Asthma inhaler adherence determinants in adults: systematic review of observational data

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Running Title**:**

Determinants of asthma inhaler use in adults

120-character summary for social media:

Major opportunities for strengthening evidence on determinants of non-adherence to asthma inhalers: methods and theory.

Key Words: asthma; inhaled medication; adherence; adult; systematic review; observational

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Abstract

Non-adherence to inhaled medication leads to poor asthma control and increased health care utilization. Many studies exploring adherence determinants have been conducted, but summaries of the evidence are scarce. We performed a systematic review of observational research on determinants of asthma inhaler adherence among adults.

We searched for articles in English reporting quantitative observational studies on inhaler adherence correlates among adults in developed countries, published in EMBASE, Medline, PsychInfo, and PsychArticles in 1990-2014. Two coders independently assessed eligibility, extracted data, and assessed study quality. Results were summarized qualitatively into social and economic, health care, therapy, condition, and patient-related factors.

The 51 studies included mainly examined patient-related factors and found consistent links between adherence and stronger inhaler necessity beliefs, and possibly older age. There was limited evidence on the relevance of other determinants, partly due to study heterogeneity regarding the types of determinants examined. Methodological quality varied considerably and studies performed generally poorly on their definitions of variables and measures, risk of bias, sample size, and data analysis.

A broader adoption of common methodological standards and health behaviour theories is needed before a cumulative science on the determinants of adherence to asthma inhalers among adults can develop further.

The introduction of inhaled medication as primary asthma treatment has led to substantial improvements in asthma control (1,2). However, uncontrolled asthma is still common and represents a considerable burden to patients and society (3,4). An important reason for poor asthma control and consequently increased health care expenditure, is suboptimal adherence to the prescribed regimen (5–7). To date, few adherence interventions evaluated in asthma treatment have been found (cost-)effective (8–10). A systematic review of observational evidence on adherence determinants could help identify the patients most at-risk for non-adherence and the key drivers of non-adherence that can be modified in adherence interventions.

Although several narrative reviews on determinants of adherence to asthma medication have been conducted (11–18), only two systematic reviews on observational research are available. Both examined adherence to inhaled corticosteroids (ICs): one focused on children (19), the other exclusively evaluated the role of illness and treatment perceptions in adults (20). Neither examined the quality of the methodology of included studies, which is important in interpreting empirical evidence (21–23). To our knowledge, no comprehensive systematic review of factors related to adherence to inhaled medication in adults with asthma has been published to date.

The objective of this study was to synthesize the current observational evidence on determinants of inhaler adherence in asthmatic adults through a systematic review, including a critical appraisal of the methodological quality of the studies, and develop recommendations for future research in this domain.

Methods

Literature search and study selection

EMBASE, Medline, PsychInfo, and PsychArticles were searched for manuscripts published between 1 January 1990 and 26 June 2014 with keywords on asthma, adherence, persistence, compliance, concordance, determinant, cause, influence, barrier, and facilitator (see Supplementary Material 1). Eligibility was determined using the following criteria: peer-reviewed article in English, reporting an empirical quantitative observational study (cross-sectional or longitudinal designs), presenting results on adult (>18 years) asthma patients living in developed countries (24), investigating one or more predictors of adherence to inhaled asthma medication, and describing the adherence measurement procedure. The selection was initially based on the information in the title and abstract; if inconclusive,

the entire manuscript was examined. Two reviewers (AD and OC) examined the search results independently. Disagreements were reconciled by a third reviewer (MdB) and through consensus.

Data extraction

Two coders (AD and OC) extracted information on study characteristics (objectives, methodology, country, language, setting, sample size, age, gender, asthma severity and type of inhaled medication studied), adherence behaviours and determinants (definition, measurement and psychometrics), and statistical data (type of analysis and results reported). The data extraction procedure was piloted on articles not included in the review. Each coder extracted data from 50% of papers. The accuracy of the recorded information was verified by the other coder, and disagreements were discussed and reconciled.

Quality rating

Two coders (AD and GH) rated methodological quality based on six criteria adapted from the STROBE guidelines which are considered key requirements for observational studies (25,26). Scoring was performed on a 4-level response format, from no information reported to adequate reporting of appropriately used methodology (coding sheet in Supplementary Material 2). The studies were judged on methods clarity and pertinence in six domains: (1) selection of participants (e.g., sampling strategy, eligibility criteria and methods for assessing eligibility), (2) definition of variables (i.e., outcomes, determinants and confounders), (3) description of data sources and measurement procedures for all variables, (4) addressing potential sources of bias (e.g., medical surveillance, recall, or response bias), (5) sample size justification (e.g., power analysis, multiple comparisons correction), and (6) data analysis (e.g., data preparation, controlling for confounding and data collection, sensitivity analyses). Disagreements were discussed and reconciled.

Data analysis

The data on study characteristics and adherence measurement were summarized descriptively. The results on the relationships between adherence determinants and behaviours were grouped separately for reliever (e.g., short-acting beta agonists; SABA) and controller (e.g., ICs) medication as they relate to different recommendations (daily versus as needed use). Controller adherence was examined separately for the three stages of adherence (27): starting treatment (initiation), accuracy of medication use (implementation), and continuing treatment (persistence). Determinants were classified using the five dimensions of the World Health Organization (WHO) taxonomy (26,27): (1) social and economic, (2)

health care team and system-related, (3) condition-related, (4) therapy-related, and (5) patient-related factors, each with additional sub-dimensions. We summarized results regarding the statistical significance and direction of relationships for all studies. Adjusted results obtained by multivariate analyses were prioritized over unadjusted when available.

Metric properties of the 6 study quality items were investigated. Reliability was assessed by estimating inter-rater agreement with weighted Kappa, considered appropriate for ordinal scores (28), and interpreted based on established thresholds for poor, fair, moderate, good, and excellent agreement (.20, .40, .60, and .80 respectively) (29). Mokken Scaling and correlational analyses were performed on consensus scores to evaluate structural validity and examine the relationships between criteria. Total quality scores were computed adding scores on the criteria with adequate metric properties; studies were classified as higher versus lower quality via median split. Statistical analyses were performed with IBM SPSS Statistics 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and R (30) *mokken* package (31,32).

Results

Study selection

The database search identified 2878 unique articles (Figure 1). The two coders agreed on the selection of 213 articles as potentially relevant (Cohen's Kappa = .60). The third coder reviewed 235 disagreements and selected 86 additional articles. Thus, 299 articles were reviewed to confirm they fulfil all inclusion criteria; 213 were excluded based on title and abstract, and 35 after full manuscript examination. Finally, 51 studies were included in the review. Reasons for exclusion are detailed in Figure 1.

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Study characteristics

Characteristics of studies are showed in Table 1. Most studies were conducted in European countries (*n*=21) or the United States (*n*=19). Settings of studies were diverse: primary and secondary care, pharmacies, general population, and various prescription and insurance claims databases. Eleven studies used existing databases, while 40 studies collected data directly from patients. Thirty two studies

focused solely on adults (>18 years), while 19 studies included adults and children. Sample sizes ranged from 34 to 292738 participants (median 204, interquartile range 906). Most studies included more women than men. Asthma severity was reported in 16 studies and ranged from mild to severe asthma.

Table 1. Study characteristics of empirical studies on inhaled medication adherence in adults with asthma (chronological order)

First author, publication year (country)	*Objectives*	*Study design*	*Data sources*	*Sample size*	*Age, years - mean (SD) [range]*	*Female gender - count (%)*	*Asthma severity - FEV1%*	*Inhaled medication*
Tettersell, 1993 (UK) (33)	Relationship between knowledge and treatment adherence	CS (ASD)	Primary care	100	50.1(20.6)	9%	Moderate to severe	NR
Bosley, 1995 (UK) (34)	Psychological factors related to asthma self-care and compliance	PC (DPA)	Primary care & outpatient clinic	72	45 (15)	62	NR	ICs+LABA ICs/LABA
Apter, 1998 (US) (35)	Patient characteristics related to adherence to twice daily ICs treatment	PC (DPA & ASD)	Outpatient clinics	50	46 (14)	37 (74)	75% ± 21%	ICs
Bennett, 1998 (UK) (36)	Associations between protection motivation theory factors (health threat, outcome, self-efficacy) and adherence to preventive ICs use	CS (ASD)	Primary care	71	47 (19.25)	40	NR NR	ICs
Chambers, 1999 (US) (37)	Factors associated with regular ICs use	CS (ASD)	Primary care	394	36 median	(75)	NR	ICs
Schmaling, 2000 (US) (38)	Development of measures to assess psychological factors important to adherence with medication regimens	CS (ASD)	Private asthma clinic & hospital	53	36.1 (9.6)	(62.3)	NR	ICs, LABA, SABA
Horne , 2002 (UK)	Relation between reported adherence to preventer medication and perceptions and asthma	CS (ASD)	Primary care	100	49.3 (18.1)	(61)	NR	NR

(39)	medication							
van Schayck, 2002 (NL) (40)	Influence of inhalation device, patients' inhaler perceptions, daily frequency, and duration of treatment on medication compliance	PC (DPA & ASD)	Primary care	34	37 (13)	19	NR	LABA or SABA
Apter, 2003 (US) (41)	Barriers to adherence as explanations of racial-ethnic differences in adherence	PC (DPA & ASD)	Primary & secondary care	85	47 (15)	61 (72)	65% ± 19%	ICs
Jessop, 2003 (UK) (42)	Relation between cognitive and emotional representations of asthma and adherence to inhaled preventative asthma medication	CS (ASD)	Primary care	330	57.2 (17.9)	204 (61.8)	NR	NR
Labrecque, 2003 (CA) (43)	Assess compliance to asthma guidelines and influence of age on SABA utilization	RC (ASD)	Health insurance database claims	987(394+ 593)	[5-45]	NR	severe asthma excluded	SABA (with or without ICs)
Nishiyama, 2003 (UK) (44)	Determine if the Jones Morbidity Index can be used in community pharmacy to identify those who have poor control	CS (ASD)	Pharmacy database	306	38.5 (20.6)	(54.5)	NR	ICs and SABA
Balkrishnan, 2005 (US) (45)	Asthma-related health care costs and medication adherence ICs and newly started on MON versus salmeterol (SAL)	RC (DPA)	Health insurance database claims	198	22 (19.5) MON; 24 (18.2) SAL	(52.5) MON; (59.8) SAL	NR	ICs+LABA vs ICs+MON
Lacasse, 2005 (CA) (46)	Describe patterns of compliance and identify factors determining the compliance to ICs in adults	PC (DPA & ASD)	NR	124	47 (15)	73	Mild-moderate	ICs
Stempel, 2005 (US)	Patient adherence with several medication regimens: FP/SAL, FP+SAL, FP+MON, FP, MON	RC (ASD)	Health insurance database claims	3503	38.7 (17)	(64.5)	NR	ICs, LABA, MON

(47)								
Bender, 2006 (US) (48)	Factors related to refill adherence to FP/SAL	RC (ASD)	Pharmacy database	5504	54 (22)	(60.2)	NR	ICs/LABA
Chatkin, 2006 (BR) (49)	Rate of compliance with preventive treatment for moderate and severe persistent asthma	PC (DPA)	Primary care	131	44.4 (16.6)	(71)	severe persistent	ICs/LABA
Hasegawa, 2006 (JA) (50)	Comparison between compliance to fluticasone propionate diskus (FPdk) versus diskhaler (FPdh)	RC (ASD)	Pharmacy database	337	54.2 (16.8) FPdh; 57.7 (18.2) FPdk	(56.3) FPdh; (57) FPdk	NR	ICs
Marceau, 2006 (CA) (51)	Compare persistence, adherence, and effectiveness between patients with asthma starting combination or concurrent therapies (ICs and LABA).	PC (DPA & ASD)	Health insurance database claims	5118	32.6 (8.2)	(63,3)	NR	ICs/LABA vs ICs + LABA
Ohm, 2006 (US) (52)	Explore asthma symptom perception and its relationship with adherence to asthma treatment	CS (ASD)	asthma/allergy clinics	120	44.8 (9.27)	(78)	mild to severe	ICs
Tavasoli, 2006 (IR) (53)	Factors related to patients' compliance with prescribed Metered Dose Inhaler drugs	CS (ASD)	outpatient department	160	47.67 (12.78)	105 (65,6)	NR	ICs, LABA, SABA
Ulrik, 2006 (DNK) (54)	Patient-related aspects of adherence among adult asthmatics	CS (ASD)	Community (web-based panel for market research)	509	[18-45]	317 (62)	mild 77%, moderate 12% severe 11%	ICs, ICs+LABA
Williams,	Factors associated with ICs adherence among	RC	Health	176	40.8 (7.7)	115	NR	ICs

Joseph, Peterson, Moon, 2007 (US) (55)	patients with asthma, and among African American and white patients separately	(ASD)	maintenance organization			(68,1)		
Williams, Joseph, Peterson, Wells, 2007 (US) (56)	Estimate rates of primary non-adherence and explore associated factors	RC (ASD)	Health maintenance organization	1064	31.9 (16.5)	(59,8)	NR	ICs
Breekveldt-Postma, 2008 (NL) (57)	Determinants of persistence with ICs	PC (DPA)	Pharmacy database	5563	[0-34]	(51.5) – (57.2)	NR	ICs, ICs+LABA
Janson, 2008 (US) (58)	Describe asthma medication adherence, identify predictors of ICs underuse and SABA or LABA overuse	CS (DPA & ASD)	Primary & secondary care (random-digit dialling)	158	48.7 (7.4) 46.7 (8.5) 46.5 (8.8) 46.2 (7.3)	(68)	NR	ICs and SABA or LABA
Martínez-Moragón, 2008 (SP) (59)	Relationship between failure to perceive dyspnea associated with bronchial obstruction and treatment non-adherence in asthmatic patients	CS (ASD)	Outpatient respiratory clinics	48	48(14) 44(15)	(50)	moderate	ICs/LABA
McGann, 2008 (US) (60)	Relationship between denial of illness and compliance with inhaled controller asthma medications	PC (DPA)	Asthma clinics, advertisements, local college	51	42 (14.99); [18-68]	(82.3)	NR	NR (controller)
Menckeberg, 2008 (NL) (61)	Relationship between beliefs about ICs (necessity and concerns) and adherence	CS/RC (ASD)	Pharmacy database	238	36.2 (6.3)	(67)	NR	ICs

Wells, 2008 (US) (62)	Factors that contribute to ICs adherence among African-American and white adults with asthma	RC (ASD)	Health maintenance organization	1006	43.1 (10.4)	716 (71.2)	NR	ICs
Axelsson, 2009 (SWE) (63)	Personality traits related to asthma control, health-related quality of life and adherence to regular asthma medication	CS (ASD)	Epidemiological study	109	[21-23]	(61.6)	NR	ICs/LABA, ICs; LABA; SABA
Bae, 2009 (KO) (64)	Baseline information about ICs adherence in Korea; factors related to ICs adherence; clinical implications of ICs adherence for asthma control	CS/RC (ASD)	Clinical centres in university hospitals	185	NR	NR	NR	ICs or ICs/LABA
Laforest, 2009 (FR) (65)	Characteristics of patients with interruptions of ICs, intentional or accidental	CS (ASD)	Primary care database	204	53.8 (19.6)	(59.3)	all ranges	ICs only or in combination
Ponieman, 2009 (US) (66)	Impact of potentially modifiable medication beliefs on adherence with ICs therapy across time.	PC (DPA & ASD)	General internal medicine clinics	261	48 (13) [20-87]	(82)	persistent asthma	ICs
Friedman, 2010 (US) (67)	Adherence and asthma control in adolescents and young adults with mild asthma who began treatment with mometasone furoate (MF) or FP	RC(ASD)	Health insurance claims database	1384	16.3 MF; 16.5 FP; [12-25]	(51.3) MF; (55.3) FP	mild	ICs
Takemura, 2010 (JA) (68)	Assess factors and mechanisms that contribute to and clinical outcomes relating to adherence	CS (ASD)	Respiratory clinic	176	57 (15)	89	NR	ICs, ICs/LABA
Bolman, 2011 (NL) (69)	Explain ICs adherence by the attitude, social influence and self-efficacy model and habit strength (moderation and mediation relationships)	CS (ASD)	Pharmacy	139	31.5 (5.6)	98 (70.5)	NR	ICs
Emilsson,	Influence of personality traits and beliefs about	CS	NR	35	52.8 (14.7)	25	NR	ICs/LABA;

2011 (SWE) (70)	medicines on asthma medication adherence	(ASD)						ICs+LABA; ICs; LABA
Small, 2011(UK) (71)	Relationship between inhaler satisfaction and patient compliance. Influence on health and patient-reported outcomes	CS (ASD)	Specialists' and primary care	2135	NR (adults)	NR	NR	NR
Suzuki, 2011 (JA) (72)	Associations between several factors of asthma therapy (patients adherence, asthma severity)	RC(ASD)	University Hospital	50	36.3 (7.9)	(46)	NR	ICs
Foster, 2012 (AU) (73)	Identify potentially modifiable beliefs and behaviours that predict ICs/LABA adherence	PC (ASD)	Community pharmacies, advertising, primary care, volunteer database	99	47.6 (15.8)	57	83% ± 23%	ICs/LABA
Ahmedani, 2013 (US) (74)	Relationships between locus of control factors (God, doctors, other people, change and internal) and ICs adherence	CS (ASD)	Primary care	1025	37.6 (14.8)	675 (65.9)	NR	ICs
Axelsson, 2013 (SWE) (75)	To determine the mediating effects of medication beliefs between personality traits and adherence	CS (ASD)	Community	516	47.4 (15.6)	(60)	NR	ICs/LABA, ICs; LABA; SABA
Price, Lee, 2013 (UK) (76)	Identify characteristics of patients who prefer once-daily controller regimen	RC (ASD)	Primary care database	3731	45.6 (15) [2-94]	2174 (58.3)	NR	ICs; ICs+LABA
Price, Thomas, 2013 (UK) (77)	Compare real life effectiveness of extrafine and larger particle beclometasone	C-C (DPA)	Primary care databases	30354	[12-80]	17808 (58.7%)	NR	ICs

Schatz, 2013 (US) (78)	Develop a questionnaire that reflects nonadherence risk and identifies adherence barriers	PC (DPA & ASD)	Health maintenance organization	420	41.6 (9.1)	280 (66.7)	NR	ICs; SABA
Wells, 2013 (US) (79)	Determine whether once daily dosing is associated with higher ICs adherence than 2 or more times daily dosing	RC (DPA)	Health maintenance organization	1302	28.2 (15.8) once daily; 31.6 (16.0) ≥ 2 daily	113 (51.1) once daily; 656 (60.7) ≥ 2 daily	Low to severe	ICs
Baddar, 2014 (Oman) (80)	Relationships between patient compliance, inhaler technique and asthma control level	CS (ASD)	University Hospital	218	[12-72]	(65.1)	NR	ICs; ICs/LABA; ICs+LABA
Federman, 2014 (US) (81)	Associations of self-management behaviours (e.g. medication adherence and inhaler technique) with health literacy	PC (DPA)	Outpatient clinics	433	67; 45% 60-64, 39% 65-74, 16% ≥75	(83.8)	Moderate or severe	ICs only or in combination
Taylor, 2014 (UK) (82)	To develop an annual measure of ICs adherence from prescribing data and statistically model ICs adherence controlling for patient factors	RC (DPA)	Primary care database	292738	38.7 (15.4)	NR	BTS/SIGN step 2-5	ICs
Van Steenis, 2014 (NL) (83)	Relationship between ICs necessity and concerns beliefs and subjectively- and objectively-measured adherence and the agreement between these measures	CS (ASD)	Pharmacy	93	43.7 (14.5) [18-77]	55 (59.1)	NR	ICs only or in combination

Note: Abbreviations are: *SD: standard deviation; FEV1%: forced expiratory volume for 1 second expressed as a percentage of the forced vital capacity*; NR: not reported; *for country*: UK: United Kingdom; US: United States; NL: Netherlands; CA: Canada; BR: Brazil; JA: Japan; IR: Ireland; DNK: Denmark; SP: Spain; SWE: Sweden; KO: South Korea; FR: France; AU: Australia; *for study design*: CS: Cross- sectional; RC: Retrospective Cohort; C-C: case-control study; PC: Prospective cohort*;*

ASD: adherence simultaneous with determinants measurement; DPA: determinants preceding adherence measurement; *for asthma severity:* BTS/SIGN: British Thoracic Society/Scottish Intercollegiate Guidelines Network; *for medication*: SABA: short-acting $beta_2$- agonists; LABA: long-acting $beta_2$-agonists; ICs: inhaled corticosteroids.

Twenty studies focused on adherence to ICs only, eight assessed adherence to inhaled asthma medication as a generic treatment category, and 23 studies focused on various types of medication, including ICs and long- or short-acting beta-agonists (LABA and SABA), either in monotherapy or in fixed (ICs/LABA) or free (ICs+LABA) combinations. Two studies analysed repeated measures of adherence in longitudinal cohort designs, prospectively (66) or retrospectively (82). All other studies collected data cross-sectionally, retrospectively, or prospectively (22, 16, and 12 studies respectively) and analysed relationships between determinants and single adherence measures.

There were substantial differences between studies in operationalization and measurement of both adherence determinants and behaviours (see Supplementary Material 3). Of the 68 adherence behaviour assessments (several studies used multiple measures; see Table 2), 31 relied on patient reports, 24 accessed medical records (prescription and refill data), seven employed electronic monitoring, four used canister weighting, one used dose counters, and one requested physician reports. Fifteen of the patient-reported adherence assessments applied validated questionnaires like the Medication Adherence Rating Scale (MARS (39) and Revised Asthma Adherence Scale (RAAS (84), while the remainder used self-constructed non-validated questionnaires.

Table 2. Definition and measurement of adherence behaviours in the studies reviewed (chronological order).

First author, publication year	*Adherence definition/ term*	*Assessment method*	*Details*	*Validity/ reliability*
Tettersell 1993	taking inhalers as prescribed	patient-report, single item	1 item: “Do you take your inhalers as prescribed?”; 4 response options: “Always”, “Majority of the time (8 out of 10 doses)”, “About half of the time”, “Only during or following an attack”	NR
Bosley, 1995	noncompliance; taking less than 70% of prescribed doses or omitting all doses for 1 week or more	electronic monitoring	Turbohaler Inhalation Computer; computed for two 6-week periods as (no of doses taken)/(no of doses prescribed)*100	NR
Apter, 1998	use of ICs in the last 35 days	electronic monitoring	MDILog, last 35 of 42 days considered, computed for 12-hour periods as (recorded - prescribed actuations)*100; mean truncated adherence computed per subject; dichotomized (< or >70%)	NR
Bennett, 1998	adherence to preventive ICs use	patient-report, published scale	RAAS (84)	α .75
Chambers, 1999	frequency of ICs use	patient-report, single item	Item content not specified; 4 response options: “I use it at least twice a day almost every day”, “Some days I use it at least twice, but on other days I don’t use it at all”, I used to use it, but now I don’t”, “I never used it”; dichotomized into 'regular, twice daily' and 'less than regular'	NR
Schmaling, 2000	as-needed medication use	canister weighting	total number of medication inhalations for each day in the prescription period	NR
	daily medication adherence	canister weighting	predicted use (no. days * no. puff per day) compared to actual use; computed as percent of prescribed medication used	NR
Horne, 2002	medication adherence	patient-report, published	MARS (39)	α .85

		scale		
van Schayck, 2002	medication compliance rate	canister weighting	medication used as a percentage of medication prescribed	NR
Apter, 2003	use of ICs in the last 42 days	electronic monitoring	MDILog, 42 days, computed for 12-hour periods as (recorded - prescribed actuations)*100; mean truncated adherence computed per subject; divided into 4 categories (<20%, 20-<50%, 50-<75%, 75%-100%)	NR
Jessop, 2003	adherence to preventative inhaled medication in the last 3 months	patient-report, published scale (adapted)	RAAS (84) and two extra items on accidental non-adherence	α .92
Labrecque, 2003	conformity of SABA prescription use with accepted good use criteria	medical (refill) records	dichotomous; good use criteria: for SABA with no ICs use, the interval between the targeted SABA prescription and the following refill corresponds to a maximum daily use of two inhalations; for SABA with ICs use, the criterion above, and a daily ICs dose below a fixed threshold	NR
Nishiyama, 2003	reliever compliance	patient-report, interview	patients were required to state the drugs and dosage regimens they used; their reports were compared with prescription information; 3 values coded: “good’’; “overused”; “underused” (first two applied also to reliever)	NR
	preventer compliance	patient-report, interview		NR
Balkrishnan, 2005	adherence to controller pharmacotherapy	medical (refill) records	computed as (days of prescription supply dispensed)/(days between prescription refills - number of days person was hospitalized); dichotomized as compliant (0.5-1.5) or not	NR
Lacasse, 2005	non-compliance	electronic monitoring	MDILog; calculated for 12 weeks daily as proportion of prescribed daily dose actually inhaled; dichotomised as compliant (>75%) or not	NR
Stempel, 2005	asthma medication refill rate	medical (refill) records	number of 1-month supply during the 12-month post-index period	NR
	number of treatment days	medical (refill) records	For monotherapy: total days supplied of medication; for combination: total days supplied of ICs	NR

	SABA refill rates	medical (refill) records	number of 1-month supply during the 12-month post-index period	NR
Bender, 2006	adherence to ICs/LABA	medical (refill) records	total days supplied during follow-up period	NR
	persistence	medical (refill) records	time to discontinuation computed as number of days from index date to date preceding the pre-specified gap when supply was exhausted	NR
Chatkin, 2006	compliance	canister weighting	(total quantity of medication used)/ (quantity prescribed, i.e. 3 canisters in 3 months); dichotomised as compliant (>85%) or not	NR
Hasegawa, 2006	drug compliance	medical (prescription and refill) records	computed for 6 months as (number of medicines dispensed)/(number of medicines prescribed)*100; capped at 100%	NR
Marceau, 2006	persistence versus discontinuation - having prescriptions continuously renewed within the period	medical (refill) records	computed as the sum of 3 times the duration of the current prescription (in days) plus all overlaps accumulated since therapy start; discontinuation date was the end date of the last filled prescription plus all overlaps	NR
Ohm, 2006	use of ICs+LABA	electronic monitoring	Advair diskhaler; computed as (number of counted doses)/(number of prescribed doses)*100. Dichotomized as good adherence (≥80%) or not	NR
	medication adherence	patient-report, published scale	MARS (39)	NR
Tavasoli, 2006	compliance to prescribed MDI drugs	patient-report, interview	4 items: "Do you use your prescribed spray (MDI drug) regularly?", "Have you ever had any history of not using your spray?", "Do you still use your last prescribed spray?", "How do you use your spray? Show me"; response scales from 0 to 4	NR
Ulrik, 2006	intentional non-adherence	patient-report, single item	1 item: “How often do you decide not to take your controller medication?”; 5 response options: “almost every day”, “a couple of times every week”, “a couple of times every month”, “a couple of times every year”, “hardly ever”	NR
	adherence	patient-report,	item not specified; responses reported on a 3-level scale: taking controller	NR

		single item	therapy as prescribed, less, or more than prescribed	
Williams, Joseph, Peterson, Moon, 2007	ICs adherence	medical (refill) records	(cumulative days supplied)/ (total number of days between refills for 1-year study period); analyses performed also with adherence stratified (0%, 0-80%, ≥80%)	NR
Williams, Joseph,	primary non-adherence	medical (refill) records	no prescription fill information recorded for 3 months after index prescription	NR
Peterson, Wells, 2007	ICs adherence	medical (refill) records	computed as (total days supplied)/(number of days of observation)*100; adherence stratified (0%, 0-80%, ≥80%)	NR
Breekveldt-Postma, 2008	persistence during the first year;	medical (refill) records	computed as number of days from start to time of first failure to continue renewal of initial prescription, based on (number of units dispensed)/(number of units to be used per day as defined in pharmacy)	NR
Janson, 2008	ICs nonadherence during the last 14 days	patient-report, interview	nurse home assessment of ICs prescription and use, based on inspection of current asthma medication and 2 questions: “How many puffs and how many times per day did your doctor tell you to use this?”, “During the past 14 days, how many puffs and how many times per day have you used this?”; dichotomized as adherent (≥7 days of use in previous 14 days) or not	NR
	SABA or LABA overuse	patient-report, interview	nurse home assessment on SABA and LABA prescription and use, dichotomized as overuse (average >8 puffs of SABA or >2 puffs of LABA - single or combination- per day) or adherent	NR
Martínez-Moragón, 2008	frequency of ICs use	patient-report, single item	1 item, not specified, adapted after (37); 4 response options, from “never” to “at least twice a day almost every day”, dichotomized into “almost every day” versus “rarely if ever”	NR
McGann, 2008	"how closely an individual’s medication-taking behaviors, as measured by the DOSER, approximated prescribed use instructions provided by the health care provider"	electronic monitoring	DOSER; ratio of the number of observed correct prescribed use days between day 3 and 14	agreement with other measures (not specified) 84.32%

Menckeberg, 2008	medication acquisition	medical (refill) records	(total days supplied) /(total number of days from first and last refill date)*100	
	medication adherence	patient-report, published scale	MARS (39)	α .81
Wells, 2008	ICs adherence; the proportion of time that the patient had medication available during last 6 months	medical (refill) records	(total days supplied)/(number of days of observation)*100	NR
Axelsson, 2009	medication adherence	patient-report, published scale	MARS (39)	α .71
Bae, 2009	prescription refill adherence	medical (refill) records	(number of ICs refills)/12*100; categorized as appropriate use (>80%), underuse (50-80%), or extreme underuse (<50%)	NR
	subjective self-reported adherence	patient-report, single item	1 item: “How often did you take your ICs as prescribed for last 1 year?”; response on a visual analogue scale from 0% to 100%; categorized as appropriate use (>80%), under-use (50-80%), and extreme under-use (<50%)	NR
Laforest, 2009	Intentional interruption	patient-report, single item	Six items included: (1) accidental interruption, (2) intentional interruption when feeling better, (3) intentional interruption when feeling worse, (4) reduced use when feeling better, (5) more frequent use of ICs in case of preliminary signs of asthma attack and (6) intentional changes of doses independently of physician; analyses performed on intentional (when feeling better) and accidental interruption.	NR
	Accidental interruption	patient-report, single item		
Ponieman, 2009	medication adherence	patient-report, published scale	MARS (39); dichotomised as good adherence (≥ 4.5) or not	α .86
Friedman, 2010	prescription fills	medical (refill) records	total number of prescription refills during the post-index period	NR

	percentage days covered	medical (refill) records	(number of days patients had medication on hand)/(total number of post-index days = 365)*100	NR
Takemura, 2010	self-reported adherence to inhalation regimen	patient-report, published scale (adapted)	modification of RAAS (84) concerning the use of inhaled controller medications; mean adherence score computed; dichotomized as good adherence (≥4.0) or not	NR
Bolman, 2011	medication adherence	patient-report, published scale	MARS (39)	α .89
Emilsson, 2011	medication adherence	patient-report, published scale	MARS (39)	α .77
Small, 2011	physician-perceived compliance; "the extent to which the patients are perceived to follow their physician's prescribing instructions and advice"	physician-report, bespoke scale	2 items (not specified) on physician-perceived patients' compliance regarding frequency of use and inhaler use; 5 response options from 'not at all compliant' to 'fully compliant'	α .92
Suzuki, 2011	ICs adherence	medical (prescription and refill) records	ratio of doses dispensed in the pharmacy divided by prescribed doses documented in medical charts	NR
Foster 2012	Adherence with ICs/LABA	electronic monitoring	Smartinhaler; daily adherence calculated as (no. recorded actuations/no puffs prescribed)*100, capped at 100% and averaged for the last 4 weeks of 2 months monitored	NR
		patient-report, published scale	Morisky adherence scale [ref]	NR
		patient-report, single item	Estimation of own inhaler use (days/week and puff/day) in the last 4 weeks	NR
Ahmedani,	ICs adherence	medical	(total days supplied)/(3-month observation period)*100	NR

2013		(prescription and refill) records		
Axelsson, Cliffordson, 2013	medication adherence	patient-report, published scale	MARS (39)MARS (39)	α .75
Price, Lee, 2013	ICs adherence	patient-report, published scale	MARS (39), categorized as 'low'(´often´ or ´always´ response to any question), 'borderline' (´sometimes´ responses to > 1 question), and 'good' (any other answer)MARS (39), categorized as 'low'(´often´ or ´always´ response to any question), 'borderline' (´sometimes´ responses to > 1 question), and 'good' (any other answer)	NR
Price, Thomas 2013	ICs adherence	Medical (prescription) records	(total days supplied)/(365-day observation period)*100	NR
Schatz, 2013	Questionnaire low adherence	patient-report, published scale	Response to 'how often are you actually taking your IC medication now' compared to response to 'based on your doctor's most recent instructions, how often were you advised to be taking your IC medication now' (less frequently)	NR
	Percent of days covered	Medical (refill) records	Days' supply of dispensed canisters over the follow-up at 3, 6, and 12 months	NR
Wells, 2013	ICs adherence	medical (prescription and refill) records	Continuous multiple-interval measure of medication availability = number of days' supply for each fill/total number of days between the present and next fill; averaged for the observation period	NR
Baddar, 2014	Compliance with controller treatment	Interview cross-checked with electronic patient records	Good = taking 100% of daily prescribed medication & ≤ 2 missed doses/administrations per week; partial = taking more or less than their daily prescribed medication; poor = any other inhaler use patterns	NR
Federman,	ICs adherence	Dose count	Review of dose counters for all dry powder inhaler devices during the first 3	NR

2014 [ref]			months and 30 days after each new prescription; dichotomized as < and ≥80%	
Taylor, 2014	Adherence to ICs prescriptions	Medical (prescription) records	Prescription possession ratio = (number of days prescribed during calendar year)/(number of days in the interval)*100	NR
van Steenis, 2014	ICs adherence	patient-report, published scale (adapted)	Morisky adherence scale [ref], adapted	NR
	ICs adherence	Medical (refill) records	Proportion of days covered = (number of days supply)/(365 or truncated if medication gap ≥ 182)*100; dichotomized as < and ≥80%	NR

Note**:** Abbreviations are: ICs: inhaled corticosteroids; LABA: long-acting $beta_2$-agonists; SABA: short-acting $beta_2$- agonists; MDI: metered-dose inhaler; RAAS: Revised Asthma Adherence Scale; MARS: Medication Adherence Rating Scale; NR: not reported; α: Cronbach's α test.

As most results focused on implementation of controller medication, we chose to summarize these both graphically and in text (Figures 2 and 3). The results on controller initiation and persistence and on reliever use were limited and therefore only described textually.

Determinants of controller medication adherence

Initiation: Determinants of controller initiation were examined in one study (56) that reported a higher probability of non-initiation for patients of younger age, female, of African-American ethnicity (versus white), and with fewer SABA fills in the preceding year. No associations were found with socio-economic status, comorbidity, costs of treatment, and various health care utilisation indicators.

Implementation: We identified 544 results in 47 studies, of which 457 relationships between a determinant and an adherence measure could be assessed in terms of significance and direction of relationship. Figures 2 provides details on the WHO determinant sub-dimensions with at least three results; as different measures of adherence may lead to different associations with determinants, we distinguished between objective measures, medical records, and subjective reports with each type of measure. Results from higher quality studies are presented separately in Figure 3. Determinants with less than three results are described briefly only in text.

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INSERT Figure 2 ABOUT HERE

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INSERT Figure 3 ABOUT HERE

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Social and economic factors were investigated in 15 studies. Higher income was related to adherence in three of eight results reported (35,41,54–56,58–60), more prescription coverage in one of four results (35,41,46,60), lower treatment costs in two of seven results (48,55,56,62,78), and less perceived social norms in one of three results (69,73,78). Several other variables were reported as unrelated to adherence less than three studies: geographical area (48), urban location (60), immigration

status (53), crime rate in area of residence (55), social modelling (69), and social support (41,69). Minority status was related to adherence in one study (35), and employment status in one of two studies (53,60).

Eight studies examined **health care team and system factors**, with education provision relating to adherence in three of four results (33,46,68). Several other variables were examined in less than three studies: lower adherence was linked to inability to get an appointment when needed in one study (62), to patient-provider communication in one of two studies (35,41), and to the time interval being registered with the same prescriber in one study (82), while receiving a prescription from a specialist versus a generalist was unrelated to adherence (60).

Therapy-related factors were investigated in 18 studies. Adherence was mostly unrelated to the number of drugs in the treatment regimen (three of four results; (64,71,79), the number of daily doses (five of seven results; (40,48,65,68,79), and having reliever inhalers prescribed (four of five results; (35,48,49,65). Using dry-powder versus metered-dose inhalers (DPIs and MDIs) was linked to adherence in two of four results (67,68). Some variables examined in a single study were unrelated to adherence: prescribed use of peak flow meter or action plan (46), treatment duration (68), using various other drugs (45,49,53,58,65), using autohalers versus other MDIs (40). Other single-study variables were related to higher adherence: using diskus DPIs versus diskhaler DPIs (50), using ultrafine versus large-particle formulation (77), not using a spacer (53), and receiving more refills in a prescription (48). Three studies have compared ICs/LABA regimens with different types of alternative regimens and reported better adherence to ICs/LABA compared to ICs and/or LABA and/or SABA (63), and compared to ICs in monotherapy or in combination with LABA or montelukast (47), but no differences in intentional or accidental non-adherence between ICs/LABA and ICs+LABA regimens (65).

Condition-related factors were investigated in 26 studies, with non-significant results regarding asthma duration (nine results (35,36,39,42,46,53,62,68), pulmonary function (six of eight results; (35,41,46,52,58,59), and presence of current symptoms (19 of 22 results; (35,36,42,44,46,49,53,58,59,62,63,65,71,80,83). Asthma exacerbations showed 13 non-significant (35,41,49,56,58,68,74,82), but also five positive (37,56,74,82) and six negative associations (53,68,71) with adherence. Higher health-related quality of life was associated with better adherence in four of 11 results (46,58,63,65,68,71), and higher asthma severity was linked to better adherence in five results (49,69,72,79,82), compared to one negative (82) and 6 nonsignificant results (41,53,65,71,72)

Patient-related factors were investigated in 40 studies. Patient demographics such as age and gender were included in numerous studies. Older age related to better adherence in 16 of 28 results

(33,35,36,39,41,42,46,48,53–56,58,59,62,64,65,68,70,71,73,74,79,82,83). Gender showed 24 non-significant results (35,39,41,42,46,48,49,53–56,58–60,62–65,68,69,71,72,74,80,83), females showing better adherence in three results (42,48,54) and males in other three (62,73,79). Being of white ethnicity was linked with better adherence in five of ten results (41,49,55,56,58,60,62,71,74,79), while participants with higher education levels were more adherent in four of ten results (35,39,41,46,49,53,54,58–60).

Few studies found significant roles of variables related to patients' general health status. Smoking status was consistently unrelated to adherence (41,49,53,58,59,64,65,72), as was depression (41,46,58,59). Higher comorbidity was associated with better adherence in two of eight results (48,49,55,56,58,64), while less health care utilisation was linked to better adherence in two of 11 results (35,39,41,56,71). Asthma knowledge was found unrelated to adherence (33,54), while medication knowledge was reported as related to adherence only in one of five results (35,41,62,78). Asthma beliefs (i.e. perceptions of the asthma impact in terms of severity, consequences, timeline, etc.) showed inconsistent relations with adherence, with eight positive (36,37,42,54,73), ten nonsignificant (36,39,42,54,58,59), and one negative result (39).

The role of treatment beliefs was studied extensively. Stronger beliefs in the necessity of using inhalers were associated with better adherence in 14 of 16 results (39,41,54,61,62,66,70,75,78,83), beliefs in their effectiveness in four of seven results (36,41,53,54,78), while more broadly-framed positive beliefs in inhaler usefulness or benefits in one of three results (35,35). Having fewer concerns about medication was related to better adherence in nine of 17 results (39,41,61,65,66,69,73,75), lower perceived side effects in two of four results (73,78), lower beliefs that medication in general is overused in one of three results (61,78), and stronger beliefs in inhaler necessity relative to concerns in two of three studies (69,70,73). Readiness to use inhalers showed positive associations to adherence in three results (38,62), indicators of self-efficacy in four of nine results (33,36,41,58,66,69) , and stronger adherence routines in three results (54,69,73). A better ability to perceive asthma symptom changes was related to adherence in three of five results (52,59), while lower confidence in the ability to monitor symptoms was related to adherence in one of three results (42,54).

Numerous other patient-level variables were examined in less than three studies, most with nonsignificant results: general health status and body mass index (58), marital status (49), number of causal attributions for asthma (39), extent of attributing asthma to internal causes (42), general health self-efficacy (66), self-control (46), and various personality and medical history characteristics (35,40,46,53,59,63,69,70,72,74,75). Several exceptions referred to better adherence in people who

consider medication as less harmful (two results; (61), display lower neuroticism, higher agreeableness and conscientiousness (one of two results; (70,75), and believe stronger that their asthma can be controlled (39,42). Several single results showed better adherence in people with a family history of asthma (72), asthma onset at younger age (59), lower impulsivity (63), high literacy (81). Other single findings suggested that more adherent people attribute their asthma more to external factors (42), believe that God is less in control of their health and attribute more control to physicians (74), perceive themselves less vulnerable to side effects, report higher intention to use inhalers (73), have better inhaler use skills (80), are more satisfied with the device (71), prefer to use inhalers rather than pills (33), have no preferences regarding daily inhaler dosage (76), believe stronger in participating actively in care (37), and report no symptom improvement due to herbal drugs (53).

Persistence: Controller persistence determinants were investigated in three studies, and results are presented here per study. Patients receiving prescriptions from a specialist, using MDIs, having a lower dose recommended, once-daily dosing frequency, having used LABAs in the previous year, and having had previous asthma-related hospitalizations were more likely to persist using single ICs treatment during one year, while adolescents and patients with more than twice daily dosing frequency were more likely to discontinue (57). For ICs/LABA therapy, persistence was less likely for adults compared to children, for people with longer therapy duration, higher daily dose, and having used antibiotics in the previous year (57). Patients using ICs/LABA were more likely to persist with therapy compared to those using ICs+LABA, as were male patients, older, receiving social assistance, with lower daily dosage, receiving prescriptions from a specialist, and using more medications currently and in the previous year (51). Time to discontinuation of ICs/LABA therapy was longer for male patients, older, paying moderately for treatment, having more refills included in the first prescription, having prescriptions also for other conditions, and having had relievers prescribed before study start (48).

Determinants of reliever use

Reliever use recommendations was examined in three studies. Reliever overuse (as indicator of non-adherence to reliever recommendations) was linked to increased symptoms in two of three results (44,58), to older age in one of two results (43,58), and to lower education, higher self-perceived asthma severity and lower general health status in one study (58). Other factors were unrelated to overuse (e.g. gender, ethnicity, socio-economic status, smoking status, and various health status indicators).

Study quality

The 51 studies received relatively good quality scores regarding participant selection methods and measurement of variables, with 19 and 14 studies receiving the maximum score respectively (Table 3; Supplementary Material 4). Scores were considerably lower on appropriateness of data analysis, measures taken to protect against bias, study size justification and clarity of definitions for the variables included. Common limitations in reporting patient selection were omitting methods of sampling and checking eligibility, and not specifying response rates. The concept definitions often overlapped with the description of measurement methods, or only variable labels were reported. Many studies did not describe measurement methods for all main variables. The majority of studies did not mention any source of bias, and none gave a clear sample size justification or reported optimally on study size decisions. Some studies reported power computations for unspecified analyses, did not correct for multiple comparisons, dichotomized adherence scores without giving a valid rationale, did not control for potential confounders, and offered unclear descriptions of statistical procedures. Inter-rater agreement for the six quality rating criteria (Table 3) were poor to moderate, but all discrepancies were resolved through discussion between the two coders. Participant selection methods, measurement of variables, clarity of variable definitions, and appropriateness of analyses formed a homogenous scale, with a homogeneity and standard error of H(S.E.)=.64(.07). Performance on the two remaining criteria (addressing bias and justifying sample size) was only weakly related to the quality scores on the other four criteria (item properties not shown for brevity).

Table 3. Study quality – frequencies and inter-rater agreement for quality criteria (N=51)

Quality criterion	Unknown (no description available)	Low (unclear and/or not appropriate)	Medium (mostly clear and appropriate, with few omissions)	High (clear and appropriate)	Inter-rater agreement (weighted Kappa)
Participant selection	0	10	22	19	.41
Definition of variables	2	11	35	33	.31
Measurement of variables	0	16	21	14	.38
Addressing sources of bias	27	14	8	2	.38

Study size	29	19	5	0	.17
Data analysis	0	24	19	8	.33

Discussion

This systematic review aimed to qualify and synthesize the observational evidence on determinants of inhaled medication adherence in adults with asthma. In the 51 studies included, patient-related factors associated with controller implementation were the most frequently studied, and health care team and system factors the least; the more robust evidence linked stronger treatment necessity beliefs to better implementation. The few studies assessing controller initiation and persistence mainly suggests a possible influence of therapy-related factors and patient demographics. Studies on reliever use were scarce, with reliever overuse related to several patient-related factors. This limited evidence offers only provisional guidance for developing inhaler adherence interventions. Furthermore, the findings regarding each adherence determinant and behaviour should be interpreted with caution and within each study context due to the heterogeneity among studies. Our review reveals important knowledge gaps that need to be addressed in the coming years, and also highlights crucial methodological limitations that can inform researchers regarding concrete steps to take for accumulating sound evidence in future studies.

Regarding the results on determinants of controller use implementation, the substantial focus on patient-related determinants was noted in previous reviews in asthma (19,20) and in other chronic conditions (85–87), and reflects an interest in both identifying at-risk groups and understanding patient perspectives as proximal determinants of patient behaviours. Demographic and clinical characteristics and patients' knowledge of asthma and of medication were generally unrelated to controller use, except a possible higher risk of non-adherence in younger adults. Treatment necessity beliefs were consistently related to better controller implementation but moderate evidence exists on the role of other positive treatment beliefs and of concerns. These results confirm a previous review on treatment beliefs (20) and support the relevance of addressing patients' views regarding their condition and treatment in adherence interventions.

Determinant categories not related to patients were substantially less studied and should be prioritized in future research. Condition and therapy-related factors seemed unrelated to controller implementation behaviours or showed inconsistent results. Among these factors, several medical outcomes such as asthma exacerbations, severity or symptoms showed contradictory results, suggesting that their relationships with adherence might vary depending on other parameters which would need

careful examination. Despite the relevance of social and economic factors identified in previous reviews (85–87), only financial information was examined more extensively but showed inconsistent results. Limited data was available on the influence of the social environment in adults with asthma, despite the key role of social factors identified in children's asthma management (19) and in adherence to other long-term treatments for chronic conditions in general (85,88). Health care team and system factors were rarely studied, although the improvement of health services for chronic conditions is currently a priority (89) and adherence-enhancing interventions usually include changes in the structure of health care delivery (10). This highlights the need for further research on the structure and content of adherence support in routine clinical care, which can have a major impact on patient behaviours and treatment success rates (90,91). Future studies could also benefit from adopting broader theoretical approaches that also explore factors beyond the individual patient level, such as the Precede-Proceed framework, which would facilitate behaviour change intervention design (92).

The barriers to evidence consolidation identified during the present review raise an important question: what methodological standards would future studies apply to obtain quality evidence on determinants of inhaler adherence? Table 4 summarizes nine main barriers and several recommendations for improvement, formulated considering the existing methodological advice for observational research (26) and adherence research (93) in order to invite further dialogue on this topic. The first barrier identified was the substantial study heterogeneity, not only in sample characteristics but also in variable selection, definition, and measurement, study design, and statistical analyses. Second, the studies lacked a unifying theoretical approach which led to differences in variable selection and thus to many determinants being examined only in single studies, often without a theoretical justification. Third, the results gave limited insight regarding causal influences, as only two studies involved repeated measures of adherence (66,82) and only 17 studies measured determinants before adherence. Moreover, many studies showed limitations in the six quality criteria assessed, although several studies performed well (see Supplementary Material 4). To address these barriers, we endorse the practical recommendations provided in STROBE (26) and provide brief advice based on STROBE and our experience in this review. Theoretical frameworks and taxonomies of adherence behaviours and determinants are available (27,94,95) and should be used more extensively. Conducting research on common theoretical and measurement foundations would allow the field to progress from identifying bivariate or multivariate associations in heterogeneous prediction models towards testing more homogeneous and comprehensive causal models.

Table 4. Barriers and recommendations for a solid evidence base on asthma inhaler adherence determinants

Current limitations	When conducting a new study…
1. Heterogeneity in variable selection, definition and measurement, study design, statistical analyses	- Consider previous similar studies when selecting determinants and behaviours - Clarify variable definitions in relation to previous studies - Consider using established measures of adherence behaviours and determinants if available - Consider using established study designs and data analysis methods if appropriate
2. Limited theoretical basis for variable selection and lack of an integrated theoretical approach	- Use existing behavioural theory to select variables - Focus on testing multi-determinant models instead of a few preferred determinants - If testing new models, clarify the choice and relations with existing theory
3. Lack of robust study designs for causal inferences in most studies	- Prioritize the use of repeated-measures longitudinal designs - Assess adherence determinants prior to behaviours - Choose time lags in which causal influence is likely - Control for other possible causal influences
4. Low or medium quality of participant selection in some studies	- Use prior literature to decide on clear inclusion criteria that allow comparisons with other studies. - Employ systematic procedures for participant selection - Report participant selection procedures clearly and completely
5. Insufficient description of variable definitions and measurement	- Provide a clear rationale and description for variables included - Provide comprehensive descriptions of measurement tools or methods in manuscript or supplementary materials
6. Low quality of measurement	- Select or develop psychometrically sound measures - Examine psychometrics as preliminary analyses - Report results of psychometric evaluation
7. Sources of bias rarely addressed	- Reflect on possible sources of bias (e.g., response, recall, surveillance bias) and take steps to minimize their effect
8. Study size rarely addressed	- Consider the probability of type I and type II errors given the research question, population, and resources available
9. Low or medium quality of data analysis procedures in most studies	- Consult methodological literature relevant for the analyses intended - Perform and report on preparatory analyses (e.g. missing data) - Do not group continuous data unless solid justification exists and analyses are performed with both continuous and grouped data - Control for possible confounders and justify their selection - Adjust for sampling strategy and hierarchical data structures

Beyond the practical recommendations for future inhaler adherence studies, our review also highlighted the need to develop consensus on several methodological aspects. The fact that few studies reported on variable definitions, sources of bias and study size suggests that many researchers might not be aware of their importance for observational studies. The latter two aspects were unrelated to the overall study quality, suggesting that even in higher-quality studies, bias and sample size are not systematically considered. More discussion is needed among methodologists and researchers to establish their relevance and specify concrete steps to implement them. These results add to previously-expressed concerns regarding the lack of validated tools to evaluate quality in observational studies (23), and highlight a general need for further detailing and clarifying methodological guidelines in this area. Our experience with coding quality exposed the difficulties of assessing these broad criteria given the diversity of designs and brief descriptions permitted by space constraints. We would therefore encourage adherence-specific methodological guidelines that can be reported in a standard format as supplementary materials in published studies.

Our review has several limitations. First, interpreting the summary based on both adjusted and unadjusted results requires caution, as multivariate analyses control for different sets of confounders, while bivariate analyses ignore any additional influences and may reflect biased relationships. We chose to prioritize adjusted over unadjusted data to avoid this, but we acknowledge that the findings may be biased and we recommend the use of theory-based models to provide more valid and replicable results. Second, inter-rater reliability for quality scores was low, which may reflect suboptimal study reporting, difficulty of applying the criteria based on the given definitions, or insufficient training of coders. Although the coders were able to reach consensus, these difficulties illustrate the need for more concrete definitions applicable across studies by coders with diverse research backgrounds. Third, we focused our review on developed nations, as the contribution of determinant dimensions on adherence may be different in developing nations, particularly regarding access to care (87) but only nineteen studies were excluded based on this criterion. Last, meta-analyses were not possible due to the substantial heterogeneity, therefore we opted for a qualitative summary and for identifying methodological improvements that would make future studies more amenable to meta-analytic approaches.

Our findings suggest that adults with asthma implement controller use recommendations better if they believe stronger in the necessity of using inhalers, and possibly if they hold other positive beliefs and less concerns about using inhalers. Younger adult patients may be more at risk of non-adherence.

Other patient-, condition-, and therapy-related factors are either mostly unrelated to adherence, or partly studied, and little is known about the role of social, economic and health care factors. Initiation and discontinuation of controller use, and reliever use behaviours were scarcely explored. Moreover, the methodological limitations identified diminish the strength of current evidence. Our key recommendations for further research are to improve methodology and use established theoretical frameworks, which should enable the development of a cumulative evidence-base of causes of non-adherence to asthma inhalers among adults.

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Statement of interest

None declared.

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Captions

Figure 1. Flow diagram of article selection process

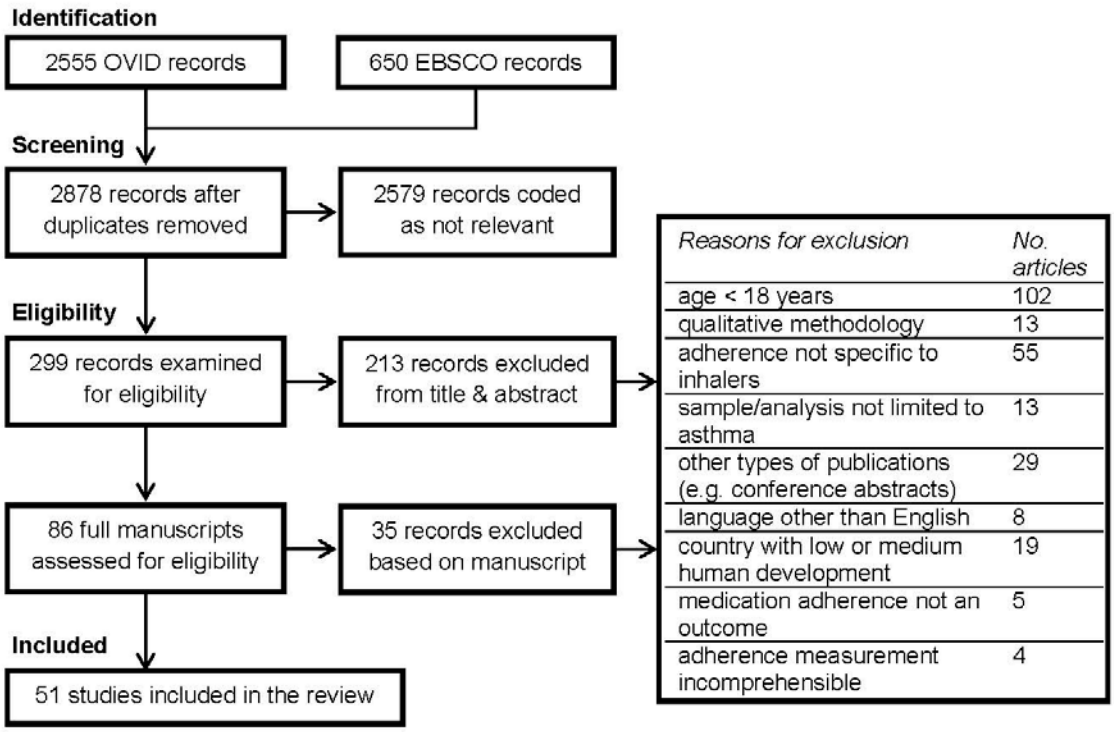

Figure 2. Determinants of controller implementation - number of positive, nonsignificant and negative relations with adherence indicators for determinants with three or more results identified.

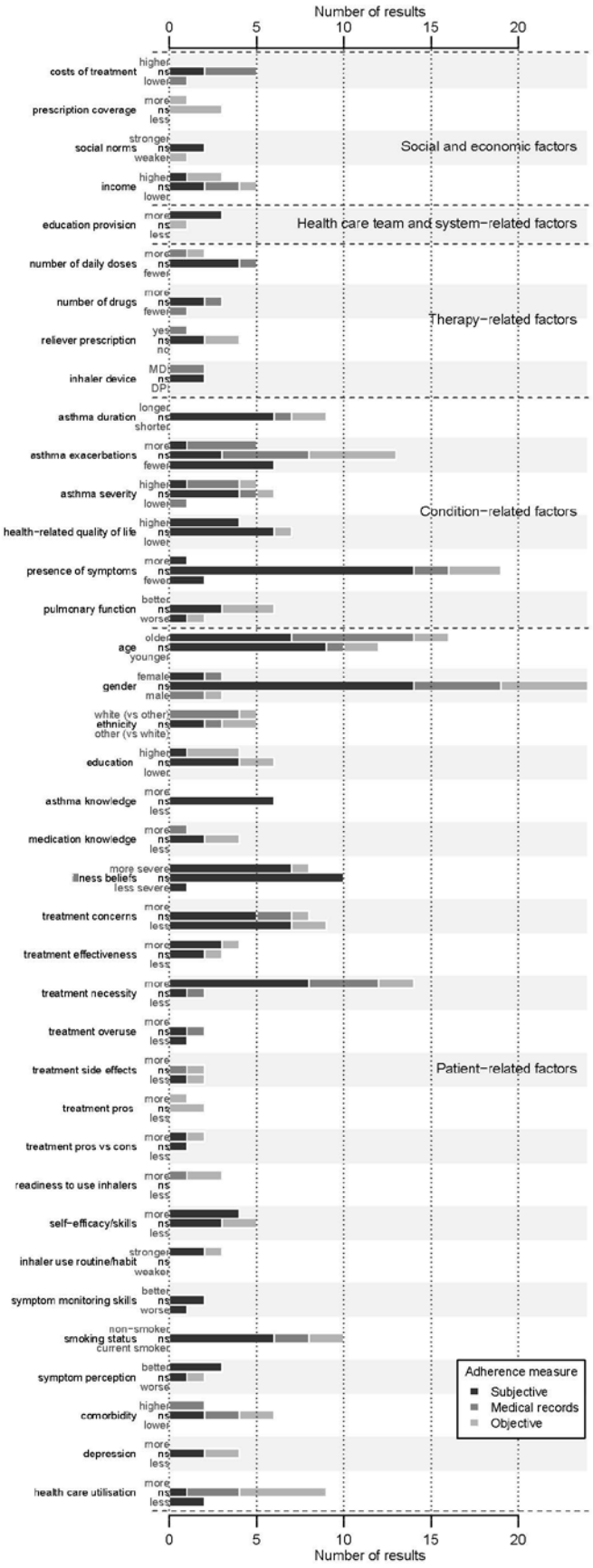
Number of results
0
5
10
15
20
costs of treatment
higher
ns
lower
prescription coverage
more
ns
less
social norms
stronger
ns
weaker
income
higher
ns
lower
Social and economic factors
education provision
more
ns
less
Health care team and system−related factors
number of daily doses
more
ns
fewer
number of drugs
more
ns
fewer
reliever prescription
yes
ns
no
inhaler device
MDI
ns
DPI
Therapy−related factors
asthma duration
longer
ns
shorter
asthma exacerbations
more
ns
fewer
asthma severity
higher
ns
lower
health−related quality of life
higher
ns
lower
presence of symptoms
more
ns
fewer
pulmonary function
better
ns
worse
Condition−related factors
age
older
ns
younger
gender
female
ns
male
ethnicity
white (vs other)
ns
other (vs white)
education
higher
ns
lower
asthma knowledge
more
ns
less
medication knowledge
more
ns
less
illness beliefs
more severe
ns
less severe
treatment concerns
more
ns
less
treatment effectiveness
more
ns
less
treatment necessity
more
ns
less
treatment overuse
more
ns
less
treatment side effects
more
ns
less
treatment pros
more
ns
less
treatment pros vs cons
more
ns
less
readiness to use inhalers
more
ns
less
self−efficacy/skills
more
ns
less
inhaler use routine/habit
stronger
ns
weaker
symptom monitoring skills
better
ns
worse
smoking status
non−smoker
ns
current smoker
symptom perception
better
ns
worse
comorbidity
higher
ns
lower
depression
more
ns
less
health care utilisation
more
ns
less
Patient−related factors
Adherence measure
Subjective
Medical records
Objective
0
5
10
15
20
Number of results

Figure 3. Determinants of controller implementation (results from higher quality studies) - number of positive, nonsignificant and negative relations with adherence indicators for determinants with three or more results identified.