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

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ABSTRACT Nonadherence to inhaled medication leads to poor asthma control and increased healthcare utilisation. 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 and extracted data, and assessed study quality. Results were summarised qualitatively into social and economic, and healthcare-, 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 cumulative science on the determinants of adherence to asthma inhalers among adults can develop further.

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Introduction

The introduction of inhaled medication as the primary treatment for asthma 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 healthcare expenditure is suboptimal adherence to the prescribed regimen [5–7]. To date, few adherence interventions evaluated in asthma treatment have been found to be (cost-)effective [8–10]. A systematic review of observational evidence on adherence determinants could help identify the patients most at-risk for nonadherence and the key drivers of nonadherence 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 synthesise 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 January 1, 1990 and June 26, 2014 with keywords on asthma, adherence, persistence, compliance, concordance, determinant, cause, influence, barrier and facilitator (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 (aged >18 years) asthma patients living in developed countries [24]; investigating one or more predictor 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 (A.L. Dima and O. Cunillera) examined the search results independently. Disagreements were reconciled by a third reviewer (M. de Bruin) and through consensus.

Data extraction

Two coders (A.L. Dima and O. Cunillera) extracted information on: study characteristics (objectives, methodology, country, language, setting, sample size, age, sex, 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 the papers. The accuracy of the recorded information was verified by the other coder, and disagreements were discussed and reconciled.

Quality rating

Two coders (A.L. Dima and G. Hernandez) rated methodological quality based on six criteria adapted from the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, which are considered key requirements for observational studies [25, 26]. Scoring was performed on a four-level response format, from no information reported to adequate reporting of appropriately used methodology (Supplementary material 2). The studies were judged on clarity of methods 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, and sensitivity analyses). Disagreements were discussed and reconciled.

Data analysis

The data on study characteristics and adherence measurement were summarised descriptively. The results on the relationships between adherence determinants and behaviours were grouped separately for reliever (*e.g.* short-acting β_2-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]: 1) starting treatment (initiation); 2) accuracy of medication use (implementation); and 3) continuing treatment (persistence). Determinants were classified using the five dimensions of the World Health Organization (WHO) taxonomy [26, 27]: 1) social and economic factors, 2) healthcare team and system-related factors, 3) condition-related factors, 4) therapy-related factors, and 5) patient-related factors; each with additional sub-dimensions. We summarised results regarding the statistical significance and direction of relationships for all studies. Adjusted results obtained by multivariate analyses were prioritised over unadjusted when available.

Metric properties of the six study quality items were investigated. Reliability was assessed by estimating inter-rate agreement with weighted kappa, considered appropriate for ordinal scores [28], and interpreted based on established thresholds for poor, fair, moderate, good and excellent agreement (0.20, 0.40, 0.60 and 0.80) [29]. A 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 SPSS version 21 (IBM Corp., Armonk, NY, USA) and the R-project (www.R-project.org) *mokken* package [30, 31].

Results

Study selection

The database search identified 2878 unique articles (fig. 1). The two coders agreed on the selection of 213 articles as potentially relevant (Cohen's κ=0.60). The third coder reviewed 235 disagreements and selected 86 additional articles. Thus, 299 articles were reviewed to confirm they fulfilled all inclusion criteria. 213 articles were excluded based on title and abstract, and a further 35 articles were excluded after full manuscript examination. Finally, 51 studies were included in the review. The reasons for exclusion are presented in figure 1.

Study characteristics

Characteristics of studies are showed in table 1. Most studies were conducted in European countries (n=22) or the USA (n=19). Settings of studies were diverse, and included: primary and secondary care; pharmacies; general population; and various prescription and insurance claims databases. 11 studies used existing databases, while 40 studies collected data directly from patients. 32 studies focused solely on adults (aged >18 years), while 19 studies included adults and children. Sample sizes ranged from 34 to 292 738 participants (median (interquartile range) 204 (906)). Most studies included more females than males. Asthma severity was reported in 16 studies and ranged from mild to severe asthma.

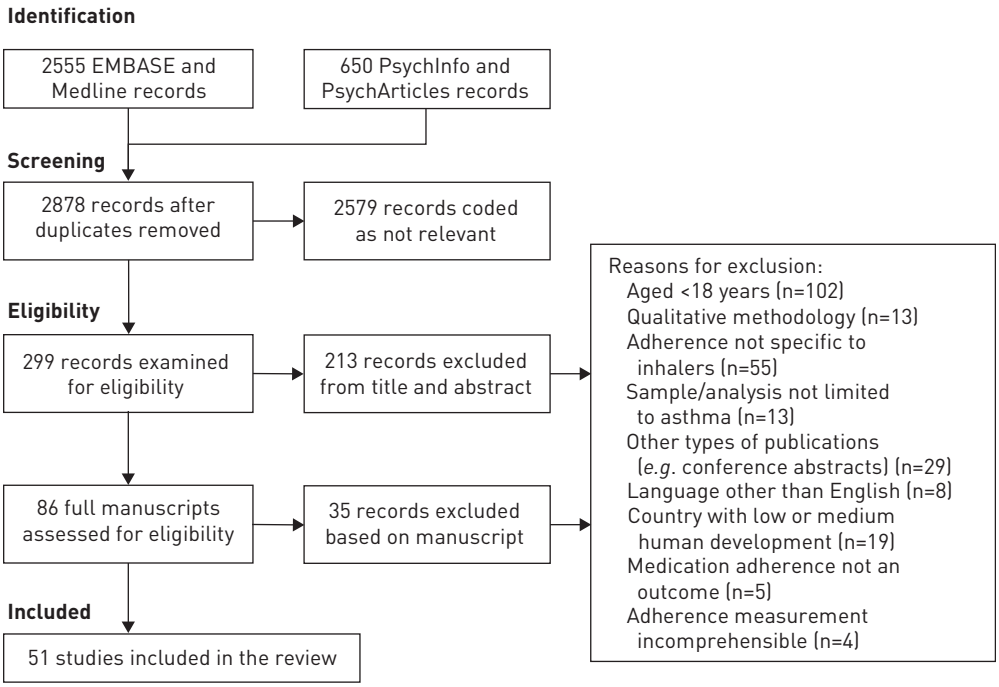

FIGURE 1 Flow diagram of article selection process.

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TABLE 1 Study characteristics of empirical studies on inhaled medication adherence in adults with asthma

First author [ref.]	Country	Year	Objectives	Study design	Data sources	Sample size n	Age years	Females	Asthma severity: FEV_1 %	Inhaled medication
Tettersell [32]	UK	1993	Relationship between knowledge and treatment adherence	Cross-sectional (ASD)	Primary care	100	50.1±20.6	9%	Moderate to severe	NR
Bosley [33]	UK	1995	Psychological factors related to asthma self-reported care and compliance	Prospective (DPA)	Primary care and outpatient clinic	72	45±15	n=62	NR	ICS+LABA, ICS/LABA
Apter [34]	USA	1998	Patient characteristics related to adherence to twice daily ICS treatment	Prospective (DPA and ASD)	Outpatient clinics	50	46±14	n=37 (74%)	75±21	ICS
Bennett [35]	UK	1998	Associations between protection motivation theory factors (health threat, outcome, self-reported efficacy) and adherence to preventive ICS use	Cross-sectional (ASD)	Primary care	71	47±19.25	n=40	NR	ICS
Chambers [36]	USA	1999	Factors associated with regular ICS use	Cross-sectional (ASD)	Primary care	394	Median: 36	75%	NR	ICS
Schmaling [37]	USA	2000	Development of measures to assess psychological factors important to adherence with medication regimens	Cross-sectional (ASD)	Private asthma clinic and hospital	53	36.1±9.6	62.3%	NR	ICS, LABA, SABA
Horne [38]	UK	2002	Relationship between reported adherence to preventer medication and perceptions and asthma medication	Cross-sectional (ASD)	Primary care	100	49.3±18.1	61%	NR	NR
Van Schayck [39]	Netherlands	2002	Influence of inhalation device, patients' inhaler perceptions, daily frequency, and duration of treatment on medication compliance	Prospective (DPA and ASD)	Primary care	34	37±13	n=19	NR	LABA or SABA
Apter [40]	USA	2003	Barriers to adherence as explanations of racial-ethnic differences in adherence	Prospective (DPA and ASD)	Primary and secondary care	85	47±15	n=61 (72%)	65±19	ICS
Jessop [41]	UK	2003	Relationship between cognitive and emotional representations of asthma and adherence to inhaled preventative asthma medication	Cross-sectional (ASD)	Primary care	330	57.2±17.9	n=204 (61.8%)	NR	NR
Labrecque [42]	Canada	2003	Assess compliance to asthma guidelines and influence of age on SABA utilisation	Retrospective (ASD)	Health insurance database claims	987	Range: 5–45	NR	Severe asthma excluded	SABA (with or without ICS)

Continued

TABLE 1 Continued

First author [ref.]	Country	Year	Objectives	Study design	Data sources	Sample size n	Age years	Females	Asthma severity: FEV_1 %	Inhaled medication
Nishiyama [43]	UK	2003	Determine if the Jones Morbidity Index can be used in community pharmacy to identify those who have poor control	Cross-sectional (ASD)	Pharmacy database	306	38.5±20.6	54.5%	NR	ICS and SABA
Balkrishnan [44]	USA	2005	Asthma-related healthcare costs, medication adherence, ICS and newly started on MON *versus* SAL	Retrospective (DPA)	Health insurance database claims	198	22±19.5 MON 24±18.2 SAL	52.5% MON 59.8% SAL	NR	ICS+LABA *versus* ICS +MON
Lacasse [45]	Canada	2005	Describe patterns of compliance and identify factors determining the compliance to ICS in adults	Prospective (DPA and ASD)	NR	124	47±15	n=73	Mild–moderate	ICS
Stempel [46]	USA	2005	Patient adherence with several medication regimens: FP/SAL, FP+SAL, FP+MON, FP, MON	Retrospective (ASD)	Health insurance database claims	3503	38.7±17	64.5%	NR	ICS, LABA, MON
Bender [47]	USA	2006	Factors related to refill adherence to FP/SAL	Retrospective (ASD)	Pharmacy database	5504	54±22	60.2%	NR	ICS/LABA
Chatkin [48]	Brazil	2006	Rate of compliance with preventive treatment for moderate and severe persistent asthma	Prospective (DPA)	Primary care	131	44.4±16.6	71%	Severe persistent	ICS/LABA
Hasegawa [49]	Japan	2006	Comparison between compliance to FP diskus *versus* FP diskhaler	Retrospective (ASD)	Pharmacy database	337	54.2±16.8 FP diskhaler 57.7±18.2 FP diskus	56.3% FP diskhaler 57% FP diskus	NR	ICS
Marceau [50]	Canada	2006	Compare persistence, adherence and effectiveness between patients with asthma starting combination or concurrent therapies (ICS and LABA)	Prospective (DPA and ASD)	Health insurance database claims	5118	32.6±8.2	63.3%	NR	ICS/LABA *versus* ICS +LABA
Ohm [51]	USA	2006	Explore asthma symptom perception and its relationship with adherence to asthma treatment	Cross-sectional (ASD)	Asthma/allergy clinics	120	44.8±9.27	78%	Mild to severe	ICS
Tavasoli [52]	Ireland	2006	Factors related to patients' compliance with prescribed metered dose inhaler drugs	Cross-sectional (ASD)	Outpatient department	160	47.67±12.78	n=105 (65.6%)	NR	ICS, LABA, SABA
Ulrik [53]	Denmark	2006	Patient-related aspects of adherence among adult asthmatics	Cross-sectional (ASD)	Community (web-based panel for market research)	509	Range: 18–45	n=317 (62%)	Mild: 77% Moderate: 12% Severe: 11%	ICS, ICS +LABA

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TABLE 1 Continued

First author [ref.]	Country	Year	Objectives	Study design	Data sources	Sample size n	Age years	Females	Asthma severity: FEV_1 %	Inhaled medication
Williams [54]	USA	2007	Factors associated with ICS adherence among patients with asthma, and among African–American and white patients separately	Retrospective (ASD)	Health maintenance organisation	176	40.8±7.7	n=115 (68.1%)	NR	ICS
Williams [55]	USA	2007	Estimate rates of primary nonadherence and explore associated factors	Retrospective (ASD)	Health maintenance organisation	1064	31.9±16.5	59.8%	NR	ICS
Breekveldt-Postma [56]	Netherlands	2008	Determinants of persistence with ICS	Prospective (DPA)	Pharmacy database	5563	Range: 0–34	51.5–57.2%	NR	ICS, ICS +LABA
Janson [57]	USA	2008	Describe asthma medication adherence, identify predictors of ICS underuse and SABA or LABA overuse	Cross-sectional (DPA and ASD)	Primary and secondary care (random-digit dialling)	158	48.7±7.4 ICS adherent, 46.7±8.5 ICS non-adherent, 46.5±8.8 SABA adherent, 46.2±7.3 SABA over use	68%	NR	ICS and SABA or LABA
Martínez-Moragón [58]	Spain	2008	Relationship between failure to perceive dyspnoea associated with bronchial obstruction and treatment nonadherence in asthmatic patients	Cross-sectional (ASD)	Outpatient respiratory clinics	48	45: range 30–60	50%	Moderate	ICS/LABA
McGann [59]	USA	2008	Relationship between denial of illness and compliance with inhaled controller asthma medications	Prospective (DPA)	Asthma clinics, advertisements, local college	51	42±14.99; range: 18–68	82.3%	NR	NR (controller)
Menckeberg [60]	Netherlands	2008	Relationship between beliefs about ICS (necessity and concerns) and adherence	Cross-sectional/ retrospective (ASD)	Pharmacy database	238	36.2±6.3	67%	NR	ICS
Wells [61]	USA	2008	Factors that contribute to ICS adherence among African–American and white adults with asthma	Retrospective (ASD)	Health maintenance organisation	1006	43.1±10.4	n=716 (71.2%)	NR	ICS
Axelsson [62]	Sweden	2009	Personality traits related to asthma control, health-related quality of life and adherence to regular asthma medication	Cross-sectional (ASD)	Epidemiological study	109	Range: 21–23	61.6%	NR	ICS/LABA, ICS, LABA, SABA

Continued

TABLE 1 Continued

First author [ref.]	Country	Year	Objectives	Study design	Data sources	Sample size n	Age years	Females	Asthma severity: FEV_1 %	Inhaled medication
Bae [63]	South Korea	2009	Baseline information about ICS adherence in Korea, factors related to ICS adherence, clinical implications of ICS adherence for asthma control	Cross-sectional/ retrospective (ASD)	Clinical centres in university hospitals	185	NR	NR	NR	ICS or ICS/ LABA
Laforest [64]	France	2009	Characteristics of patients with interruptions of ICS, intentional or accidental	Cross-sectional (ASD)	Primary care database	204	53.8±19.6	59.3%	All ranges	ICS only or in combination
Ponieman [65]	USA	2009	Impact of potentially modifiable medication beliefs on adherence with ICS therapy across time	Prospective (DPA and ASD)	General internal medicine clinics	261	48±13; range 20–87	82%	Persistent asthma	ICS
Friedman [66]	USA	2010	Adherence and asthma control in adolescents and young adults with mild asthma who began treatment with MF or FP	Retrospective (ASD)	Health insurance claims database	1384	Mean: 16.3 MF; 16.5 FP; range: 12–25	51.3% MF 55.3% FP	Mild	ICS
Takemura [67]	Japan	2010	Assess factors and mechanisms that contribute to and clinical outcomes relating to adherence	Cross-sectional (ASD)	Respiratory clinic	176	57±15	n=89	NR	ICS, ICS/ LABA
Bolman [68]	Netherlands	2011	Explain ICS adherence by the attitude, social influence and self-efficacy model and habit strength (moderation and mediation relationships)	Cross-sectional (ASD)	Pharmacy	139	31.5±5.6	n=98 (70.5%)	NR	ICS
Emilsson [69]	Sweden	2011	Influence of personality traits and beliefs about medicines on asthma medication adherence	Cross-sectional (ASD)	NR	35	52.8±14.7	n=25	NR	ICS/LABA, ICS+LABA, ICS, LABA
Small [70]	UK	2011	Relationship between inhaler satisfaction and patient compliance Influence on health and patient-reported outcomes	Cross-sectional (ASD)	Specialists' and primary care	2135	NR in adults	NR	NR	NR
Suzuki [71]	Japan	2011	Associations between several factors of asthma therapy (patients adherence, asthma severity)	Retrospective (ASD)	University hospital	50	36.3±7.9	46%	NR	ICS

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TABLE 1 Continued

First author [ref.]	Country	Year	Objectives	Study design	Data sources	Sample size n	Age years	Females	Asthma severity: FEV_1 %	Inhaled medication
Foster [72]	Australia	2012	Identify potentially modifiable beliefs and behaviours that predict ICS/LABA adherence	Prospective (ASD)	Community pharmacies, advertising, primary care, volunteer database	99	47.6±15.8	n=57	83%±23%	ICS/LABA
Ahmedani [73]	USA	2013	Relationships between locus of control factors (God, doctors, other people, change and internal) and ICS adherence	Cross-sectional (ASD)	Primary care	1025	37.6±14.8	n=675 (65.9%)	NR	ICS
Axelsson [74]	Sweden	2013	To determine the mediating effects of medication beliefs between personality traits and adherence	Cross-sectional (ASD)	Community	516	47.4±15.6	60%	NR	ICS/LABA, ICS, LABA, SABA
Price [75]	UK	2013	Identify characteristics of patients who prefer once-daily controller regimen	Retrospective (ASD)	Primary care database	3731	45.6±15; range: 2–94	n=2174 (58.3%)	NR	ICS, ICS +LABA
Price [76]	UK	2013	Compare real life effectiveness of extra-fine and larger particle beclometasone	Case–control (DPA)	Primary care databases	30354	Range: 12–80	n=17808 (58.7%)	NR	ICS
Schatz [77]	USA	2013	Develop a questionnaire that reflects nonadherence risk and identifies adherence barriers	Prospective (DPA and ASD)	Health maintenance organisation	420	41.6±9.1	n=280 (66.7%)	NR	ICS, SABA
Wells [78]	USA	2013	Determine whether once daily dosing is associated with higher ICS adherence at least twice daily	Retrospective (DPA)	Health maintenance organisation	1302	28.2±15.8 once daily 31.6±16.0 ⩾twice daily	n=113 (51.1%) once daily n=656 (60.7%) ⩾ twice daily	Low to severe	ICS
Baddar [79]	Oman	2014	Relationships between patient compliance, inhaler technique and asthma control level	Cross-sectional (ASD)	University hospital	218	Range: 12–72	65.1%	NR	ICS, ICS/LABA, ICS +LABA
Federman [80]	USA	2014	Associations of self-management behaviours (*e.g.* medication adherence and inhaler technique) with health literacy	Prospective (DPA)	Outpatient clinics	433	Mean: 67; 45% aged 60–64, 39% aged 65–74, 16% aged ⩾75	83.8%	Moderate or severe	ICS only or in combination

Continued

TABLE 1 Continued

First author [ref.]	Country	Year	Objectives	Study design	Data sources	Sample size n	Age years	Females	Asthma severity: FEV_1 %	Inhaled medication
Taylor [81]	UK	2014	To develop an annual measure of ICS adherence from prescribing data and statistically model ICS adherence controlling for patient factors	Retrospective (DPA)	Primary care database	292738	38.7± 15.4	NR	BTS/SIGN step 2–5	ICS
Van Steenis [82]	Netherlands	2014	Relationship between ICS necessity and concerns, beliefs and subjectively and objectively measured adherence and the agreement between these measures	Cross-sectional (ASD)	Pharmacy	93	43.7±14.5; range: 18–77	n=55 (59.1%)	NR	ICS only or in combination

Data are presented as mean±SD, unless otherwise stated. FEV_1: forced expiratory volume in 1 s; ASD: adherence simultaneous with determinants measurement; NR: not reported; DPA: determinants preceding adherence measurement; ICS: inhaled corticosteroids; LABA: long-acting β_2-agonists; SABA: short-acting β_2-agonists; MON: montelukast; SAL: salmeterol; FP: fluticasone proprionate; MF: mometasone furoate; BTS: British Thoracic Society; SIGN: Scottish Intercollegiate Guidelines Network.

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20 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-acting β_2-agonists (LABA) or 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 [65] or retrospectively [81]. All other studies collected data cross-sectionally, retrospectively or prospectively (n=22, n=16 and n=12 studies, respectively) and analysed relationships between determinants and single adherence measures.

There were substantial differences between studies in operationalisation and measurement of both adherence determinants and behaviours (Supplementary material 3). Of the 68 adherence behaviour assessments (several studies used multiple measures) (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. 15 of the patient-reported adherence assessments applied validated questionnaires, such as the Medication Adherence Rating Scale [38] and Revised Asthma Adherence Scale [83], while the remainder used self-constructed nonvalidated questionnaires.

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

Determinants of controller medication adherence

Initiation

Determinants of controller initiation were examined in one study that reported a higher probability of non-initiation for younger patients, females, African–American ethnicity (*versus* white), and with fewer SABA fills in the preceding year [55]. No associations were found with socioeconomic status, comorbidity, costs of treatment and various healthcare 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. Figure 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 measurement. Results from higher quality studies are presented in figure 3. Determinants with less than three results are only described briefly in the text.

Social and economic factors were investigated in 15 studies. Adherence was related to higher income in three out of eight reported results [34, 40, 53–55, 57–59]; more prescription coverage in one out of four results [34, 40, 45, 59]; lower treatment costs in two out of seven results [47, 54, 55, 61, 77]; and lower perceptions of social norms in one out of three results [68, 72, 77]. Several other variables were identified in fewer than three results and were found to be unrelated to adherence: geographical area [47]; urban location [59]; immigration status [52]; crime rate in area of residence [54]; social modelling [68]; and social support [40, 68]. Minority status was related to adherence in one result [34], and employment status in one out of two results [52, 59].

Eight studies examined healthcare team and system factors, with education provision relating to adherence in three out of four results [32, 45, 67]. Several other variables were examined in fewer than three results: lower adherence was linked to inability to get an appointment when needed in one result [61], to patient–provider communication in one out of two results [34, 40], and to the time interval being registered with the same prescriber in one result [81], while receiving a prescription from a specialist *versus* a generalist was unrelated to adherence [59].

Therapy-related factors were investigated in 18 studies. Adherence was mostly unrelated to the number of drugs in the treatment regimen (three out of four results; [63, 70, 78]), the number of daily doses (five out of seven results; [39, 47, 64, 67, 78]), and having reliever inhalers prescribed (four out of five results [34, 47, 48, 64]). Using dry-powder inhalers (DPIs) *versus* metered-dose inhalers (MDIs) was linked to adherence in two out of four results [66, 67]. Some variables examined in a single result were unrelated to adherence: prescribed use of peak flow meter or action plan [45]; treatment duration [67]; using various other drugs [44, 48, 52, 57, 64]; using autohalers *versus* other MDIs [39]. Other single result variables were related to higher adherence: using diskus DPIs *versus* diskhaler DPIs [49]; using ultrafine *versus* large-particle formulation [76]; not using a spacer [52]; and receiving more refills in a prescription [47]. Three studies compared ICS/LABA regimens with different types of alternative regimens and reported

TABLE 2 Definition and measurement of adherence behaviours in the studies reviewed

First author [ref.]	Year	Adherence definition/term	Assessment method	Details	Validity/ reliability
Tettersell [32]	1993	Taking inhalers as prescribed	Patient-reported, single item	One item: "do you take your inhalers as prescribed?"; four 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 [33]	1995	Noncompliance; taking <70% of prescribed doses or omitting all doses for ⩾1 week	Electronic monitoring	Turbuhaler Inhalation Computer; computed for two 6-week periods as (no. of doses taken)/(no. of doses prescribed)×100	NR
Apter [34]	1998	Use of ICS in the last 35 days	Electronic monitoring	MDI_{log}, last 35 of 42 days considered, computed for 12-h periods as (recorded – prescribed actuations)×100; mean truncated adherence computed per subject; dichotomised (<or>70%)	NR
Bennett [35]	1998	Adherence to preventive ICS use	Patient-reported, published scale	RAAS [83]	α=0.75
Chambers [36]	1999	Frequency of ICS use	Patient-reported, single item	Item content not specified, four 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"; dichotomised into "regular, twice daily" and "less than regular"	NR
Schmaling [37]	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 [38]	2002	Medication adherence	Patient-reported, published scale	MARS [38]	α=0.85
van Schayck [39]	2002	Medication compliance rate	Canister weighting	Medication used as a percentage of medication prescribed	NR
Apter [40]	2003	Use of ICS in the last 42 days	Electronic monitoring	MDI_{log}, 42 days, computed for 12-h periods as (recorded – prescribed actuations)×100; mean truncated adherence computed per subject; divided into four categories (<20%, 20–<50%, 50–<75%, 75–100%)	NR
Jessop [41]	2003	Adherence to preventative inhaled medication in the last 3 months	Patient-reported, published scale (adapted)	RAAS [83] and two extra items on accidental nonadherence	α=0.92
Labrecque [42]	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

Continued

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TABLE 2 Continued

First author [ref.]	Year	Adherence definition/term	Assessment method	Details	Validity/ reliability
Nishiyama [43]	2003	Reliever compliance	Patient-reported, interview	Patients were required to state the drugs and dosage regimens they used; their reports were compared with prescription information; three values were coded: "good"; "overused"; "underused" (first two also applied to reliever)	NR
		Preventer compliance	Patient-reported, interview		NR
Balkrishnan [44]	2005	Adherence to controller pharmacotherapy	Medical (refill) records	Computed as: (days of prescription supply dispensed)/(days between prescription refills – number of days person was hospitalised); dichotomised as compliant (0.5–1.5) or not	NR
Lacasse [45]	2005	Non-compliance	Electronic monitoring	MDI_{log}; calculated for 12 weeks daily as proportion of prescribed daily dose actually inhaled; dichotomised as compliant (>75%) or not	NR
Stempel [46]	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 [47]	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 [48]	2006	Compliance	Canister weighting	(Total quantity of medication used)/(quantity prescribed, *i.e.* three canisters in 3 months); dichotomised as compliant (>85%) or not	NR
Hasegawa [49]	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 [50]	2006	Persistence *versus* discontinuation: having prescriptions continuously renewed within the period	Medical (refill) records	Computed as the sum of three 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 [51]	2006	Use of ICS+LABA	Electronic monitoring	Advair diskhaler; computed as (number of counted doses)/(number of prescribed doses)×100; dichotomised as good adherence (⩾80%) or not	NR
		Medication adherence	Patient-reported, published scale	MARS [38]	NR

Continued

TABLE 2 Continued

First author [ref.]	Year	Adherence definition/term	Assessment method	Details	Validity/ reliability
Tavasoli [52]	2006	Compliance to prescribed MDI drugs	Patient-reported, interview	Four 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 [53]	2006	Intentional nonadherence	Patient-reported, single item	One item: "how often do you decide not to take your controller medication?"; five 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-reported, single item	Item not specified; responses reported on a three-level scale: taking controller therapy as prescribed, less, or more than prescribed	NR
Williams [54]	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 [55]	2007	Primary non-adherence	Medical (refill) records	No prescription fill information recorded for 3 months after index prescription	NR
		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 [56]	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 [57]	2008	ICS nonadherence during the last 14 days	Patient-report, interview	Nursing home assessment of ICS prescription and use, based on inspection of current asthma medication and two 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?"; dichotomised as adherent (⩾7 days of use in previous 14 days) or not	NR
		SABA or LABA overuse	Patient-reported, interview	Nursing home assessment on SABA and LABA prescription and use, dichotomised as overuse (average >8 puffs of SABA or >2 puffs of LABA -single or combination- per day) or adherent	NR

Continued

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TABLE 2 Continued

First author [ref.]	Year	Adherence definition/term	Assessment method	Details	Validity/ reliability
Martínez-Moragón [58]	2008	Frequency of ICS use	Patient-reported, single item	One item, not specified, adapted after (37); four response options, from "never" to "at least twice a day almost every day", dichotomised into "almost every day" *versus* "rarely if ever"	NR
McGann [59]	2008	"How closely an individual's medication taking behaviours, as measured by the DOSER, approximated prescribed use instructions provided by the healthcare 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 [60]	2008	Medication acquisition	Medical (refill) records	(Total days supplied)/(total number of days from first and last refill date)×100	
		Medication adherence	Patient-reported, published scale	MARS [38]	α=0.81
Wells [61]	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 [62]	2009	Medication adherence	Patient-reported, published scale	MARS [38]	α=0.71
Bae [63]	2009	Prescription refill adherence	Medical (refill) records	(Number of ICS refills)/12×100; categorised as appropriate use (>80%), underuse (50–80%), or extreme underuse (<50%)	NR
		Subjective self-reported adherence	Patient-reported, single item	One item: "how often did you take your ICS as prescribed for last 1 year?"; response on a visual analogue scale from 0% to 100%; categorised as appropriate use (>80%), underuse (50–80%), and extreme underuse (<50%)	NR
Laforest [64]	2009	Intentional interruption	Patient-reported, 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-reported, single item		
Ponieman [65]	2009	Medication adherence	Patient-reported, published scale	MARS [38]; dichotomised as good adherence (⩾4.5) or not	α=0.86
Friedman [66]	2010	Prescription fills	Medical (refill) records	Total number of prescription refills during the post-index period	NR
		Percentage of days covered	Medical (refill) records	(Number of days patients had medication on hand)/(total number of post-index days=365)×100	NR

Continued

TABLE 2 Continued

First author [ref.]	Year	Adherence definition/term	Assessment method	Details	Validity/ reliability
Takemura [67]	2010	Self-reported adherence to inhalation regimen	Patient-reported, published scale (adapted)	Modification of RAAS [83] concerning the use of inhaled controller medications; mean adherence score computed; dichotomised as good adherence (⩾4.0) or not	NR
Bolman [68]	2011	Medication adherence	Patient-reported, published scale	MARS [38]	α=0.89
Emilsson [69]	2011	Medication adherence	Patient-reported, published scale	MARS [38]	α=0.77
Small [70]	2011	Physician-perceived compliance; "the extent to which the patients are perceived to follow their physician's prescribing instructions and advice"	Physician-reported, bespoke scale	Two items (not specified) on physician-perceived patients' compliance regarding frequency of use and inhaler use; five response options from "not at all compliant" to "fully compliant"	α=0.92
Suzuki [71]	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 [72]	2012	Adherence with ICS/LABA	Electronic monitoring	Smart inhaler; 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-reported, published scale	Morisky adherence scale [84]	NR
			Patient-report, single item	Estimation of own inhaler use (days/week and puffs per day) in the last 4 weeks	NR
Ahmedani [73]	2013	ICS adherence	Medical (prescription and refill) records	(Total days supplied)/(3-month observation period)×100	NR
Axelsson [74]	2013	Medication adherence	Patient-reported, published scale	MARS [38]	α=0.75
Price [75]	2013	ICS adherence	Patient-reported, published scale	MARS [38], categorised as "low"("often" or "always" response to any question), "borderline" (´sometimes´ responses to > 1 question), and "good" (any other answer)	NR
Price [76]	2013	ICS adherence	Medical (prescription) records	(Total days supplied)/(365-day observation period)×100	NR
Schatz [77]	2013	Questionnaire low adherence	Patient-reported, published scale	Response to "how often are you actually taking your ICS medication now" compared to response to "based on your doctor's most recent instructions, how often were you advised to be taking your ICS 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 [78]	2013	ICS adherence	Medical (prescription and refill) records	Continuous multiple-interval measure of medication availability equals number of days' supply for each fill/total number of days between the present and next fill; averaged for the observation period	NR

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TABLE 2 Continued

First author [ref.]	Year	Adherence definition/term	Assessment method	Details	Validity/ reliability
Baddar [79]	2014	Compliance with controller treatment	Interview cross-checked with electronic patient records	Good equals taking 100% of daily prescribed medication and ⩽2 missed doses/administrations per week; partial equals taking more or less than their daily prescribed medication; poor equals any other inhaler use patterns	NR
Federman [80]	2014	ICS adherence	Dose count	Review of dose counters for all dry powder inhaler devices during the first 3 months and 30 days after each new prescription; dichotomised as <80% and ⩾80%	NR
Taylor [81]	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 [82]	2014	ICS adherence	Patient-reported, published scale (adapted)	Morisky adherence scale [84], adapted	NR
		ICS adherence	Medical (refill) records	Proportion of days covered: (number of days' supply)/(365 or truncated if medication gap ⩾182)×100; dichotomised as <80% and ⩾80%	NR

NR: not reported; ICS: inhaled corticosteroids; RAAS: Revised Asthma Adherence Scale; MARS: Medication Adherence Rating Scale; MDI: metered-dose inhaler; SABA: short-acting β_2-agonists; LABA: long-acting β_2-agonists; α: Cronbach's α test.

better adherence to ICS/LABA compared to ICS and/or LABA and/or SABA [62], and compared with ICS in monotherapy or in combination with LABA or montelukast [46], but no differences in intentional or accidental nonadherence between ICS/LABA and ICS+LABA regimens [64].

Condition-related factors were investigated in 26 results, with nonsignificant results regarding asthma duration (nine results [34, 35, 38, 41, 45, 52, 61, 67]), pulmonary function (six out of eight results [34, 40, 45, 51, 57, 58]), and presence of current symptoms (19 out of 22 results [34, 35, 41, 43, 45, 48, 52, 57, 58, 61, 62, 64, 70, 79, 82]). Asthma exacerbations showed 13 nonsignificant [34, 40, 48, 55, 57, 67, 73, 81], but also five positive [36, 55, 73, 81] and six negative associations [52, 67, 70] with adherence. Higher health-related quality of life was associated with better adherence in four out of 11 results [45, 57, 62, 64, 67, 70], and higher asthma severity was linked to better adherence in five results [48, 68, 71, 78, 81], compared to one negative [81] and six nonsignificant results [40, 52, 64, 70, 71].

Patient-related factors were investigated in 40 studies. Patient demographics such as age and sex were included in numerous studies. Older age related to better adherence in 16 out of 28 results [32, 34, 35, 38, 40, 41, 45, 47, 52–55, 57, 58, 61, 63, 64, 67, 69, 70, 72, 73, 78, 81, 82]. Sex showed 24 nonsignificant results [34, 38, 40, 45, 48, 52, 54, 55, 57–59, 62–64, 67, 68, 70, 71, 73, 79, 82], with females showing better adherence in three results [41, 47, 53] and males in another three [61, 72, 78]. Being of white ethnicity was linked with better adherence in five out of 10 results [40, 48, 54, 55, 57, 59, 61, 70, 73, 78], while participants with higher education levels were more adherent in four out of 10 results [34, 38, 40, 45, 48, 52, 53, 57–59].

Few studies found significant roles of variables related to patients' general health status. Smoking status was consistently unrelated to adherence [40, 48, 52, 57, 58, 63, 64, 71], as was depression [40, 45, 57, 58]. Higher comorbidity was associated with better adherence in two out of eight results [47, 48, 54, 55, 57, 63], while less healthcare utilisation was linked to better adherence in two out of 11 results [34, 38, 40, 55, 70]. Asthma knowledge was found to be unrelated to adherence [32, 53], while medication knowledge was reported to be related to adherence in only one out of five results [34, 40, 61, 77]. Asthma beliefs (*i.e.* perceptions of the asthma impact in terms of severity, consequences, timeline, *etc.*) showed inconsistent relationships with adherence, with eight positive results [35, 36, 41, 53, 72], 10 nonsignificant results [35, 38, 41, 53, 57, 58], and one negative result [38].

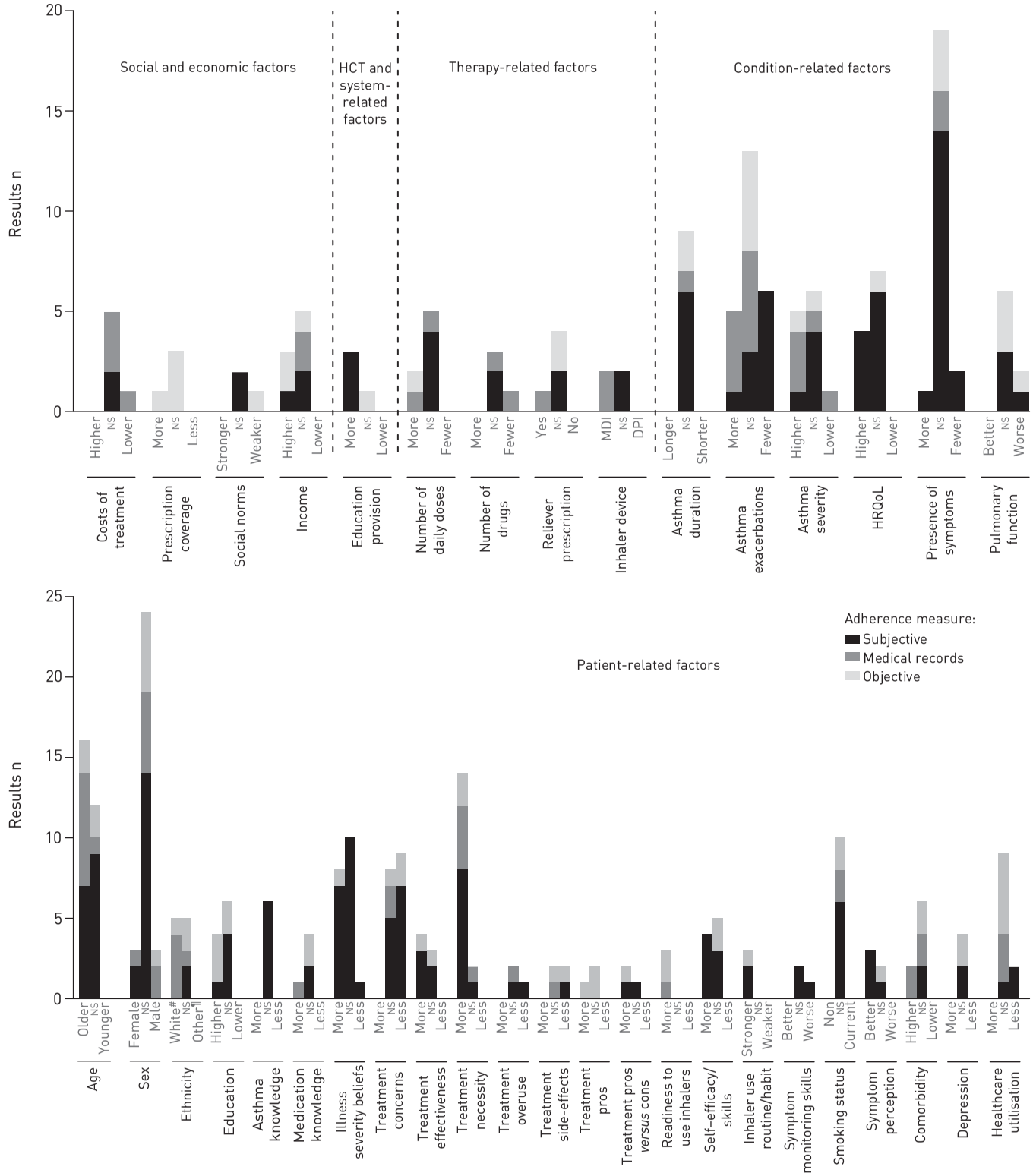

FIGURE 2 Determinants of controller implementation. Number of positive, nonsignificant and negative relationships with adherence indicators for determinants with three or more results identified. HCT: healthcare team; NS: nonsignificant; MDI: metered-dose inhalers; DPI: dry-powder inhalers; HRQoL; health-related quality of life. #: *versus* other; ¶: *versus* white.

The role of treatment beliefs was studied extensively. Stronger beliefs in the necessity of using inhalers were associated with better adherence in 14 out of 16 results [38, 40, 53, 60, 61, 65, 69, 74, 77, 82], beliefs in their effectiveness in four out of seven results [35, 40, 52, 53, 77], and more broadly-framed positive

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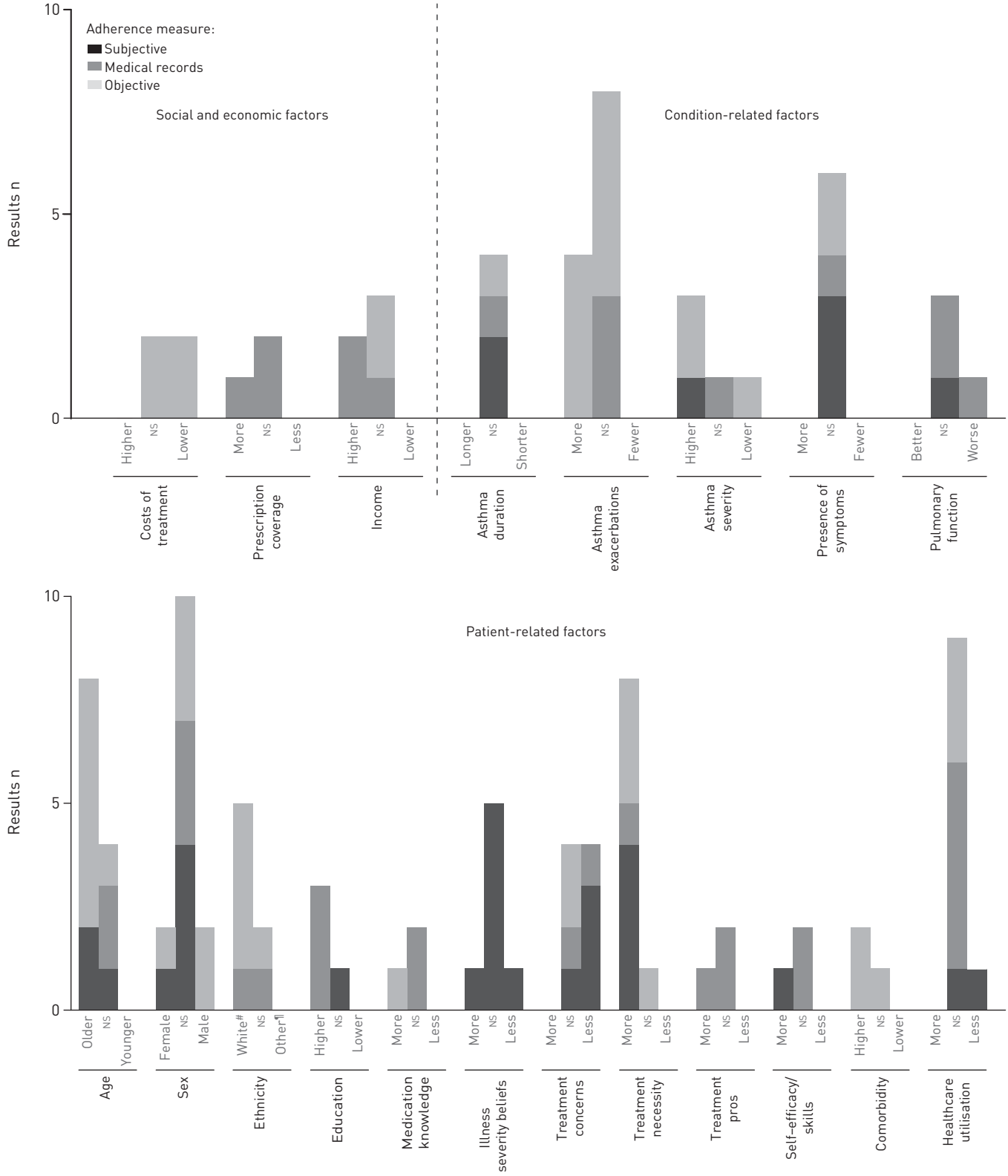

FIGURE 3 Determinants of controller implementation (results from higher quality studies). Number of positive, nonsignificant and negative relationships with adherence indicators for determinants with three or more results identified. NS: nonsignificant. #: *versus* other; ¶: *versus* white.

beliefs in inhaler usefulness or benefits in one out of three results [34]. Having fewer concerns about medication was related to better adherence in nine out of 17 results [38, 40, 60, 64, 65, 68, 72, 74], lower perceived side-effects in two out of four results [72, 77], lower beliefs that medication in general is

overused in one out of three results [60, 77], and stronger beliefs in inhaler necessity relative to concerns in two out of three results [68, 69, 72]. Readiness to use inhalers showed positive associations to adherence in three results [37, 61], indicators of self-efficacy in four out of nine results [32, 35, 40, 57, 65, 68], and stronger adherence routines in three results [53, 68, 72]. A better ability to perceive changes in asthma symptoms was related to adherence in three of five results [51, 58], while lower confidence in the ability to monitor symptoms was related to adherence in one of three results [41, 53].

Numerous other patient-level variables were examined in fewer than three analyses, most with nonsignificant results: general health status and body mass index [57]; marital status [48]; number of causal attributions for asthma [38]; extent of attributing asthma to internal causes [41]; general health self-efficacy [65]; self-control [45]; and various personality and medical history characteristics [34, 39, 45, 52, 58, 62, 68, 69, 71, 73, 74]. Several exceptions referred to better adherence in people who consider medication as less harmful (two results [60]), display lower neuroticism, higher agreeableness and conscientiousness (one out of two results [69, 74]), and believe more strongly that their asthma can be controlled [38, 41]. Several single results showed better adherence in people with a family history of asthma [71], asthma onset at younger age [58], lower impulsivity [62] and high literacy [80]. Other single findings suggested that more adherent people attribute their asthma more to external factors [41], believe that God is less in control of their health and attribute more control to physicians [73], perceive themselves less vulnerable to side-effects, report higher intention to use inhalers [72], have better inhaler use skills [79], are more satisfied with the device [70], prefer to use inhalers rather than pills [32], have no preferences regarding daily inhaler dosage [75], believe more strongly in participating actively in care [36], and report no symptom improvement due to herbal drugs [52].

Persistence

Controller-persistence determinants were investigated in three studies, and results are presented below. Patients receiving prescriptions from a specialist, using MDIs, having a lower recommended dose, having once-daily dosing frequency, having used LABAs in the previous year, and having had previous asthma-related hospitalisations were more likely to persist using single ICS treatment during 1 year, while adolescents and patients with more than twice daily dosing frequency were more likely to discontinue [56]. 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 [56]. Patients using ICS/LABA were more likely to persist with therapy compared to those using ICS+LABA, as were male patients, older patients, those receiving social assistance, those with lower daily dosage, those receiving prescriptions from a specialist, and those using more medications currently and in the previous year [50]. Time to discontinuation of ICS/LABA therapy was longer for male patients, older patients, those paying moderately for treatment, having more refills included in the first prescription, having prescriptions for other conditions, and having had relievers prescribed before the start of the study [47].

Determinants of reliever use

Reliever use recommendations were examined in three studies. Reliever overuse (as indicator of nonadherence to reliever recommendations) was linked to increased symptoms in two out of three results [43, 57], to older age in one out of two results [42, 57], and to lower education, higher self-perceived asthma severity and lower general health status in one result [57]. Other factors were unrelated to overuse (*e.g.* sex, ethnicity, socioeconomic 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, dichotomised 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) was 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±SE of 64±0.07. Performance

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TABLE 3 Study quality: frequencies and inter-rate agreement for quality criteria[#]

Quality criterion	Unknown[¶]	Low[+]	Medium[§]	High[f]	Inter-rate agreement weighted κ
Participant selection	0	10	22	19	0.41
Definition of variables	2	11	35	33	0.31
Measurement of variables	0	16	21	14	0.38
Addressing sources of bias	27	14	8	2	0.38
Study size	29	19	5	0	0.17
Data analysis	0	24	19	8	0.33

[#]: n=51. [¶]: no description available; [+]: unclear and/or not appropriate; [§]: mostly clear and appropriate, with a few omissions; [f]: clear and appropriate.

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).

Discussion

This systematic review aimed to qualify and synthesise 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 healthcare 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 suggest 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 future, 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 nonadherence 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 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 studied substantially less and should be prioritised 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 were 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]. Healthcare 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 healthcare 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 summarises nine main barriers and several recommendations for improvement, formulated considering the existing methodological advice for observational research [26] and adherence

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

Current limitations	When conducting a new study
Heterogeneity in variable selection, definition and measurement, study design and 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
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 relationships with existing theories
Lack of robust study designs for causal inferences in most studies	Prioritise the use of repeated measure longitudinal designs Assess adherence determinants prior to behaviours Choose time lags in which causal influence is likely Control for other possible causal influences
Low or medium quality 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
Insufficient description of variable definitions and measurement	Provide a clear rationale and description for included variables Provide comprehensive descriptions of measurement tools or methods in the manuscript or supplementary materials
Low quality of measurement	Select or develop psychometrically sound measures Examine psychometrics as preliminary analyses Report results of psychometric evaluation
Sources of bias rarely addressed	Reflect on possible sources of bias (*e.g.* response, recall, surveillance bias) and take steps to minimise their effect
Study size rarely addressed	Consider the probability of type I and type II errors given the research question, population and resources available
Low or medium quality data analysis procedures in most studies	Consult methodological literature relevant for the intended analyses 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

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, measurement, study design and statistical analyses. Secondly, 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. Finally, the results gave limited insight regarding causal influences, as only two studies involved repeated measures of adherence [65, 81] and only 17 studies measured determinants before adherence. Moreover, many studies showed limitations in the six quality criteria assessed, although several studies performed well (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.

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

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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 material 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 prioritise 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. Secondly, inter-rate 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. Thirdly, 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 [86], but only 19 studies were excluded based on this criterion. Finally, 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 more strongly 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 nonadherence. 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 healthcare 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 nonadherence to asthma inhalers among adults.

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