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Title: Prevalence and predictors of adherence to controller therapy in adult patients with severe/difficult to treat asthma – a systematic review and meta-analysis

Authors

Maged Hassan, Sarah E Davies, Samuel P Trethewey, Adel H Mansur

Birmingham Regional Severe Asthma Service and Centre for Respiratory Medicine,
University Hospitals Birmingham, Birmingham, UK

Corresponding author

Maged Hassan

MIDRU Building, Heartlands Hospital, Bordesely Green East, Birmingham, B9 5SS,
United Kingdom

magedhmf@gmail.com

+447960357965

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Abstract

Objective: Non-adherence to prescribed treatment is an important cause for poor asthma control. This systematic review aimed to determine the prevalence and determinants of non-adherence in adult patients with severe asthma.

Data sources: Embase and Pubmed were searched for publications in English studying adult patients and containing the keywords 'severe asthma', 'adherence' and 'compliance'.

Study selection: Only studies utilizing objective methods for monitoring adherence and clear definition of the level of asthma severity were included. Predominantly pediatric studies or studies of less severe asthma were excluded.

Results: The search returned 488 reports, of which 14 reports (of 2297 patients) were included. The weighted mean age of patients was 44 years and 64% were females. In studies using a cut-off of acquiring 50% or less of the medication an overall rate of non-adherence was 42.9%. For studies reporting non-adherence of a continuous scale, the weighted mean non-adherence was 42.9% (95% CI 28.2 – 49.5). Meta-analysis of adherence predictors showed that male sex was associated with adherence with an odds ratio of 2.25 and higher asthma quality of life questionnaire (AQLQ) scores with a mean difference 0.47 points in adherent patients. Other predictors were reported to have significant association with adherence (e.g. older age, more knowledge about asthma, simpler medication schedules) but these were from single studies.

Conclusion: non-adherence to therapy is a common problem in the management of patients with severe asthma. More robust and objective methods are needed to homogenize and improve the accuracy of assessment methods. More studies are needed from developing countries.

Systematic review registration number: CRD42018114669

Keywords: reviews, management/control, pharmacotherapy, quality of life

Introduction

Severe and difficult to treat asthma are terms used interchangeably to describe a subset of patients with asthma who require high dose preventer therapy to control their asthma or remain uncontrolled .(1,2) It is estimated that 4-10% of patients with asthma suffer from severe disease^{3,4} However, most of the healthcare costs associated with asthma are dedicated for the management of severe asthma patients.(5)

Non-adherence to prescribed medication is an important causes of difficult to treat asthma, which is associated with poor clinical outcomes including increased risk of near-fatal asthma attacks.(5) Therefore, assessment of adherence is strongly recommended as an essential component of asthma patient review particularly in patients labelled as having severe disease.
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The prevalence of non-adherence to inhaled corticosteroids (ICS) in asthma has been estimated to vary between 30 to 50%,² but these rates are usually reported by studies of general asthma cohorts and it is not clear whether these figures are applicable to patients with more severe disease. Moreover, estimates of non-adherence vary widely between studies, at least partially, due to differences in methods of adherence assessment and the cut-offs used to denote sub-optimal adherence. It has been found that subjective methods of adherence assessment such as questionnaires and scales are not reliable and tend to underestimate the problem, prompting the need to use objective methods to assess adherence.(5-7)

Identifying risk factors for non-adherence is key to addressing this issue. A previous systematic review of determinants of adherence to inhalers in adults with asthma found that stronger belief in the necessity of taking inhalers and possibly older age were associated with adherence.(8) However, this review addressed asthmatic patients of all degrees of severity and included studies that utilized both objective and subjective methods of adherence monitoring. We conducted this systematic review to examine the available literature for the prevalence of non-adherence to controller therapy specifically among adult patients with severe asthma in studies using objective methods of assessment. We also aimed to study the different characteristics/predictors associated with non-adherence in this patient population.

Methods

Protocol and registration

This study was carried out according to the Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines(9) and a protocol was prepared prior to carrying out the study and registered at the systematic reviews database, Prospero (CRD42018114669).

Search strategy and screening

Both Embase and Pubmed databases were searched using the National Institute for Health and Care Excellence (NICE) HDAS online portal (<https://hdas.nice.org.uk/>) on 31st October 2018 using the following search strategy (for Embase): (asthma AND (adherence OR non-adherence OR compliance OR concordance OR nonadherence OR noncompliance)).ti [Languages English] [Human age groups Adult 18 to 64 years OR Aged 65+ years]. The reference lists of the retrieved papers were also searched for eligible studies.

Two reviewers (MH and ST) independently screened the titles with or without abstracts of the resulting publications for inclusion. Any disagreement in the inclusion decision was settled with discussion and consensus. Screening was carried out using the Rayyan web and mobile applications.(10)

Publications were included if the population under study were adults (at least 70% of the studied cohort) with severe or difficult-to-treat asthma with clear definition of the reason of such a classification/label. Studies were only included if adherence to controller (inhaled or oral) therapy was assessed using objective tools. Conference abstracts, reviews, publications where the population of study were not of interest (pediatric, non-severe asthma, non-asthma) and where subjective methods were used to assess adherence were excluded.

Study selection

Two reviewers (MH and SD) independently screened the retrieved full papers against the inclusion criteria. Any disagreement between the reviewers was settled with discussion until consensus was reached.

All study types (observational and interventional) were included as long as baseline prevalence and/or risk factors for non-adherence to controller therapy were reported. No formal assessment for risk of bias was performed but as a measure of quality control studies were excluded if the severity of asthma or method of adherence determination were not clearly reported or if the sample size was too small (less than 10 patients).

Data extraction

A spreadsheet was used for screening and data extraction from full papers. Two main areas were focused on during study review: a) prevalence and b) determinants of adherence.

Prevalence: the method of determination of adherence, the duration of monitoring, whether adherence to inhaled or oral corticosteroids therapy was studied, and the percentage of adherence were recorded. Whether a cut-off for optimal adherence was set and adherence determined based on this cut-off or whether adherence was determined as a continuous variable was also recorded.

Predictors: factors that were studied in relation to adherence were recorded. These were divided into: socio-demographic factors, asthma-related factors and comorbidities. The effect measures for each factor were extracted and information on whether this was based on univariate (unadjusted) or multivariate (adjusted) analysis was recorded together with the factors adjusted for.

Data were combined from different studies if similar methods of measurement were used.

Statistics

The statistics were carried out using the open-source software ‘Open meta analyst’ (<http://www.cebm.brown.edu/openmeta>).

A random-effects model was used all through in the included meta-analyses. Heterogeneity was assessed using the I^2 statistics, a value of more than 50% was considered to denote significant heterogeneity. Where pooling of data was not possible, a narrative synthesis of study effects was presented.

Prevalence: a) for studies reporting prevalence based on a cut-off, the raw numbers of adherent and non-adherent patients from each study were combined to provide the overall rate of adherence from all studies. b) for studies reporting adherence as a continuous number, the weighted mean of adherence (i.e. providing different weights to studies according to sample size) was reported as the summary measure.

Predictors: Where possible data from studies were combined together based on whether these were derived from univariate or multivariate tests. All effect measures reported in the meta-analyses were modelled to be predictive of adherence and essential transformation was performed for studies predicting non-adherence. Variables measured on continuous scale: data were combined from different studies and the mean difference was reported if a similar scale was used. The standardized mean difference was used if different scales of measurement were used.⁽¹¹⁾ Regarding variables measured on the categorical scales, for unadjusted comparisons, the raw numbers were combined and the pooled odds ratio (pOR) with 95% confidence intervals (CI) were reported. For adjusted comparisons, the ORs and 95% CI were combined and pOR was reported as previously recommended.⁽¹¹⁾

Results

The initial search returned 488 titles which were screened for inclusion and 61 full articles were retrieved and examined for eligibility. Forty seven reports were excluded for reasons detailed in the review flow diagram presented in Figure 1. Fourteen reports were included in the systematic review and the meta-analysis of non-adherence prevalence, and eight studies were included in the meta-analysis of non-adherence predictors.

Study and patient characteristics

Fourteen reports (6,12–24) describing 16 studies were included (the report by McNicholl et al(19) described three separate studies). These were nine prospective observational studies, four retrospective studies and three randomized controlled trials. Table 1 shows a summary of the included studies. The total number of patients reported was 2297 of which 1467 (63.9%) were females. Weighted mean age of studied patient was 45 years (95% CI 42.84 – 47.17).

Adherence prevalence

Four methods of adherence monitoring were reported. E-device monitoring was used in eight studies(6,12,13,15,17,18,22,23) (monitoring duration 2-6 months). Prescription ratio was used in four studies(16,19,20,24) (monitoring duration 6-12 months). Dose counting was the method in two studies(14,21) (monitoring duration 3-6 months). Fraction of inhaled nitric oxide (FeNO) suppression test in addition to an e-device were used for a period of 5-7 days in two studies.(12) All studies examined adherence to inhaled controllers (corticosteroids with or without β_2 agonists). In addition, two studies(16,20) reported data on adherence to oral corticosteroids.

Two methods of reporting prevalence were used. Prevalence was reported using a cut-off for optimal adherence (range 50 – 85%) and a percentage of those adherent based on the chosen cut-off were reported. This method was used in 10 studies reporting data on 1253 patients.(6,12,14,16,18-23) The overall adherence to inhaled medication using cut-off values was 57.1%. The values according to the monitoring method and the cut-off value used are reported in Table 2.

The second method reported adherence on a continuous scale giving each patient a percentage of adherence depending on the rate of medication collection and/or utilization and an average adherence rate was reported for the studied cohort. This method was used in eight studies reporting data on 1451 patients.(6,12,13,15,17,22-24) The weighted mean adherence to inhaled therapy according to this method was 61.15 (95% CI 50.5 – 71.8%).

Regarding adherence to oral corticosteroids (OCS), one study which used prescription records and a cut-off for sub-optimal adherence of 80% reported an adherence rate of 74%.(20) The other study used serum levels of corticosteroids in patients prescribed maintenance OCS and reported an adherence rate of 55%.(16)

Predictors of adherence

1. **Socio-demographic factors**

Sex: The effect of patient's sex on adherence was explored in six studies.(6,14,16,18,19,22) Two meta-analyses were carried out. The first was done on data from studies reporting unadjusted effects and included four studies.(6,14,16,19) This showed an association between male sex and adherence with an OR of 2.46 (95% CI 1.55 – 3.87, $p < 0.001$, I^2 statistic 0%) (Figure S1) . The other meta-analysis based on data from 2 studies(14,22) was on adjusted effects of male sex (factors adjusted for are listed in table 1). This showed a

similar pattern with an OR of 2.45 for male sex but with weaker effect (95% CI 1.05 – 4.80, p 0.037, I^2 statistic 0%) (Figure 2). Data from McGann et al(18) could not be combined into meta-analysis due to reporting adherence on a continuous scale. Their results did not show difference in adherence according to sex.

Age: Two studies examined the effect of age on adherence. One study(22) reported an adjusted OR for age (as a continuous variable) with adherence with OR of 1.11 (95% CI 1 – 1.11). The other study(18) reported the mean adherence for age brackets and found that mean adherence for patients in age bracket 29-39 years was 64% vs. 19% adherence for patients in the age bracket 19-29 years.

Minority status: Two studies from the US examined the effect of minority status. One of them(12) reported an adjusted OR of 0.35 (95% CI 0.13 – 0.95) for adherence in African American patients. The other study(18) reported a mean adherence of 37% for white patients vs. 34% for non-white patients.

Education: Four studies examined the effect of education on adherence. A meta-analysis was performed on the adjusted effects reported from three studies (12,14,22) and the pOR for higher education and adherence was 0.82 (95% CI 0.15 – 4.31, p 0.81, I^2 statistic 81.5%) (Figure 3). McGann et al(18) reported the mean adherence for those with college education and those with lower education and found it to be 54% and 25% respectively.

Other factors: One study(18) reported a mean adherence of 49% for employed patients vs. 26% for those without employment. Another study(21) performed a multivariate analysis on socio-demographic determinants of adherence and reported that living in the outskirts of cities was associated with an OR of adherence of 0.24 (95% CI 0.09 – 0.66). The same group reported that transportation difficulties were associated with an OR of adherence of 0.25 (95% CI 0.08 – 0.77).

2. Asthma-related factors

Asthma control: Four studies examined the correlation between symptom/control score and adherence. Apter et al(12) found that better control had an adjusted OR of adherence of 0.36 (0.06 – 2.10). A meta-analysis of the effects reported from three studies(6,19,21) produced a standardized mean difference of 0.61 (-0.25 – 1.47, p 0.162, I^2 statistic 84%) towards adherence (with positive results denoting more control or less symptoms) (Figure 4).

Hospitalizations/exacerbations: Apter et al(12) reported an adjusted OR of 1 (0.997 – 1.001) for adherence in those with a previous history of hospitalization. A meta-analysis of unadjusted effects of previous hospitalizations on adherence was performed on the results from four studies(14,16,19,21) and the pOR for history of hospitalization and adherence was 0.97 (95% CI 0.44 – 2.12, p 0.93, I^2 statistic 71%) (Figure S2).

Quality of life: Two studies(6,16) reported unadjusted correlation between quality of life and adherence, and both used asthma related quality of life questionnaire (AQLQ)

score (higher score, better quality). A meta-analysis of mean differences reported from the two studies showed a mean difference of 0.48 points (95% CI 0.17 – 0.78, p 0.002, I^2 statistic 0%) in favour of adherent patients (Figure 5).

Biomarkers: Two studies examined the difference in blood eosinophil count between adherent and non-adherent patients.(6,19) Lee et al(6) found that mean blood eosinophils was lower in adherent patients 0.22 ± 0.21 vs. $0.42 \pm 0.35 \times 10^3/\text{mm}^3$ in non-adherent patients. Conversely, McNicholl et al(19) found that eosinophils were higher in adherent than non-adherent patients with medians of 0.45 vs. $0.34 \times 10^3/\text{mm}^3$, respectively. Murphy et al(20) found a lower sputum eosinophil percentage in adherent patients with a mean of 2.3 ± 0.5 vs. $4.6 \pm 0.7\%$ in non-adherent patients. Two studies examined FeNO levels in adherent and non-adherent patients(6,19) and both found higher FENO levels in non-adherent patients, but without reaching statistical significance. One study(6) found adherent patients to have a mean FeNO of 27.22 ± 18 vs. 41.4 ± 30 ppb in non-adherent patients while the other study(19) reported in adherent patients a median FeNO of 107 (87-154) vs. 72 (55 – 101) ppb in non-adherent patients.

Medication schedule: Murphy et al(20) found that receiving combined ICS/LABA in a single inhaler vs. separate inhalers was associated with adherence with an OR of 3.62 (95% CI 0.7680 to 17.0538, p 0.103). Santos et al(21) found that less frequent dosing (once daily vs. twice daily) of inhalers was associated with adherence to therapy with an adjusted OR of 5.8 (95% CI 2.2 - 4.8).

3. **Psychological factors and comorbidities:**

Anxiety and depression: Two studies reported the mean hospital anxiety and depression scale (HADS) scores and its relation with adherence.(16,20) Meta-analysis of mean HADS for depression in adherent vs. non-adherent patients showed a mean difference of -0.718 points (95% CI -1.668 to 0.232, p 0.14, I^2 statistic 0%) (Figure S3). Meta-analysis of mean scores for anxiety in the same two studies revealed a mean difference of -0.597 points (95% CI -1.851 to 0.657, p 0.35, I^2 statistic 0%) denoting lower anxiety scores in adherent patients (Figure S4). Two studies(12,14) reported unadjusted OR for the presence of depressive symptoms and adherence and show a pOR of 0.990 (95% CI 0.952- 1.030, p 0.63, I^2 statistic 0%) (Figure S5). Smith et al(22) reported an adjusted OR of 0.08 (0.02 - 0.45, p< 0.01) between depressive symptoms and adherence.

Knowledge and attitudes: Two studies(12,13) examined the relation between asthma literacy (knowledge) and adherence. One study(12) reported an adjusted OR of adherence with good asthma knowledge of 0.99 (95% CI 0.9 - 1.09, p 0.84). The same study reported that a positive attitude towards the importance of inhalers in asthma management was associated with higher adherence with an adjusted OR of 1.21 (1.07 - 1.37, p 0.002). In the other study,(13) prevalence of adherence as a continuous variable was associated with asthma literacy with an adjusted beta of 1.89 (SE 1.22, p 0.13).

Smoking: Three studies examining adherence reported the smoking status.(6,14,16) The meta-analysis of the study numbers revealed a positive relation between adherence and history of smoking with a pOR for adherence of 1.311 (95% CI 0.826-2.082, p 0.25, I^2 statistic 0%) (Figure S6).

Discussion

The results of this systematic review indicate that non-adherence to therapy in patients with severe asthma is common with rates exceeding 40%. It has been recently shown utilizing 75% or more of the prescribed medication is the safe limit under which the risk of the worsened asthma outcomes increases.(25) Using this cut off of 75% of medication utilization, the reported rate of non-adherence in severe asthma was 45%. It is noteworthy that a study found that if patients with asthma fill their ICS at least 6 out of 12 months of the year, emergency department visits and hospitalizations are clinically reduced (26), which suggests that the cut off point of 75% could be higher than needed.

A systematic review has recently shown that sub-optimal adherence is associated with more severe exacerbations. (27) Non-adherence is amenable to intervention and various interventions have been devised to address this problem in different age groups and have shown to improve adherence rates. (7,28,29) It is important to note that as much as non-adherence is modifiable, adherence to medication tends to decrease over time(30). The British Thoracic Society recommends that adherence assessment be an integral component of assessment of patients with asthma and that it is checked during every follow up visit and particularly before a decision to step up medication is made.(5)

The difference in adherence rates derived from different (objective) methods should alert the clinicians to be careful when interpreting the findings of any test of adherence. Dose counting of consumed medications results in lower rates of non-adherence than prescription ratio or electronic monitors. The investigators of the studies which relied on dose counting supplied inhalers to participants who knew that it would be weighed in follow-up visits.(14,21) This could lead to spuriously higher rates of adherence while dose dumping is exercised for example. In the case of OCS, prednisolone/cortisol assays(16) (which are presumed to be more accurate) have shown higher rates of non-adherence compared to prescription ratio(20) (45 vs. 26%). This lends support to the need for biomarker tests to more accurately measure adherence. Indeed, more recently a few studies have reported the utility of simple tests to detect inhaler medications in a urine (31) or even hair(32) samples which can revolutionize the management of patients if these methods are validated and made available for widespread use.

The meta-analysis of risk factors associated with non-adherence was not possible in many instances. This was due to the variations in measuring and reporting adherence and outcomes. Where possible, effects from comparisons adjusted for confounding factors were used in meta-analyses as previously recommended because these effects are expected to show more meaningful results.(11) The two factors that were significantly associated with adherence were male sex and better asthma quality of life (as measured by AQLQ).

Additionally, there were indications that other factors were contributory to or characteristics of adherence such as better asthma control, older age, more knowledge about asthma, simpler medication schedules (less frequent dosing, less devices) and lower FeNO levels. We believe that this is useful information for clinicians to alert them to non-modifiable factors that could predict non-adherence and to modifiable factors that could be addressed more intensively.

The results of this systematic review should be interpreted with caution due to the following limitations. The majority of the data was obtained from observational studies which often employ less robust methods of measuring variables and are more prone to selective reporting. More specifically, the definition of severe asthma varied between studies, since each study used their respective national society guideline definition and this is a major source of

methodological heterogeneity. Only one study(6) used the ATS/ERS consensus definition of severe asthma(2) mainly because the other reports predated that key document. A wide range of tools were used to assess adherence which is another important methodological cause of heterogeneity. Additionally, there is substantial variability in the socio-economic and cultural environments between countries where studies were conducted limiting the power of pooling results together. Finally, the majority of the included reports were from developed countries and many factors (such as medication costs, extent of healthcare coverage, cultural factors such as shame, fear of addiction and self-(33)) are important in other parts of the world but are not represented in this review and thus these results cannot be generalized worldwide.

Conclusion

Non-adherence to therapy is a common problem in the management of patients with severe asthma. More robust and objective methods (such as electronic monitors, direct drug use measurement or indirect use of biomarkers) are needed to homogenize and improve the accuracy of the methods of assessment. More studies from developing countries are also needed to explore the impact of factors such as drug cost and availability on adherence to therapy in patients with severe asthma.

Declaration of interests and acknowledgment

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author	Study design	No	%female	Age (SD)
Apter 2003 (US)	Prospective observational study of modifiable socio-behavioural predictors of adherence	85	71.7	47+15
Apter 2013 (US)	Prospective observational study of effect of asthma literacy on adherence	284	71.1	48+14
Chatkin 2006 (Brazil)	Prospective observational study of the rate and determinants of adherence	131	70.9	44 (16.6)
Foster 2014 (US)	RCT of inhaler reminder vs personalized adherence discussion on adherence to controller medications	43 (143)	62.8	40+14
Gamble 2009 (UK)	Retrospective study of prevalence of nonadherence to controller medication	182	62.1	42+14.5
Jansen 2009 (US)	RCT of education effect on adherence	84	53.5	37+9.4
Lee 2018 (Australia)	Retrospective study of pattern and determinants of nonadherence in difficult asthma clinic	45 (69)	53.3	54+14
McGann 2008 (US)	Prospective Observational study of the relation between disease denial and compliance	51	82.3	42+14.9
McNicholl 2012 (UK)	Retrospective study of pattern of nonadherence in difficult asthma clinic	146	68.4	41+15
McNicholl 2012b	Diagnostic study of Novel FeNO suppression to estimate adherence in difficult asthma	21	57.1	
McNicholl 2012c	Phase 2 of FeNO suppression diagnostic study	40	57.5	46.6+14
Murphy 2012 (UK)	Retrospective study of adherence pattern of attendees of difficult asthma clinic in the Leicester, UK	115	63.5	
Santos 2008 (Brazil)	Prospective cohort study of predictors of adherence in adults with severe asthma	160	75	49+13.9
Smith 2006 (US)	Prospective cohort study of effect of depressive symptoms on adherence on those discharged following asthma hospitalisation	59	64.4	43+10.9
Sulaiman 2016 (Ireland)	Diagnostic study of a new device that measures adherence to asthma inhaler	239	61.9	49+16
Wislon 2010 (US)	RCT of shared decision making versus standard of care on adherence	612	56.5	47+12

Participant characteristics	Severity defining	Adherence method	Cut off	Duration of monitoring	% Adherence by cut off	Mean (SD) adherence
Moderate to severe	NHLBE	e-device	80	6 weeks	46	60 (30)
Moderate to severe	NHLBE	e-device	N/A	3 months		62 (28)
Moderate to severe	Brazilian Consensus on Asthma Management	dose counting	85%	3 months	63.9	
moderate to severe	symptom score and exacerbation	e-device	N/A	6 months		46 (24)
Symptomatic despite GINA 4 or 5	GINA 4 or 5	prescription ratio	<50%, 75	6 months	65, 47	
moderate to severe	NHLBE	e-device	N/A	6 months		82 (18)
difficult asthma	ATS/ERS criteria	e-device	75%	2 months	55.6	51.4 (20.8)
All degrees (SEVERE MORE THAN HALF)	NHLBE	e-device	80%	2 weeks	10.4	
Symptomatic despite GINA 4 or 5	GINA 4 or 5	prescription ratio	80	6 months	56.1	
Symptomatic despite GINA 4 or 5	GINA 4 or 5	FeNO suppression	N/A			
Symptomatic despite GINA 4 or 5	GINA 4 or 5	FeNO suppression	N/A		67.5	
Attendees of difficult asthma clinic	GINA 4 or 5	prescription ratio	80%	12 months	34.8	
severe	Brazilian Consensus on Asthma Management	dose counting	80	6 months	70.9	83.9
	Hospitalisation in the preceding year	e-device	50%	2 weeks (one weeks for OCS)	76	68 (CI 62-72)
severe asthma	step 3-5 GINA and recent exacerbation	e-device	80%	3 months	58.5	79 (20.7)
poorly controlled	GINA 4 or 5	prescription ratio	N/A	12 months		40 (CI 35 - 48)

Predictors studies	Factors adjusted for in determining effect size of independent variables
Minority, attitude towards importance of treatment to asthma control, level of symptoms, knowledge about asthma medications, depression	Minority, attitude towards importance of treatment to asthma control, level of symptoms, knowledge about asthma medications, depression
Health literacy	age, gender, race, and treatment assignment
Male, schooling years	gender, steady relationship level of education
N/A	N/A
Female (female 1 and male 2), lower QoL, Admission in preceding year	quality of life, gender, previous hospitalisation
N/A	
eosinophils (other determinants explored including demographics, FeNO, control, etc.)	N/A
Age group (29 - 39) higher than older and younger, higher education, employment, higher denial	N/A
Higher FeNO	N/A
gender, FEV1/FVC, previous hospitalisation, higher FENO, higher ACQ, sputum eosinophil (ns)	N/A
NA	N/A
Higher sputum eosinophil, FEV1, combined vs separate inhalers, anxiety depression scores	N/A
Residence outside city, poor control, asthma literacy, adverse reaction to inhalers, twice daily schedule, older age, male gender, not receiving medication in ED	residence, longer duration of asthma, adverse events with treatment, dosing frequency, transportation difficulty
High depressive symptoms, female, age, lower education	age, gender, education level, depressive symptoms
N/A	N/A
N/A	N/A

Table 2: Adherence rates according to different methods and cut-offs used

	Total	Adherent	Non-adherent
Adherence by cut off total	1253	716 (57.1%)	537 (42.9%)
Adherence < 50	241	164 (68%)	77 (32%)
Adherence <75	1012	552 (54.5%)	460 (45.5%)
Adherence by method			
Dose counting	291	196 (67.4%)	95 (32.6%)
E-device	459	253 (55.1%)	206 (44.9%)
Prescription	443	240 (54.2%)	203 (45.8%)

Figure legends

PRISMA Flow Diagram – Adherence in Severe Asthma

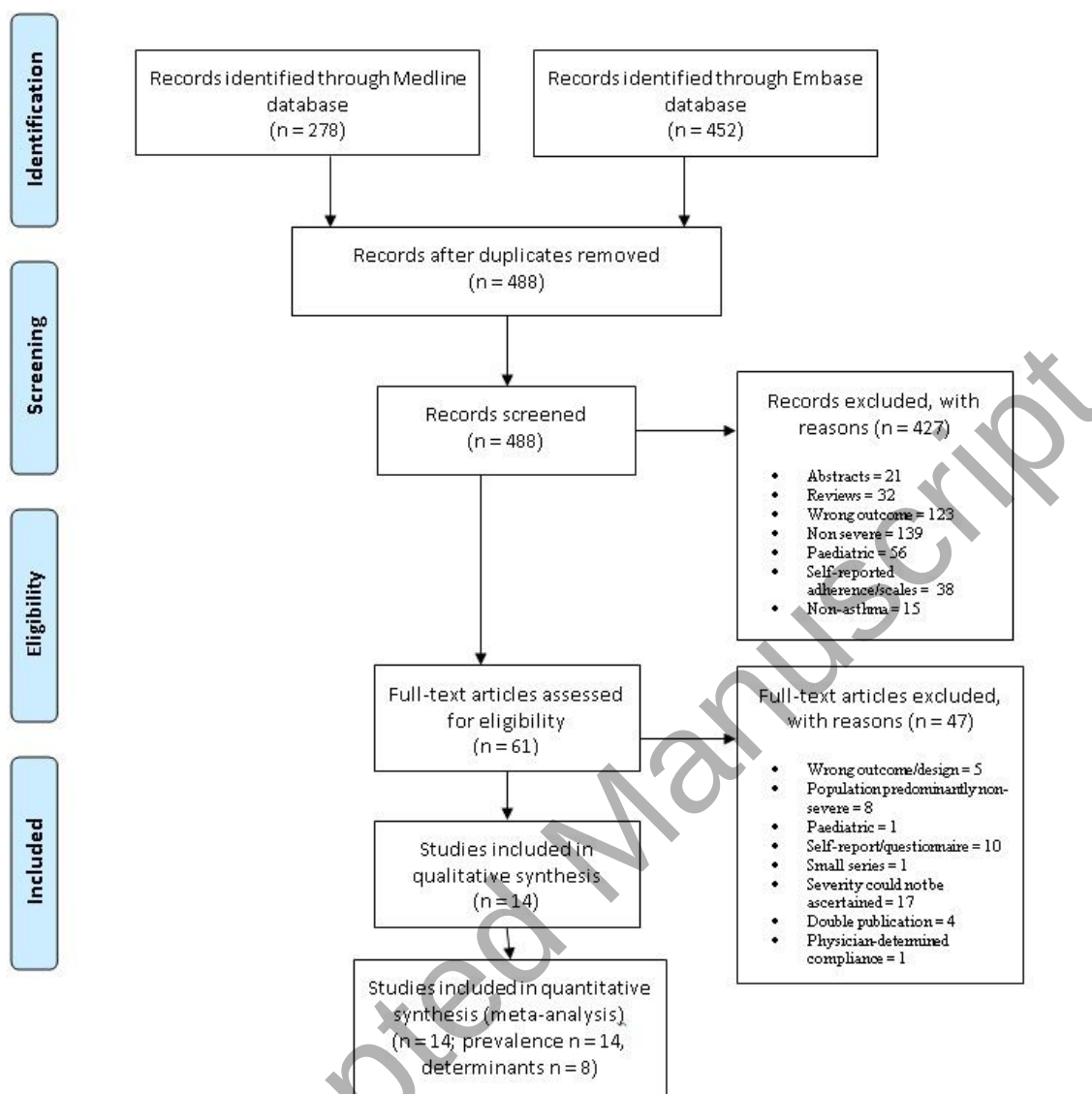


Figure 1: The flowchart of the screening of search results and study selection process.

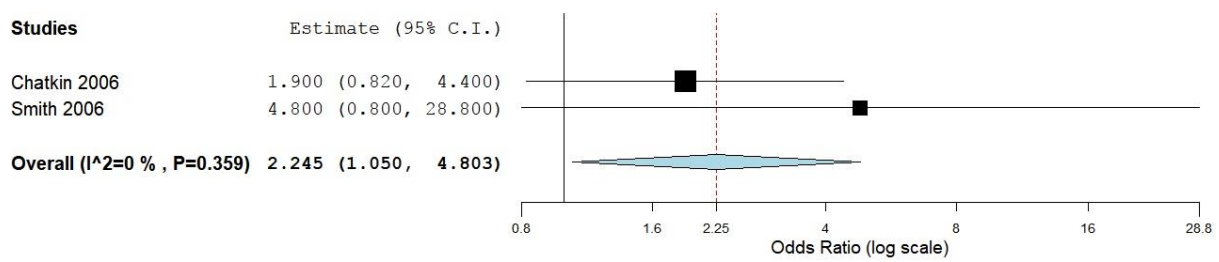


Figure 2: Meta-analysis of adjusted effects of male sex on adherence

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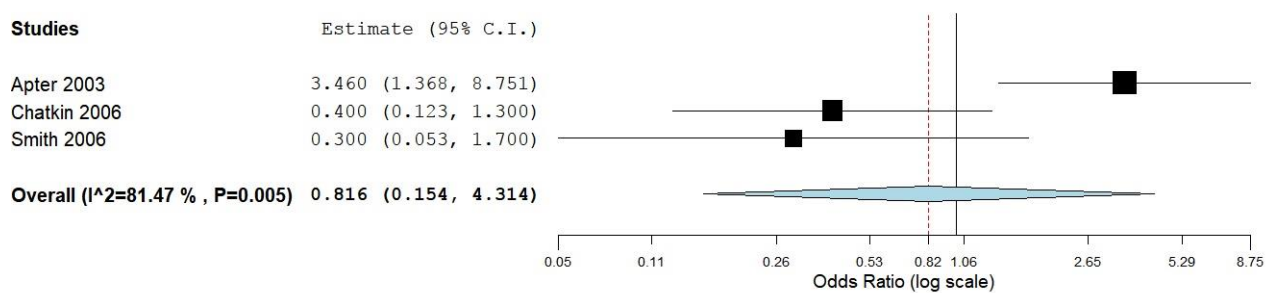


Figure 3: Meta-analysis of adjusted effects of higher education on adherence

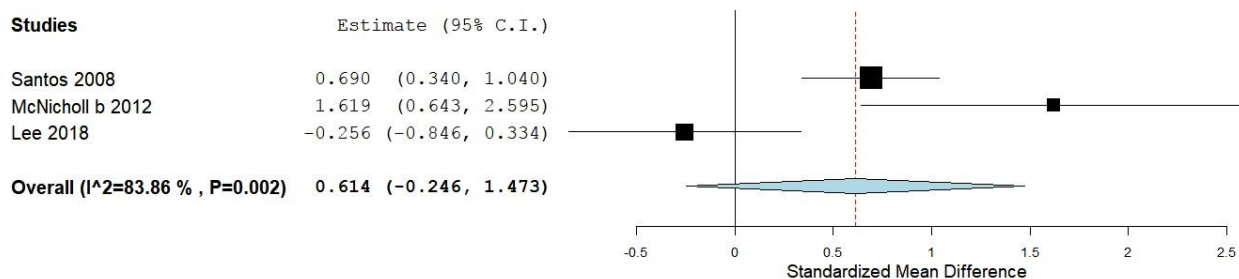


Figure 4: Meta-analysis of standardized mean difference in measures of asthma control according to adherence

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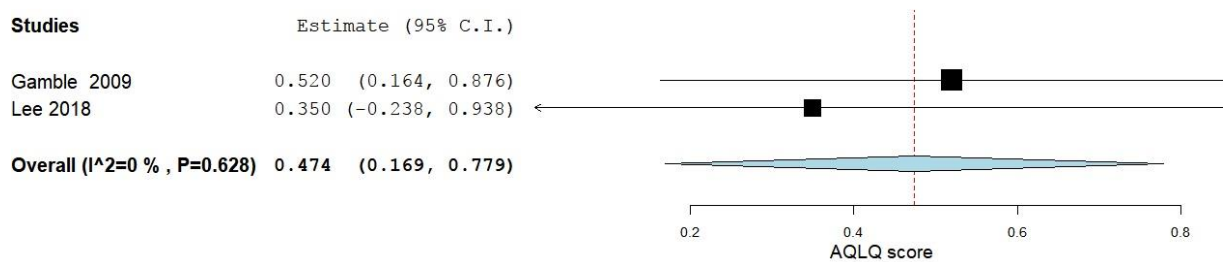


Figure 5: Meta-analysis of mean difference in AQLQ according to adherence

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