support group	Higher adherence in interventional arm, however, did not reach significance ($P = 0.06$)
Butz et al. 2006 [23]	RCT	181	Asthma education in the home including appropriate practice and symptom identification	Significantly lower prescription refill for the interventional arm, ($P = 0$ .02)
Charles et al. 2007 [24]	RCT	110	Audio-visual reminders with EM	Interventional arm showed a significantly higher adherence rate of 18%
Jan et al. 2007 [25]	RCT	153	Internet-based monitoring and educational system for asthma control	Interventional arm showed significantly higher adherence ($P < 0.05$)
Otsuki et al. 2009 [26]	RCT	167	Asthma education in-home visits and feedback for adherence	Non-significant difference between groups ($P > 0.05$)
Bender et al. 2010 [27]	RCT	50	Interactive phone calls and EM	Interventional arm showed significantly higher adherence ($P = 0.003$)
Burgess et al. 2010 [28]	RCT	26	Smart inhaler devices send feedback to parents and physicians	Interventional arm showed significantly higher adherence ($P < 0.001$)
Butz et al. 2010 [29]	RCT	156	Asthma management skill education	Non-significant adherence in the interventional arm compared to the controls ($P = 0.07$)
Chen et al. 2010 [30]	RCT	60	Support group and action plan tailored for patients	Interventional arm showed a significantly higher adherence rate ($P = 0.008$)
Standbygaard et al. 2010 [31]	RCT	26	Text messages	Interventional arm showed a significantly higher adherence rate ($P = 0.019$)
Williams et al. 2010 [32]	RCT	2,968	Patient adherence monitoring and feedback	Interventional arm showed non-significant enhancement in adherence rates ($P > 0.05$)
Ducharme et al. 2011 [33]	Single blinded RCT	309	Written action plan for asthma during acute visits	Interventional arm showed significant enhancement in adherence after 15 days of the study timeframe ($P > 0.05$)
Petrie et al. 2011 [34]	RCT	216	Text messages	Significant increase in adherence for the interventional arm vs. control arm (43.2% vs. 57.8%, $P = 0.003$, respectively)
Rickert et al. 2011 [35]	Pre and post intervention	37	Home visits for motivational interviews based on asthma self-control program	Non-significant difference within or between study groups in adherence ($P > 0.05$) on the basis of self-reports
Volimer et al. 2011 [36]	RCT	8,517	Interactive voice calls	Significant increase in adherence for the interventional arm ($P = 0.02$)
Feldman et al. 2012 [37]	Non-randomized controlled trial	85	Comparison of children predicted PEF and actual values	Interventional arm showed significantly higher adherence ($P < 0.01$)
Gustafson et al. 2012 [38]	RCT	259	Phone calls from healthcare practitioners integrated eHealth program	Non-significant difference within or between study groups in adherence ($P > 0.05$)
Duncan et al. 2013 [39]	RCT	29	Youth and parent teamwork for targeted asthma control	Non-significant difference between study groups in adherence ($P > 0.05$)
Mosnaim et al. 2013 [40]	RCT	46	Support group for asthma and recorded messages for motivation	Non-significant difference between study groups in adherence ($P > 0.05$)
Rohan et al. 2013 [41]	RCT	11	Electronic problem-solving and feedback	Interventional arm showed significantly higher adherence

Table 1 (continued)

Study ID	Study design	No. of patients	Intervention description	Outcomes
Butz et al. 2014 [42]	RCT	274	Home visits for asthma education with feedback letter to clinician	Non-significant difference between study groups in adherence ($P=0.66$)
Naar-king et al. 2014 [43]	RCT	167	Therapy-healthcare intervention	Interventional arm showed significantly higher adherence ($P=0.03$)
Abramson et al. 2015 [44]	RCT	72	4 visits in 1 year with reports and medical review	Higher adherence in interventional arm, however did not reach significance ($P=0.14$)
Bender et al. 2015 [45]	RCT	1187	Phone call for inhaler refill	Interventional arm showed significantly higher adherence ($P<0.001$)
Chan et al. 2015 [46]	RCT	220	Audio-visual reminders	Interventional arm adherence (84%) compared to 30% in the control arm
Garbutt et al. 2015 [47]	Pre and post intervention	8	Skill training and education for targeted asthma management	Baseline adherence (72%) increased significantly to 100%, ($P=0.013$)
Koufopolous et al. 2015 [48]	RCT	103	Internet-based support groups and social media	Non-significant difference between study groups ($P=0.92$)
Wiecha et al. 2015 [49]	RCT	30	Educational website for adherence promotion and teamwork with family members	Improved interventional arm adherence vs. controls, however, didn't reach significance ($P=0.460$)
Horner et al. 2016 [50]	RCT	173	Day camp for asthma followed by plan for patients	Non-significant difference between study groups ($P>0.05$)
Johnson et al. 2016 [51]	RCT	65	Text messages at pre-determined medication administration times	Significant increase in adherence in the interventional arm vs. controls ($P=0.016$)
Vasbinder et al. 2016 [52]	RCT	209	Text messages as reminders for medication	Interventional arm showed significantly higher adherence vs. control arm by 12%
Britto et al. 2017 [53]	Cross-over study	22	Text messages for asthma management reminders for 3 months	Interventional arm showed significantly higher adherence vs. the control arm ($P<0.01$)
Morton et al. 2017 [54]	RCT	77	Electronic monitoring with daily reminders	Interventional arm showed significantly higher adherence vs. the control arm ($P<0.001$)
Harrington et al. 2018 [55]	RCT	46	Morning inhaler use guided by school nurse	Non-significant difference between study arms ($P>0.05$)
Kenyon et al. 2019 [56]	RCT	32	Text messages as a reminder for inhaler use	Non-significant difference between study arms ($P>0.05$)
Kosse et al. 2019 [57]	RCT	234	Smartphone application for education, reminder, and pharmacist chat	Non-significant difference between study arms ($P>0.05$)
Kompagioti et al. 2020 [58]	RCT	78	Educational program for asthma care	Interventional arm showed significantly higher adherence vs. control arm ($P<0.001$)

RCT randomized controlled trials, *PEF* peak expiratory flow, *EM* electronic monitoring

Risk of *bias* and quality assessment

The risk of bias was assessed for all eligible trials using the Cochrane Collaboration tool. In at least one domain, we judged seven studies as having a high risk of bias (RoB). The primary reason for designating these trials as high risk was inadequate blinding procedures, randomization methods, and concealment descriptions. Two studies provided information about the blinding of investigators and participants. Using the GRADE criterion, the outcomes' overall quality varied from extremely low to high (Supplementary Table S1). Additionally, the results of the Egger regression analysis did not indicate the presence of publication bias ($P=0.62$). This finding was consistent with the observation of symmetrical funnel plots, further supporting the absence of publication bias in the analyzed data.

Discussion

There is a bidirectional and interdependent association between adherence to asthma inhalers and the disease severity. Clinicians may overestimate the degree of asthma severity if they do not assess adherence precisely. In addition, inadequate adherence to treatment may lead to the progression of asthma to a severe state if not addressed [59]. The principal objective of this meta-analysis was to evaluate the effectiveness of the applied interventions in improving adherence to asthma inhalers among pediatric and adolescent populations. Upon

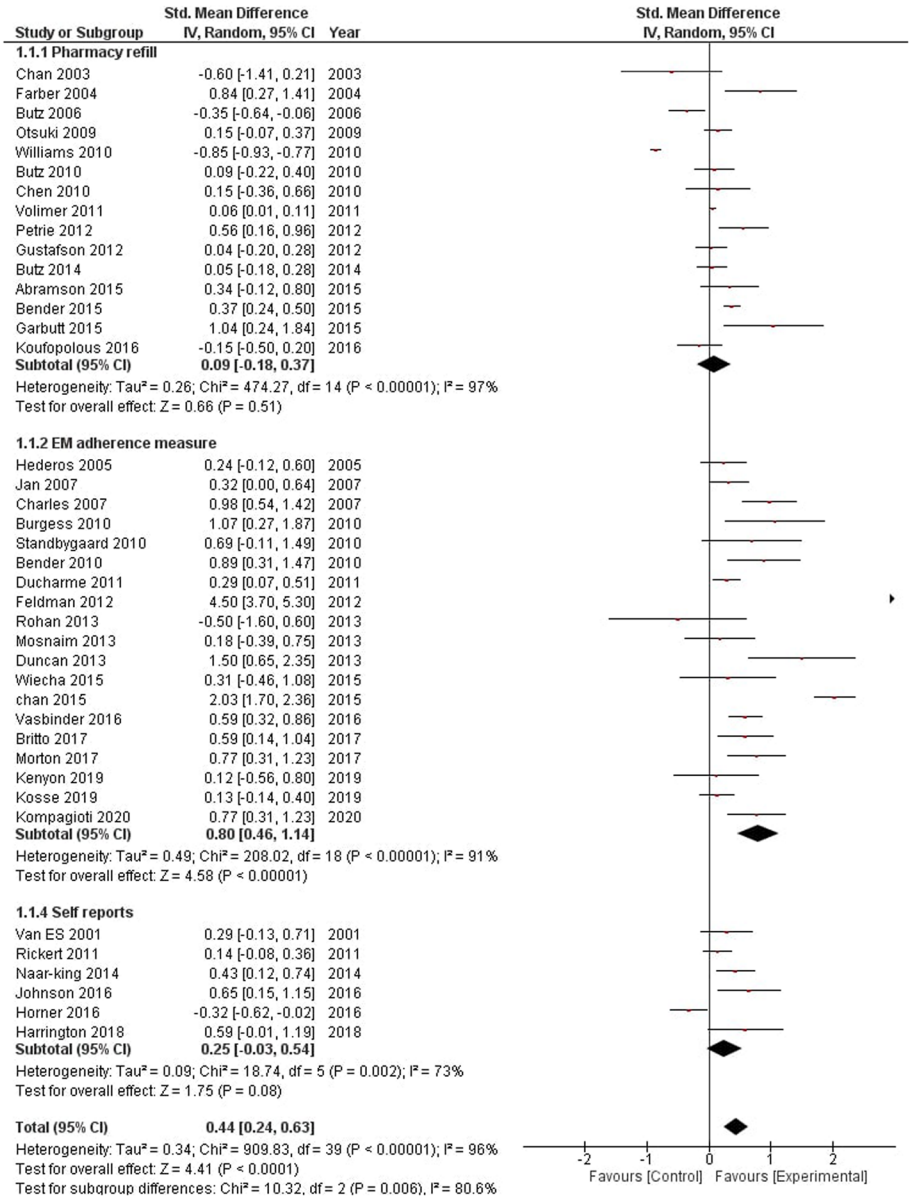

Fig. 2 Forest plot of post-interventional pooled effect sizes for adherence compared to the control

aggregating the post-intervention effect sizes from the 40 studies included, the analysis indicated a statistically significant, albeit relatively small, enhancement in inhaler adherence as a result of the implemented interventions.

Electronic monitoring is considered the gold standard approach for the evaluation of adherence in asthma management due to its ability to provide objective and detailed data. Our study results showed that the applied approach in adherence measurement impacted the observed effect of the intervention. For instance, the utilization of electronic monitoring as the method for measuring adherence showed an overall effect size of [SMD 0.80, 95% CI 0.46, 1.14, $P<0.001$], which was approximately twofold the pooled overall effect size obtained from the different adherence measures categories. This underscores the substantial impact of the chosen measurement approach on the observed outcomes.

In other words, our study findings revealed that individuals who used electronic monitoring devices to track adherence were more likely to adhere to their inhaler regimens when compared to the control group. The effect size observed when self-report adherence assessment

was employed showed a minor and non-statistically significant effect. This outcome could be attributed to the variability in the self-report measures utilized across the included studies, which encompassed a range from phone calls to single-item questionnaires to validated adherence medication questionnaires [60]. Unlike the self-report and electronic monitoring adherence measures, the pooled effect size for pharmacy refills was the lowest and appeared to favor the control group rather than the intervention group. One potential explanation for this observation could be the inclusion of a physician-based intervention in the analysis, which may have influenced the results in this specific adherence measurement category. The exclusion of this study from the sensitivity analysis resulted in a notable enhancement of the overall effect size within the pharmacy refill sub-category. This increase was statistically significant, favoring the intervention group (SMD 0.14, 95% CI 0.01, 0.28, $P=0.04$).

The findings of this meta-analysis are consistent with the findings of previous systematic reviews and meta-analyses, which suggested the effective role of different interventions in improving adherence to asthma inhalers among individuals with asthma [61, 62]. Among the studies included in the analysis, 15% (6/40) examined adherence over an extended follow-up period of up to 5 years. Interestingly, the initially significant overall effect size of the interventions diminished over time during follow-up, indicating that the improvements in inhaler adherence achieved through the interventions did not translate into long-term gains [63].

The studies included in this analysis investigated the effects of several interventions designed to enhance adherence. These interventions encompassed a range of strategies, such as home and audio-taped visits, tailored treatment regimens, the use of electronic monitoring devices, educational interventions, and the use of text messages to remind individuals to adhere to their prescribed medication doses [64]. Given the limited aggregate sample size, we propose that future investigations should employ a greater number of large-scale RCTs. These trials should employ intention-to-treat analyses to preserve the prognostic balance derived from an initial random treatment allocation and implement corrective measures for missing data to avoid bias and distortion of outcomes. The exorbitant price of electronic adherence monitoring devices may pose a constraint on affordability for youngsters from low socioeconomic backgrounds. Further research is necessary to conduct a cost-effective evaluation of electronic technologies used for adherence monitoring. Moreover, research efforts are imperative to investigate the optimal monitoring timeframe and assess the enduring impact of electronic adherence monitoring devices [63].

Limitations

When interpreting the outcomes of our meta-analysis, it is essential to acknowledge several limitations. The overall quality varied among the included studies, and some individual studies had limitations in the methodology. These limitations encompassed issues such as a high dropout rate among participants, incomplete adherence data, insufficient randomization procedures, and an absence of blinding for outcome assessors. These factors can influence the robustness and generalizability of the results.

Most interventional strategies investigated displayed a significant RoB, along with an indeterminate risk of bias in various domains. It is widely recognized that participant awareness of their assigned interventions presents a substantial bias risk and may influence behavioral outcomes, especially in terms of adherence. However, it is crucial to recognize that achieving participant blinding may not be applicable in all the applied behavioral interventions. Further limitations are tied to the criteria used for exclusions and the generalizability of the findings.

Conclusions

Our review aims to summarize the most reliable evidence obtained from a selection of trials employing a rigorous, transparent, systematic, and meta-analytical methodology. This systematic analysis highlights the substantial contribution of electronic devices for monitoring adherence in asthma management, particularly in improving adherence to inhaler usage. To effectively address medication behavior, especially in terms of adherence and the involvement of medical professionals and caregivers in the management of asthmatic patients, it is advisable to promote the use of electronic devices for adherence monitoring that can track the actuation and inhalation of medication to ensure its proper intake.

Abbreviations

ICs	Inhaled corticosteroids
RCTs	Randomized controlled trials
RoB	Risk of bias
WoS	Web of science

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43168-024-00336-4.

Supplementary Material 1: Supplementary Table S1. Summary of GRADE assessment for the main comparisons.

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Authors' contributions
Concept, planning of study design, and writing: all authors. Data collection and analysis: all authors.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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