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Adding non-randomised studies to a Cochrane review brings complementary information for healthcare stakeholders: an augmented systematic review and meta-analysis

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Abstract

Background: To reduce the burden of asthma, chronic disease management (CDM) programmes have been widely implemented and evaluated. Reviews including randomised controlled trials (RCTs) suggest that CDM programmes for asthma are effective. Other study designs are however often used for pragmatic reasons, but excluded from these reviews because of their design. We aimed to examine what complementary information could be retrieved from the addition of non-randomised studies to the studies included in a published Cochrane review on asthma CDM programmes, for healthcare stakeholders involved in the development, implementation, conduct or long-term sustainability of such programmes.

Methods: Extending a previously published Cochrane review, we performed a systematic review (augmented review) including any type of study designs instead of only those initially accepted by Cochrane and the Effective Practice and Organization of Care Review group. After double data selection and extraction, we compared study and intervention characteristics, assessed methodological quality and ran meta-analyses, by study design.

Results: We added 37 studies to the 20 studies included in the Cochrane review. The applicability of results was increased because of the larger variety of settings and asthma population considered. Also, adding non-randomised studies provided new evidence of improvements associated with CDM intervention (i.e. healthcare utilisation, days off work, use of action plan). Finally, evidence of CDM effectiveness in the added studies was consistent with the Cochrane review in terms of direction of effects.

Conclusions: The evidence of this augmented review is applicable to a broader set of patients and settings than those in the original Cochrane review. It also strengthens the message that CDM programmes have a beneficial effect on quality of life and disease severity, meaningful outcomes for the everyday life of patients with asthma. Despite the moderate to low methodological quality of all studies included, calling for caution in results interpretation and improvements in CDM evaluation methods and reporting, the inclusion of a broader set of study designs in systematic reviews of complex interventions, such as chronic disease management, is likely to be of high value and interest to patients, policymakers and other healthcare stakeholders.

Keywords: Systematic review, Meta-analysis, Asthma, Chronic disease management, Complex interventions, Study design

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Background

Asthma is a global health problem affecting over 300 million people worldwide [1] and a major cause of disability, poor quality of life, health resources utilisation, and costs [2–4]. Despite the availability of effective therapies, asthma control remains suboptimal, calling for the implementation and evaluation of effective asthma management interventions [5]. These include chronic disease management (CDM) programmes, which are more than simple patient education, encompassing a set of coherent interventions that centres on the patients' needs, focuses on education and self-management, on healthcare integration and coordination provided by various professionals, as well as on improvements in communication between patients and healthcare providers [6–12].

Summarising the evidence of CDM programmes for asthma in a systematic review is not an easy task [13]. Most often, state-of-the-art Cochrane systematic reviews of interventions include randomised controlled trials (RCTs) only [14]. However, RCTs are often not the most suitable design for evaluating complex and context-dependent interventions [15–17]. Non-randomised studies, such as controlled and uncontrolled before-after studies, are often undertaken in the pragmatic context of CDM programme implementation in communities [16]. These non-randomised studies could be very informative for the various healthcare stakeholders involved in the development, implementation, conduct and long-term sustainability of such programmes, especially in terms of contexts, key components and implementation processes. Including non-randomised studies (NRS) or non-controlled studies (NCS) in systematic reviews is challenging, however, notably when assessing study quality and the potential for selection bias and its impact on study results [14, 18]. Yet, reviews and meta-reviews have shown that non-randomised studies do not systematically lead to biased results and that there is little evidence for significant effect estimate differences between observational studies and RCTs [14, 19].

The main objective of this systematic review was to examine what complementary information could be retrieved from the addition of NRS and NCS to a published Cochrane review on asthma CDM programmes, for healthcare stakeholders involved at various levels in the development, implementation, conduct and long-term sustainability of such programmes. We also assessed how the effectiveness of asthma CDM programmes varied across included study designs.

Methods

This systematic review (augmented review throughout the text) is an extension of a previously published Cochrane review [20] evaluating the effectiveness of CDM programmes in adults with asthma, that was conducted independently

from Cochrane. We used the same methodology as in the Cochrane review, except for study designs considered, risk of bias assessments and some aspects of the statistical analyses. While major methodological elements are presented thereafter, details of the methodology of the published Cochrane review are available in the original text [20].

Identification of studies and eligible study design

In the original review, we searched the following databases: MEDLINE, EMBASE, CINHAL, PSYCINFO, CENTRAL Cochrane and the Specialized Registers of the Effective Practice and Organisation of Care (EPOC) and Airways Disease Groups up to June 2014 [20]. We also hand-searched reference lists of retrieved papers and relevant narrative or systematic reviews, and registers of clinical trials to identify new and ongoing trials. Language restrictions were not applied. Eligible study designs in the original review were RCTs, quasi-randomised controlled trials (QRCTs) (i.e. an experimental study in which participants are prospectively allocated using a method that is not random), controlled before-after studies (CBA*s) (i.e. a study in which observations are made before and after the implementation of an intervention, both in a group that receives an intervention and in a control group that does not, with at least two intervention and two control sites) and interrupted time series (ITS*s) (i.e. a study that uses observations at multiple time points before and after an intervention, with at least three data points available before and after the intervention), complying with the guidelines from the EPOC Review group [21]. In this augmented review, we did not run a new search but modified the design inclusion criteria to also include any CBAs, any ITSs, before-after studies without an external control group (BAs) (i.e. outcomes are measured before and after the implementation of an intervention, in a single group) and cross-sectional studies (XSs) (i.e. concurrent measurement of intervention and outcomes), identified in the original search of the Cochrane review and excluded because of the study design ($n = 66$). We excluded studies presenting secondary analyses and implementation results only.

Types of interventions and outcomes

We included CDM programmes targeting adult participants with a diagnosis of asthma in both reviews, if the following five criteria were all met: 1) at least one organisational component targeting patients; 2) at least one organisational component targeting healthcare professionals and/or the healthcare system; 3) presence of patient education and/or self-management support component; 4) active involvement of two or more healthcare professionals in the patient's care; 5) minimum duration of 3 months of at least one of the criteria one to three.

In both reviews we looked at the same organisational and patient-level outcomes; the ten primary outcomes,

pre-defined in the Cochrane protocol [20], were also considered in this augmented review. Organisational outcomes included organisation of care outcomes, process outcomes (use of an action plan), and healthcare use outcomes (hospitalisations, unscheduled visits to an emergency department or physician office). Patient-level outcomes included quality of life (QoL) outcomes (asthma-specific QoL), symptoms and activity level outcomes (asthma severity, asthma exacerbations, days off work/school), self-care outcomes (self-efficacy scores), lung function outcomes (forced expiratory volume in one second (FEV1) or peak expiratory flow rate (PEFR)), and patient satisfaction.

Data extraction

Two reviewers, working independently and in duplicate, re-assessed the previously excluded articles ($n = 66$) for eligibility criteria and extracted data regarding study design, country and healthcare setting, CDM intervention (number of and main component, comprehensiveness of intervention -eight or more components-, duration of the longest component), patient characteristics (age, sex, asthma severity) and reported outcomes (structure indicators, process of care and intermediate measures, clinical effect). Where required, we sought additional information by contacting authors.

Assessment of risk of bias

We assessed the methodological quality of the studies using the Cochrane Collaboration's tool modified by EPOC [22] for assessing risk of bias for RCTs, QRCTs, and CBAs, used in the original review, with additional items for BAs, ITSs and XsSs extracted from various instruments: the new Cochrane risk of bias assessment tool for non-randomised studies of interventions (ACROBAT-NRSI) [23], the checklist for the assessment of the methodological quality of both randomised and non-randomised studies of health care interventions by Downs and Black [24], and the quality assessment tool for quantitative studies by the Effective Public Health Practice Project (EPHPP) [25, 26]. Domains of bias included in the final instrument, selected by consensus among authors to discriminate the quality of all study designs and encompass all relevant bias domains, were 1) random sequence generation, 2) allocation concealment, 3) baseline characteristics similar, 4) baseline outcomes similar, 5) confounding unlikely, 6) appropriate analyses (e.g. adjusted or time trend analyses if required), 7) sample representative of source population, 8) intervention independent of other changes, 9) intervention integrity (e.g. intervention delivered as intended and consistently, adequate protection against contamination), 10) blinding of outcome assessment, 11) incomplete outcome data addressed, and 12) free of other bias (see

Additional file 1 for the risk of bias extraction form). Any disagreement was resolved by discussion or involvement of an arbitrator, or both.

Measures of treatment effect and data synthesis

Measures of treatment effect were reported separately by study design, as suggested by recent guidance on including NRS in systematic reviews [27]. For RCTs, we reported results of dichotomous outcomes as odd ratios (OR) and results of continuous outcomes as mean differences (MD) or standardized mean differences (SMD) if different instruments or scales were used for a scale-type outcome, using post intervention (follow-up) values. SMDs were calculated by dividing the difference in mean scores between the intervention and control group by an estimate of the (pooled) standard deviation, resulting in a 'scale free' estimate of the effect for each study which can be pooled across studies regardless of the scale of measurement used in each study. Using rules of thumb, SMDs lower than 0.4 represent a small effect, SMDs between 0.4 and 0.7 represent a moderate effect, and SMDs higher than 0.7 represent a large effect [28]. For QRCTs, CBA*s, and CBAs, we intended to report results derived from statistical analyses adjusting for baseline measures. However, as adjusted results were not available in the included studies, we reported OR, MD or SMD using follow-up values only. CBA*s and CBAs were analysed in the same study design group. For XsSs, we also reported unadjusted OR, MD and SMD as adjusted results were not available. For BAs, we reported OR and MD or SMD, considering the baseline data as data for the "control" group. For ITSs, we planned to compare time trends before and after the intervention, or to re-analyse the data if analyses in the original paper were inappropriate, according to EPOC guidance [29]. However, because of the lack of reported data in the ITSs, re-analysis was not possible and we considered ITS data as BA data.

We reported the number of times the ten primary outcomes were assessed, and the number of times that statistically significant results favouring CDM were found by authors (for at least one dimension in case of scale outcomes), by study design. Then, where possible, we conducted meta-analyses using the Cochrane Review Manager software [30] to calculate the overall effect size for all relevant outcomes. We pooled results of studies of similar design using the random-effects model [21] to incorporate some level of expected heterogeneity among pooled studies. All results were expressed with 95 % confidence intervals, and statistical heterogeneity among trials was examined with Cochran's Q test and by calculating the I^2 statistic describing the proportion of variability in the summary estimate that is due to heterogeneity rather than by chance.

Results

Of the 10,593 records identified in the Cochrane review, 20 studies (from 27 articles) met all inclusion criteria and 66 articles were excluded because of the study design. Of these 66 excluded articles, 29 were rejected because no outcomes were available, children represented more than 50 % of the sample, or the intervention did not fulfil the inclusion criteria after further examination, leading to 37 remaining articles to additionally consider in the augmented review. Ten other articles were found by hand searching the reference lists of included articles. We therefore included 27 Cochrane articles and 47 additional articles, for a total of 57 studies, from 74 articles, in this augmented review (see flow diagram in Fig. 1 and key components of all included studies in the supplementary table (see Additional file 2)). These 57 studies consisted of seven CBAs [31–37], 22 BAs [38–59], six ITSs [60–65] and two Xs [66, 67], in addition to the 15 RCTs [68–82], one QRCT [83, 84], and four CBA*s [85–88] of the Cochrane review.

Characteristics of included studies

Programme and recruitment setting

Details of the 57 studies are presented in Table 1 and in the supplementary table (see Additional file 2: Supplementary Table). While about half of the RCTs and CBA*s in the Cochrane review were carried out in North America (USA and Canada), only 30 % of the studies added in this augmented review were held in that region. These studies were carried out more often in Europe (Finland, Germany, Netherlands, Russia, Spain, Sweden, Switzerland, UK) and other parts of the world (Australia, Brazil, India, New Zealand, Thailand) compared to the countries represented in the RCTs, QRCT and CBA*s (Denmark, France, Germany, Netherlands, UK and Australia, Japan, Taiwan).

Also, they recruited patients from a larger variety of patient pools: five studies recruited patients from the general population compared to none in the Cochrane studies and a higher percentage of studies recruited patients in specialised clinics or outpatient hospital departments. Finally, care was delivered proportionally more often in specialised clinics or outpatient hospital departments in the studies added in this augmented review, compared to studies in the Cochrane review, which were mostly community-based.

Study population

A total of 158,907 patients (between 25 and 70,900 per study, median: 111) were included in the 51 studies reporting this information, with a mean number of patients included in the studies that differed according to study design (see Table 1): RCTs included less patients on average compared to the other designs, while all ITSs included over 10,000 patients. Patients' mean age ranged from 34.0 in the CBA*s to 48.5 in the XS reporting this information, and the mean percentage of women included in the studies ranged from 53 % in the CBA*s to 72 % in the CBAs. Compared with patients in RCTs, those included in BAs appeared to suffer from less severe asthma: the percentage of studies including patients suffering from mild to moderate asthma was higher in studies reporting this information, the mean FEV1 was higher, and the mean percentage of patients using inhaled corticosteroids (ICS) was lower.

Interventions

The mean number of independent components per CDM intervention was highest in the ITSs, which were also more often defined as comprehensive interventions (including at least eight components), while BAs included

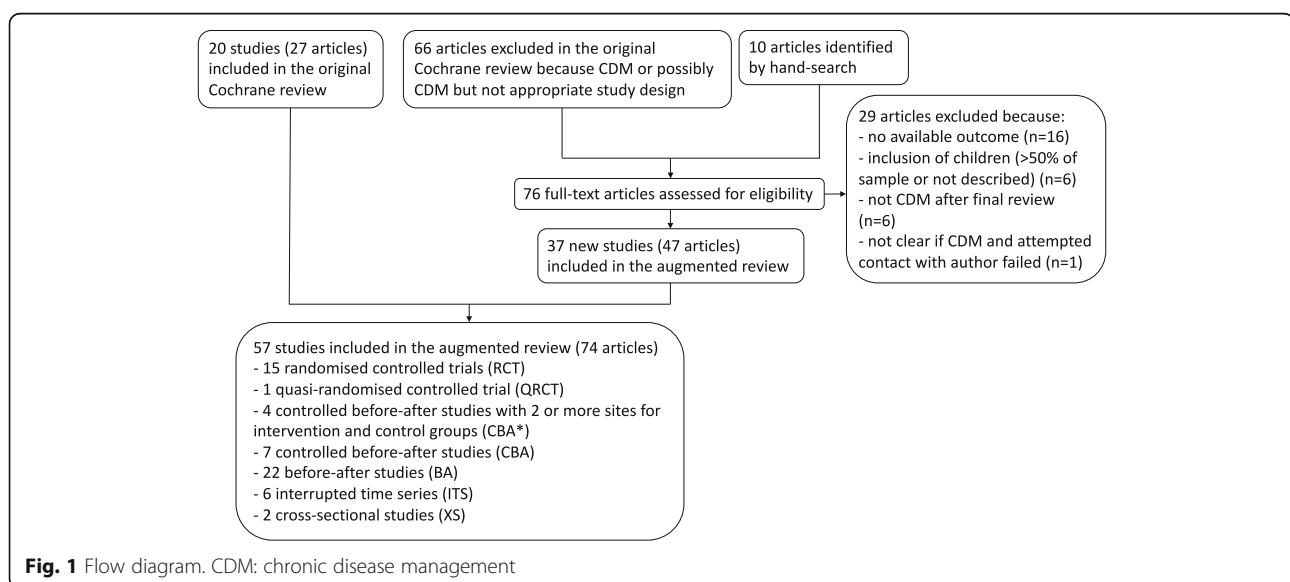


Table 1 Study and intervention characteristics, by study design

	Studies in Cochrane review			Newly added studies			
	RCT N = 15	QRCT N = 1	CBA* N = 4	CBA N = 7	BA N = 22	ITS N = 6	XS N = 2
Study characteristics:							
Publication year, mean (SD)	2004.0 (5.3)	2001	2004.8 (4.1)	2003.9 (6.1)	2002.8 (5.7)	2009.8 (4.0)	2006.5 (6.4)
Region, n (%)							
Europe	4 (26.7 %)	Denmark	1 (25.0 %)	0	9 (40.9 %)	3 (50.0 %)	Sweden
North America	8 (53.3 %)	-	2 (50.0 %)	4 (57.1 %)	6 (27.3 %)	1 (16.7 %)	0
Other	3 (20.0 %)	-	1 (25.0 %)	3 (42.9 %)	7 (31.8 %)	2 (33.3 %)	Brazil
Location of care, n (%)							
Outpatient care ^a	3 (20.0 %)	-	0	2 (28.6 %)	9 (40.9 %)	3 (50.0 %)	0
Community-based care ^b	6 (40.0 %)	1	3 (75.0 %)	3 (42.9 %)	10 (45.5 %)	1 (16.7 %)	2 (100 %)
Mixed	6 (40.0 %)	-	1 (25.0 %)	2 (28.6 %)	3 (13.6 %)	2 (33.3 %)	0
Recruitment pool, n (%)							
General population	0	-	0	0	2 (9.1 %)	3 (50.0 %)	1 (50 %)
Insurance clients	2 (13.3 %)	-	3 (75.0 %)	2 (28.6 %)	1 (4.5 %)	1 (16.7 %)	0
PCP/Pharmacy	5 (33.3 %)	1	1 (25.0 %)	2 (28.6 %)	7 (31.8 %)	0	1 (50 %)
Outpatients ^c	3 (20.0 %)	-	0	2 (28.6 %)	8 (36.3 %)	2 (33.3)	0
Inpatients	3 (20.0 %)	-	0	0	0	0	0
Multisector	2 (13.3 %)	-	0	1 (14.3 %)	4 (18.2 %)	0	0
Patients, mean (SD)	157.7 (153.1)	413	19742 (34137.3)	683.0 (1157.5)	347.4 (725.2)	32553 (16363.9)	330.5 (24.7)
Median	96	-	3717	239.5	100.0	32553	330.5
Age, mean (SD)	43.0 (6.3)	40.6	34.0 (3.6)	42.3 (5.4)	42.2 (6.8)	nr	48.5
Women, mean % (SD)	61.3 (14.7)	56.2 %	52.8 (10.6)	71.8 (4.5)	66.6 (11.1)	nr	55.5 (2.3)
Asthma severity, n (%)							
Mild-moderate	1 (6.7 %)	-	0	0	7 (31.8 %)	0	1 (50 %)
Moderate-severe	11 (73.3 %)	1	0	4 (57.1 %)	10 (45.5 %)	0	0
Not reported	3 (20.0 %)	-	4 (100.0 %)	3 (42.9 %)	5 (22.7 %)	6 (100 %)	1 (50 %)
FEV1, mean (SD)	64.6 (20.9)	nr	nr	nr	79.4 (10.4)	nr	nr
ICS use, mean % (SD)	73.8 (32.0)	nr	nr	74.4 (26.5)	52.0 (30.3)	52.8 (36.4)	44.7 %
Intervention characteristics:							
Number of intervention components, mean (SD)	8.5 (2.5)	9	7.8 (2.5)	7.1 (1.2)	6.7 (2.0)	10.0 (2.1)	7
Comprehensive intervention (≥8 components), n (%)	8 (53.3 %)	1	2 (50.0 %)	3 (42.9 %)	5 (22.7 %)	5 (71.4 %)	0
Main component, n (%)							
Educational	7 (46.7 %)	-	1 (25.0 %)	6 (85.7 %)	14 (63.6 %)	0	1 (50 %)
Org_healthcare	2 (13.3 %)	-	2 (50.0 %)	1 (14.3 %)	6 (27.3 %)	5 (71.4 %)	1 (50 %)
Org_patient	1 (6.7 %)	1	0	0	0	0	0
Multicomponent	5 (33.3 %)	-	1 (25.0 %)	0	2 (9.1 %)	1 (16.7 %)	0
Duration of intervention (months), mean (SD)	7.5 (3.2)	12	22.5 (21.0)	12.5 (12.6)	13.1 (8.0)	ongoing	4

RCT randomised controlled trial, QRCT quasi-randomised controlled trial, CBA* controlled before-after study (with at least two intervention and two control sites), CBA controlled before-after study, ITS interrupted-times-series study, BA before-after study (without external control group), XS cross-sectional study (with concurrent measurement of intervention exposure and outcomes), PCP primary care practice, SD standard deviation, FEV1 forced expiratory volume in 1 s (% predicted), ICS inhaled corticosteroids, Org organisational, nr not reported

^aOutpatient care: ambulatory care provided by specialised clinic or hospital

^bCommunity-based care: care provided at a primary care practice, pharmacy or health unit

^cOutpatients: patients seen by specialised clinic or outpatient hospital department

fewer components and were less often comprehensive (see Table 1). Education and/or self-management support was the main component in most CBAs and BAs, while the RCTs were more often multi-component. The three components most often implemented in RCTs were individual education sessions (100 % of RCTs), explicit teamwork and collaborative processes between healthcare providers (87 % of RCTs) and structured follow-up (80 % of RCTs), while the three most frequent components in the QRCT and CBA*s were individual education sessions (80 % of studies), structured follow-up (80 % of studies),

reminders, feedback and other routine reporting sheets (80 % of studies). In studies added in this augmented review, the three most frequent components were structured follow-up (68 % of studies), healthcare professionals education (68 % of studies) and providing an action plan (62 % of studies). The RCTs evaluated shorter interventions on average (mean duration less than 12 months) compared to the other designs. Thirteen of the newly added studies were ongoing (without time limitation), while none of the studies in the Cochrane review was ongoing.

Study design	Random sequence generation	Allocation concealment	Baseline characteristics similar	Baseline outcomes similar	Confounding unlikely	Appropriate analysis	Sample representative of source population	Intervention independent of other changes	Intervention integrity	Blinding of outcome assessment	Incomplete outcome data addressed	Free of other bias
Armour 2007	RCT	?	+	+	+	?			+	+	+	+
Cambach 1997	RCT	+	+	+	?	+			+	?	+	+
Castro 2003	RCT	+	+	+	?	+			+	?	+	+
Charrois 2006	RCT	+	+	+	?	+			+	?	+	+
Couturaud 2002	RCT	+	+	+	?	+			+	?	+	+
Galbreath 2008	RCT	+	+	+	?	+			+	+	?	?
Huang 2009	RCT	+	+	+	?	+			+	+	?	?
Kokubu 2000	RCT	+	+	+	?	+			+	?	?	?
Martin 2009	RCT	?	?	+	+	?			?	?	?	+
Mayo 1990	RCT	+	+	+	+	+			+	?	?	+
McLean 2003	RCT	?	+	?	?	?			+	?	?	+
Petro 2005	RCT	?	?	?	?	?			+	?	?	+
Schatz 2006	RCT	+	+	+	+	+			+	?	+	+
Smith 2005	RCT	+	+	+	+	+			+	+	+	+
Wilson 2010	RCT	+	+	+	+	+			+	+	+	+
Herborg 2001	QRCT	+	+	+	?	+			+	?	+	+
Feifer 2004	CBA*	+	?	+	+	+			+	+	?	?
Landon 2000	CBA*	+	+	?	?	+			+	?	?	?
Weng 2005	CBA*	+	+	+	+	+			+	?	?	?
Windt 2010	CBA*	+	+	+	+	+			+	+	+	?
Allen-Ramey 2002	CBA	+	+	+	+	+			+	+	+	?
Curtin 1998	CBA	+	+	?	?	+			?	?	?	+
Gaude 2014	CBA	+	?	?	?	+			?	?	?	+
Kelso 1996	CBA	+	+	+	?	+			+	+	?	+
Saini 2004	CBA	+	+	+	?	+			+	+	+	+
Saini 2008	CBA	+	+	+	?	+			+	+	+	+
Tatis 2005	CBA	+	+	?	?	+			+	?	?	+
Brandao 2009	BA						+	?	+	+	+	+
Charlton 1991	BA					+		?	+	+	+	+
Charlton 1992	BA					+		?	+	+	+	+
Dsouza 1994	BA					+		?	+	+	+	+
Dsouza 1996	BA					+		?	+	+	+	+
Emmerton 2003	BA					+	?	+	+	+	+	+
Franco 2007	BA					+		?	+	?	+	+
Franco 2009	BA					+		?	+	+	+	+
Hertzman 2005	BA					+	+	?	+	+	+	+
Ignacio-Garcia 2002	BA					+		?	+	+	+	+
Licksai 2012	BA					+		?	+	+	+	+
Lind 2006	BA					+		?	+	+	+	+
Lindberg 1999	BA					+		?	+	+	+	+
Maljanian 1999	BA					+		?	+	+	+	+
Mangiapanne 2005	BA					+	?	?	+	?	+	+
Nähri 2001	BA					+		?	+	+	+	+
Patel 2004	BA					+		?	+	+	+	+
Pauley 1995	BA					+		?	+	+	+	+
Ponte 2007	BA					+		?	+	+	+	+
Steuken 2006	BA					+		?	+	+	+	+
To 2008	BA				?	+		?	+	+	+	+
Tschopp 2002	BA					+		?	+	+	+	+
Boonsawat 2013	ITS					+		?	?	?	?	?
Fireman 2004	ITS					+		?	?	+	+	+
Hahtela 2006	ITS					+		?	?	?	?	?
Kauppi 2013	ITS					+		?	?	?	?	?
Mehring 2013	ITS					+		?	?	+	+	+
Souza-Machado 2010	ITS					+		?	?	+	+	+
Carmo 2011	XS				?	+		?	+	+	+	+
Lindberg 2002	XS					+		?	+	+	+	+

Fig. 2 Risk of bias by study design. + Low risk of bias; ? Unclear risk of bias; - High risk of bias; □ Not applicable; RCT: randomised controlled trial; QRCT: quasi-randomised controlled trial; CBA*: controlled before-after study (with at least two intervention and two control sites); CBA: controlled before-after study; ITS: interrupted-times-series study; BA: before-after study (without external control group); XS: cross-sectional study (with concurrent measurement of intervention exposure and outcomes)

Outcome measures

A large variety of outcomes were reported in the studies (all reported outcomes are listed in the supplementary table (see Additional file 2: Supplementary Table)). While RCTs reported more often self-reported scale outcomes (i.e. score on asthma-specific QoL, asthma severity, asthma knowledge and self-care), the studies added in this augmented review reported more often healthcare use and days off work/school. In addition, while the four outcomes most often measured in RCTs were asthma-specific quality of life (80 % of RCTs), medication use and ICS prescription (60 % of RCTs), hospitalisations (53 % of RCTs) and asthma severity (53 % of RCTs), the four outcomes most often reported in the QRCT and CBA*s were hospitalisations (all five studies), unscheduled visits (60 % of studies), general practitioner visits (60 % of studies) and ICS prescription (60 % of studies). In the studies added in this augmented review, the four outcomes most often reported were hospitalisations (in 65 % of studies), unscheduled visits (62 % of studies), ICS prescription (38 % of studies) and delivery of intervention (38 % of studies).

Risk of bias

In the Cochrane review, the quality of the evidence was rated as moderate to low based on the GRADE approach [89], despite the fact that most studies were RCTs. This was mainly due to study design limitations, which resulted in either unclear or high risk of bias in most cases and in wide confidence intervals. Detail assessment can be found in the Cochrane publication [20] and in Fig. 2.

In this augmented review, the overall methodological quality of the newly added studies was rated as low (see Fig. 2 for risk of bias assessment per study). More specifically, only two of the seven CBAs attempted to minimize confounding bias by stratifying patients according to asthma severity [31] and matching the control group for

age, gender, onset of asthma, healthcare use, and employment [34]. Also, across all designs, most studies were at high risk of confounding bias and did not run appropriate analyses. For instance, only two ITSs performed appropriate trend analyses, using the Cochran Armitage test for trend [64] and linear regression modelling [65]. In addition, patients were deemed representative of the source population (i.e. included patients comprising the entire source population, an unselected sample of consecutive patients or a random sample) in less than half of the included studies and most studies were at unclear risk of bias regarding the independence of the intervention from other changes. Lastly, while more than half of the studies were at high risk of detection bias (outcomes not assessed blindly), about half of the studies were at low risk of attrition bias (less than 20 % of patients lost to follow-up) and most studies were at low risk of intervention integrity (interventions delivered as intended and consistently).

Effects of asthma CDM programmes

We report in the following section the effectiveness results for the pre-defined ten primary outcomes.

Among the 57 included studies of this augmented review, 17 studies did not contribute to any meta-analysis, because of data format heterogeneity (e.g. continuous versus dichotomous data, change from baseline versus follow-up data only) and data unavailability.

Overview

Table 2 displays the number of studies reporting statistically significant effects associated with CDM for the nine primary outcomes (no data was found for asthma exacerbations, one of the primary outcomes), among studies reporting the outcome of interest, by study design. Across all outcomes, the RCTs, QRCT and CBA*s of the Cochrane review had lower proportion of outcomes that

Table 2 Study effects, by study design

Number of studies reporting SS effect / number of studies reporting outcome	<i>Studies in Cochrane review</i>			<i>Newly added studies</i>			
	RCT	QRCT	CBA*	CBA	BA	ITS	XS
	N = 15	N = 1	N = 4	N = 7	N = 22	N = 6	N = 2
Asthma-specific quality of life	9 / 12	1 / 1	1 / 1	2 / 3	5 / 5	-	-
Hospitalisations	3 / 6	0 / 1	0 / 2	3 / 4	8 / 13	3 / 6	0 / 1
ED or unscheduled visits	1 / 6	0 / 1	0 / 2	3 / 4	13 / 16	1 / 2	1 / 1
Asthma self-efficacy	4 / 5	-	1 / 1	2 / 2	3 / 3	-	1 / 1
Asthma severity	5 / 8	1 / 1	-	2 / 2	6 / 7	1 / 1	1 / 1
Days off school or work	0 / 2	-	0 / 1	0 / 1	8 / 11	-	-
Use of an action plan	1 / 2	-	2 / 2	3 / 3	4 / 5	1 / 2	1 / 1
Patient satisfaction	0 / 2	0 / 1	-	-	2 / 3	0 / 1	-
Lung function	4 / 12	0 / 1	-	1 / 1	6 / 13	-	-

RCT randomised controlled trial, QRCT quasi-randomised controlled trial, CBA* controlled before-after study (with at least two intervention and two control sites), CBA controlled before-after study, ITS interrupted-times-series study, BA before-after study (without external control group), XS cross-sectional study (with concurrent measurement of intervention exposure and outcomes), SS statistically significant, ED emergency department

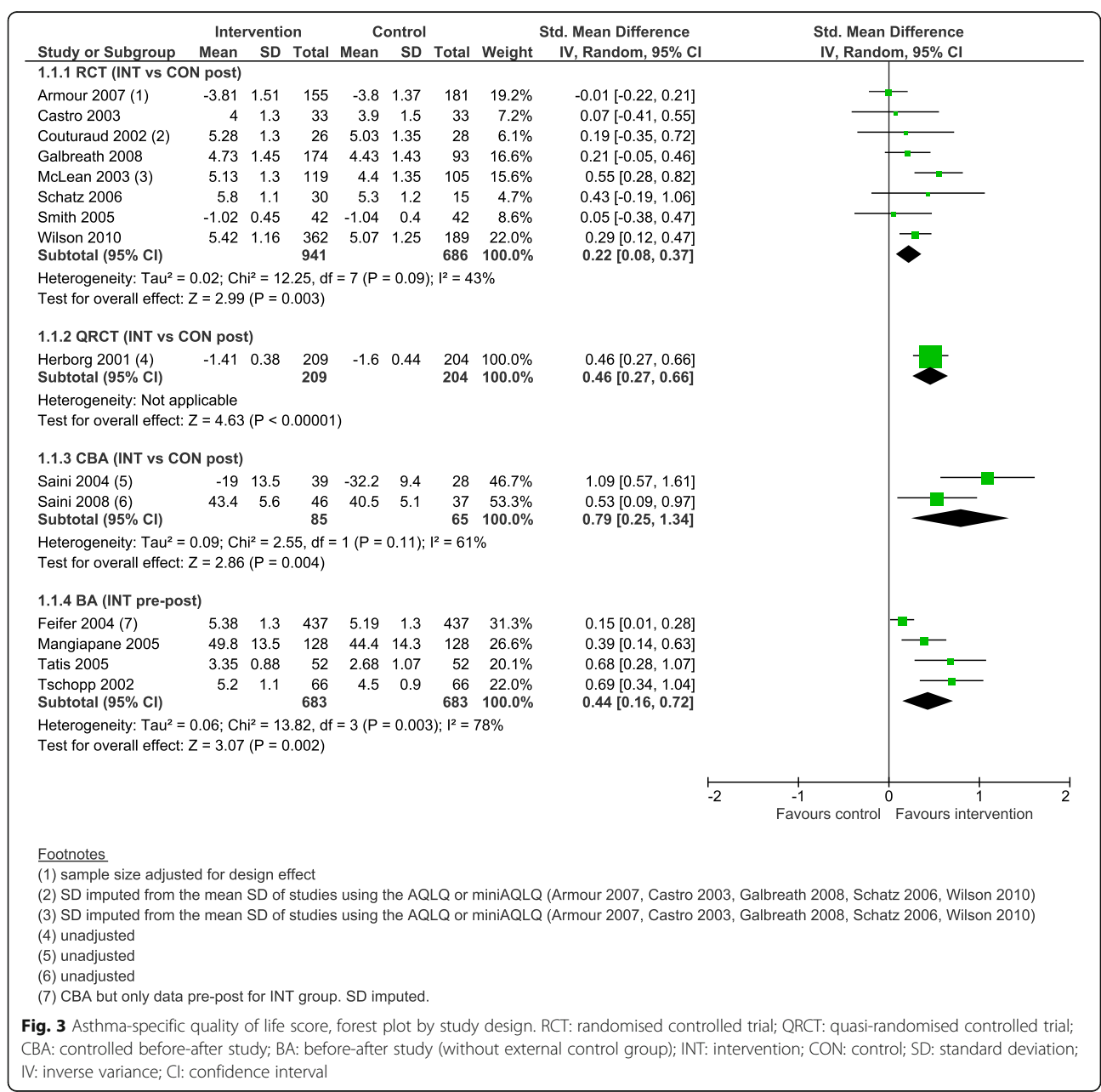
significantly improved in response to CDM (49.1, 33.3 and 44.4 %, respectively) compared to CBAs, BAs, ITsS and XsS (80.0, 72.4, 50.0 and 80.0 %, respectively). Across all designs, outcomes that significantly improved more often were asthma self-efficacy (91.7 %), asthma-specific QoL (81.8 %), asthma severity (80.0 %) and use of an action plan (80.0 %), while outcomes that improved less often were patient satisfaction (28.6 %), lung function (40.7 %), days off work or school (53.3 %) and healthcare use (hospitalisation 51.6 %, unscheduled visit 59.4 %). We present below the meta-analysis results (if available) for the ten primary outcomes, by order of a priori defined clinical significance.

Asthma-specific quality of life

CDM programmes resulted in improved asthma-specific QoL scores in all designs, with a small effect in RCTs (SMD 0.22, 95 % CI 0.08 to 0.37, 8 studies), moderate effect in BAs (SMD 0.44, 95 % CI 0.16 to 0.72, 4 studies) and the QRCT (SMD 0.46, 95 % CI 0.27 to 0.66, 1 study), and large effect in CBAs (SMD 0.79, 95 % CI 0.25 to 1.34, 2 studies) (Fig. 3).

Healthcare use: hospitalisations and unscheduled visits

While we were not able to perform meta-analysis on healthcare use data in the Cochrane review because of the wide variability in means and rates at baseline,



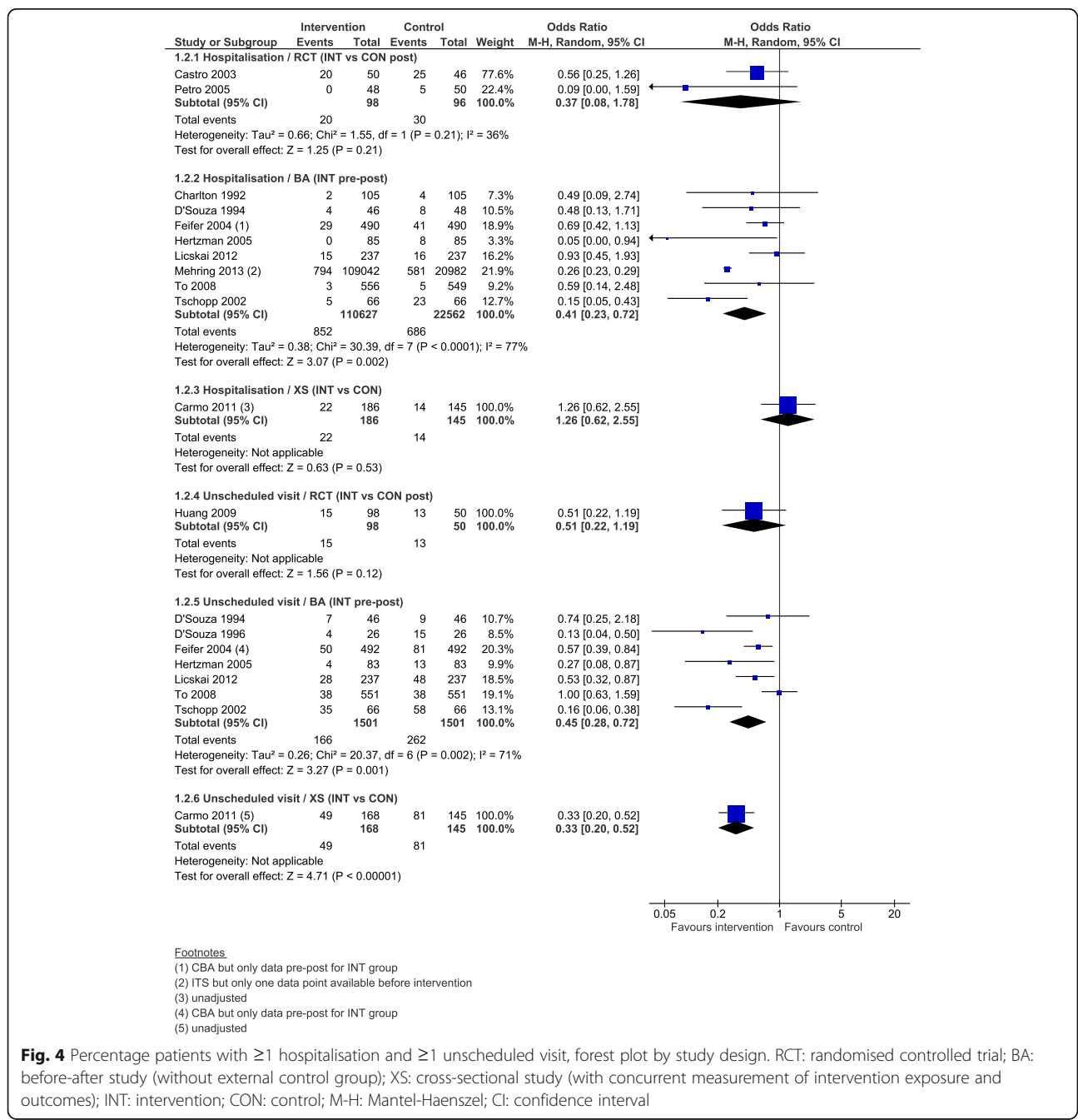
length of follow-up, data type and reasons for healthcare use (asthma-specific or all-cause), we were able in this augmented review to run meta-analyses on the percentage of patients with one or more hospitalisation and one or more unscheduled visits (Fig. 4). Only the meta-analyses for the BAs showed a significant lower likelihood of hospitalisation and unscheduled visit at follow-up compared to baseline (OR 0.41, 95 % CI 0.23 to 0.72, 8 studies and OR 0.45, 95 % CI 0.28 to 0.72, 7 studies, respectively).

Asthma exacerbations

Meta-analysis on asthma exacerbations, defined as prompting hospitalisation, an unscheduled or ED visit, or systemic rescue glucocorticoids, was not possible as data were not reported as such in the included studies.

Self-efficacy

CDM programmes were associated with improvement in asthma self-efficacy scores, with a moderate, inconclusive and heterogeneous effect in RCTs (SMD 0.51,



95 % CI -0.08 to 1.11, 5 studies, $I^2 = 91\%$), a moderate effect in CBAs (SMD 0.56, 95 % CI 0.23 to 0.89, 2 studies) and a large effect in the BA (SMD 0.88, 95 % CI 0.62 to 1.13, 1 study) (Fig. 5).

Asthma severity

Asthma severity scores improved in all designs, with a small effect in RCTs (SMD 0.18, 95 % CI 0.05 to 0.30, 6 studies) and in the BA (SMD 0.35, 95 % CI 0.10 to 0.60, 1 study), a moderate effect in the QRCT (SMD 0.47, 95 % CI 0.27 to 0.66, 1 study), and large effect in the CBAs (SMD 1.04, 95 % CI 0.66 to 1.42, 2 studies) (Fig. 6).

Days off work or school

While we were not able to pool data on days off work or school in the Cochrane review because of their heterogeneous format, we were able to pool BAs reporting the percentage of patients who missed at least one day of work or school due to asthma; it showed a moderate reduction after the intervention (OR 0.45, 95 % CI 0.29 to 0.71, 8 studies) (Fig. 7).

Use of an action plan

The pooled OR for the percentage of patients with an action plan at follow-up ranged from 2.41 (95 % CI 1.56

to 3.73) for the XS, 2.99 (95 % CI 2.39 to 3.75) for the eight BAs with a high degree of heterogeneity ($I^2 = 87\%$), 3.50 (95 % CI 0.83 to 14.85) for the RCT, to 4.99 (2.64 to 9.42) for the three CBAs (Fig. 8).

Patient satisfaction

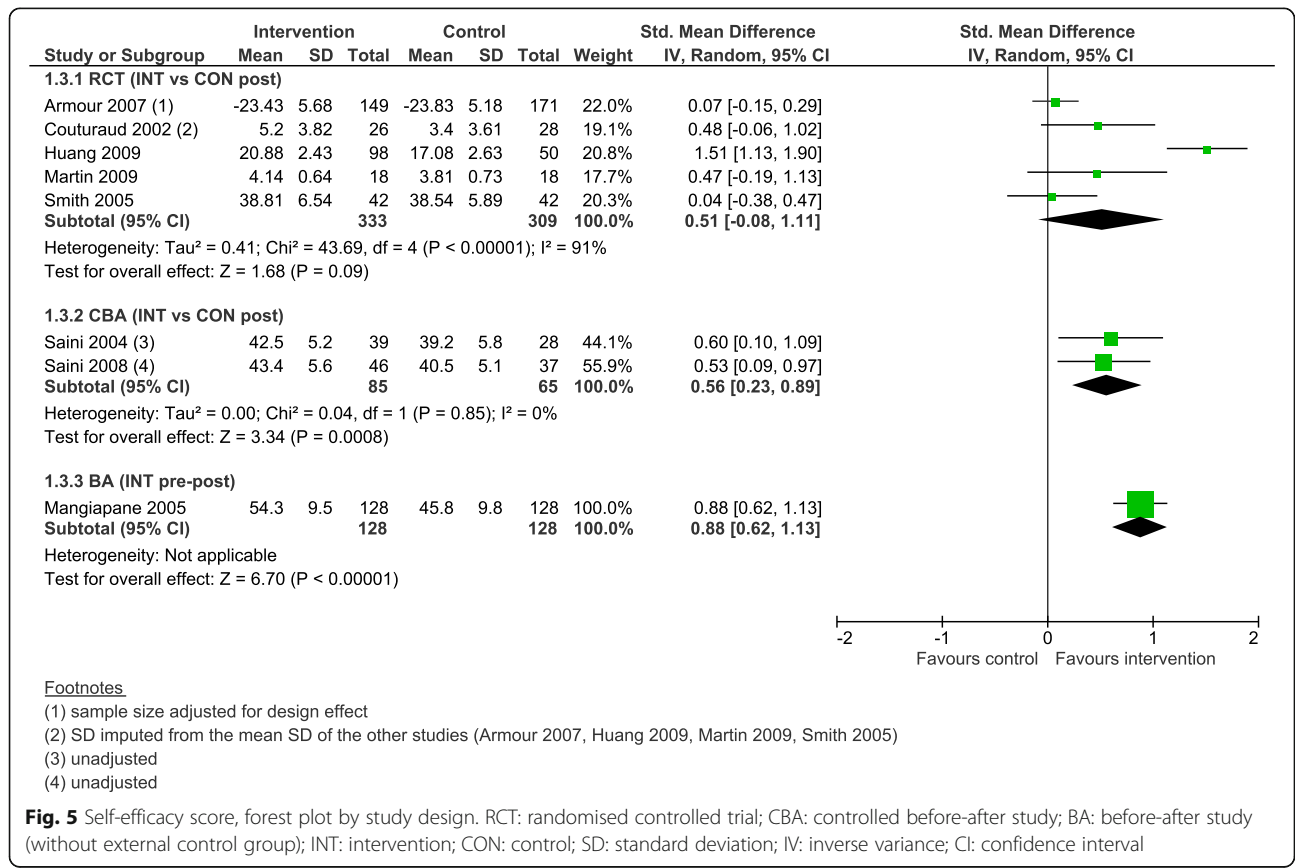
Due to the heterogeneity of patient satisfaction measures, we were unable to perform meta-analysis on patient satisfaction.

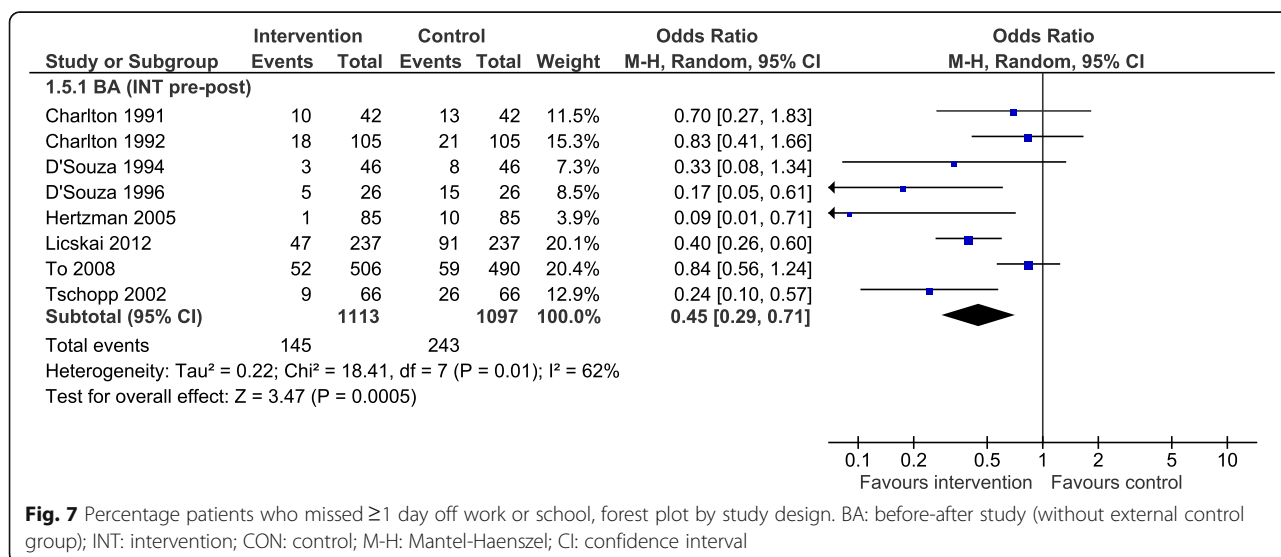
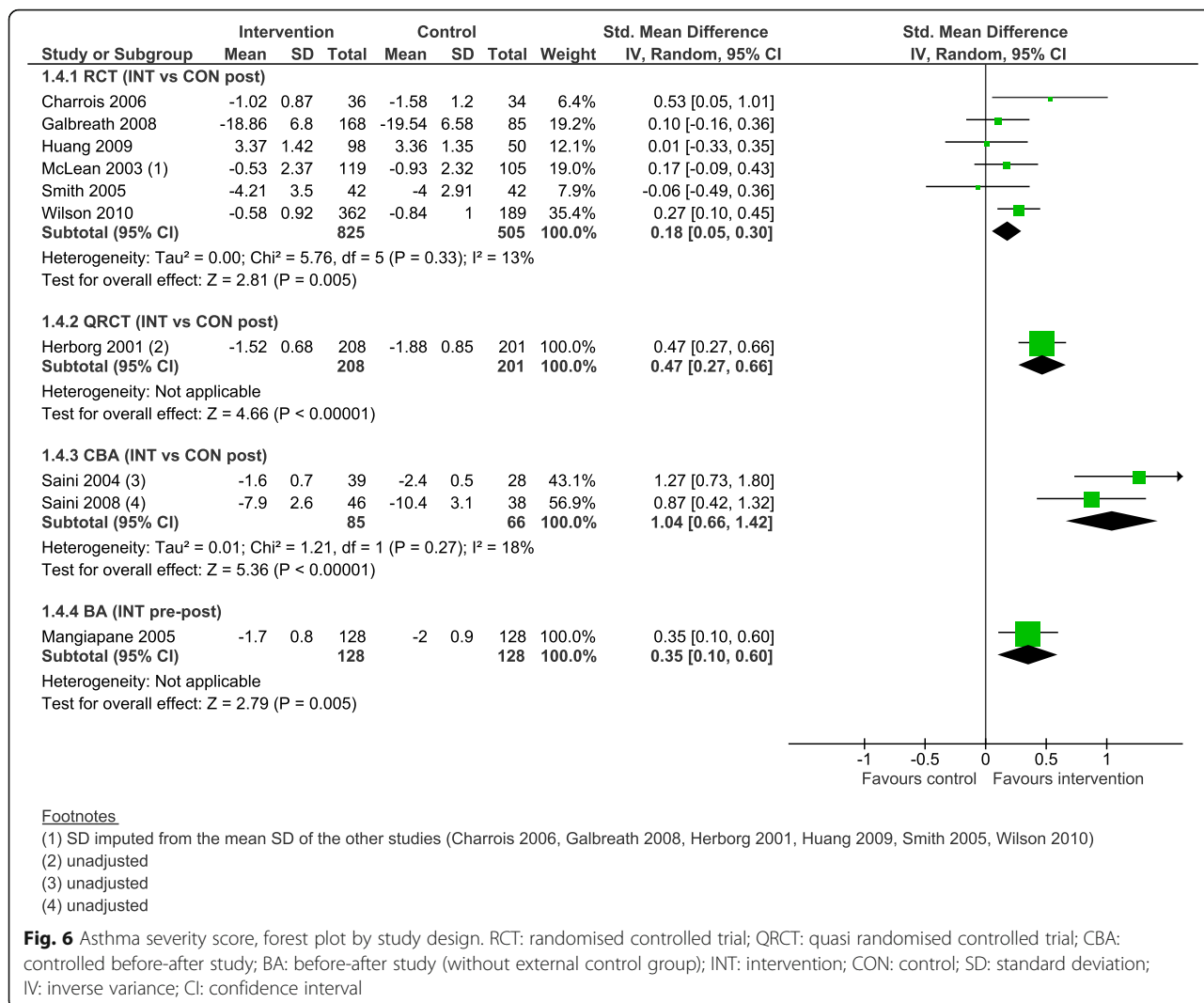
Lung function

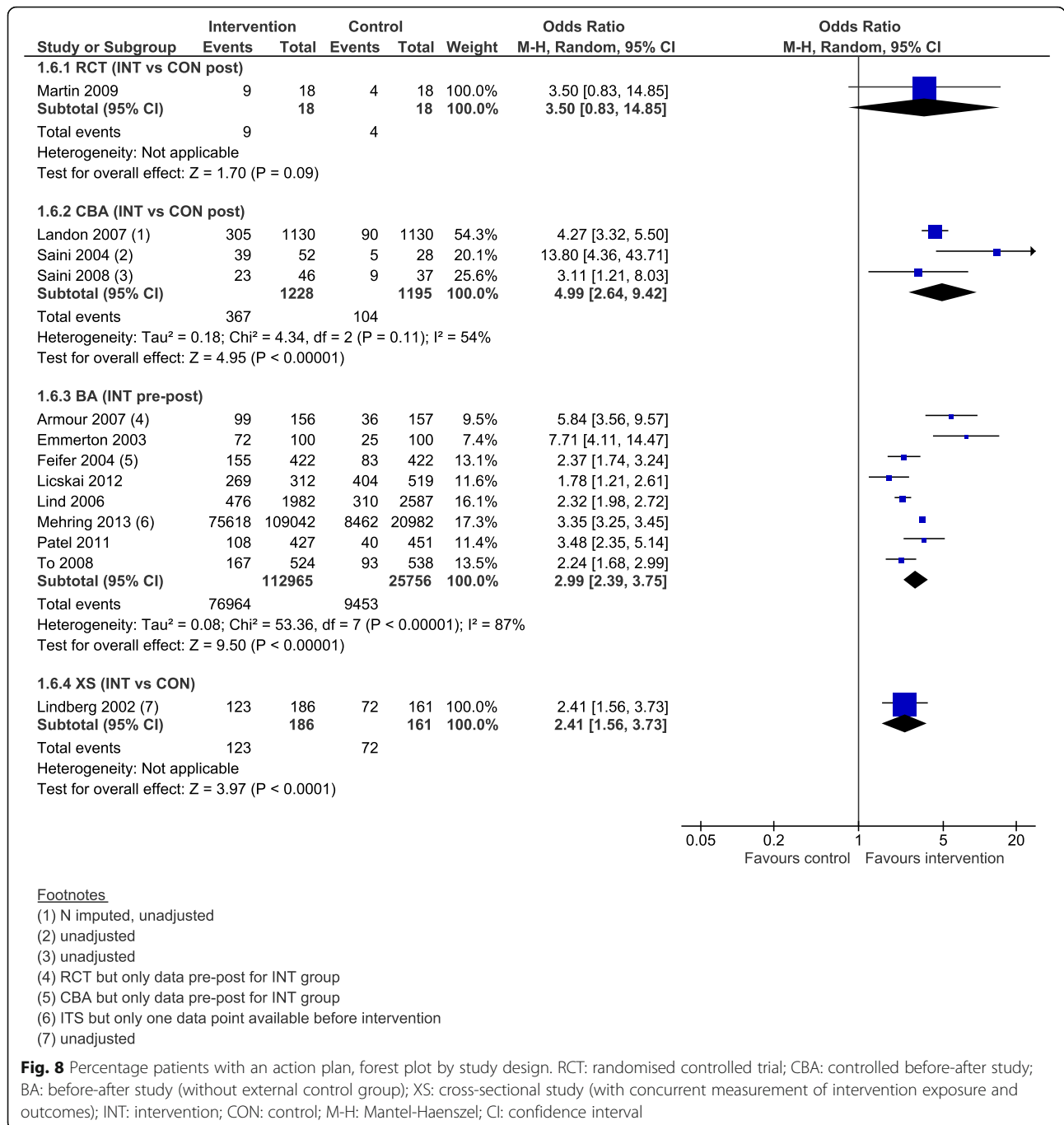
CDM programmes were associated with improvement in lung function (FEV1 or PEF value reported as per cent of predicted value or L/min) in all designs, with a small effect in all designs (SMD 0.19, 95 % CI 0.09 to 0.30 in eight RCTs, SMD 0.26, 95 % CI 0.06 to 0.45 in the QRCT, SMD 0.30, 95 % CI 0.18 to 0.42 in eight BAs) (Fig. 9).

Secondary outcomes

By adding NRS and NCS, we were able to examine one secondary outcome and run two additional meta-analyses on two secondary outcomes reported in sufficient studies to allow comment and analysis in the following paragraphs.



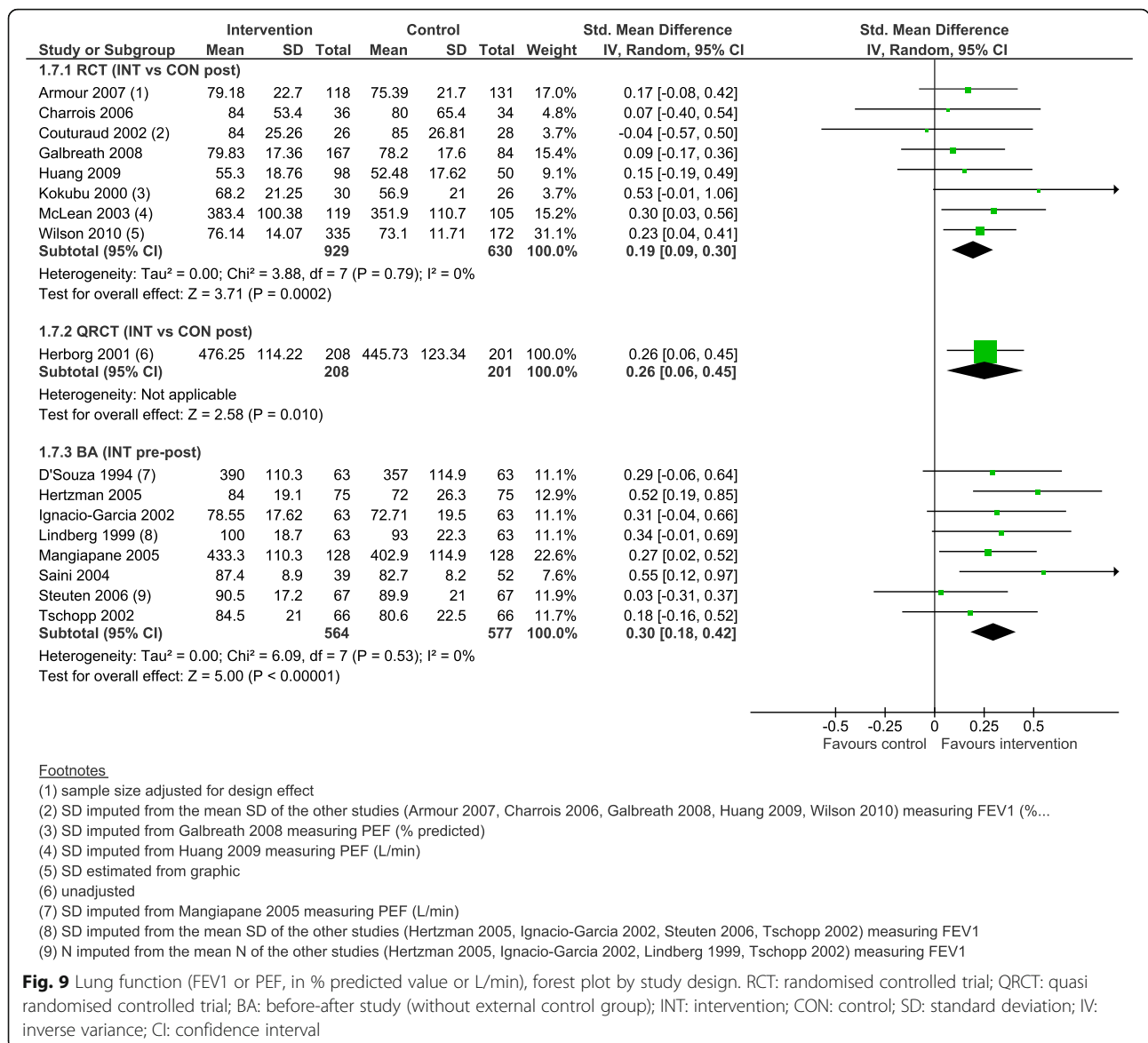




The impact of CDM programmes on the frequency of GP visits was bi-directional. One RCT found less frequent GP visits in the intervention group compared to the control group [78], while one QRCT [83] and one CBA [87] found more frequent GP visits. Two BAs found more frequent GP visits per patient at follow-up compared to baseline [44, 45], while five BAs and one ITS found on the contrary that the number of GP visits per patient decreased in the intervention group compared to baseline [39–42, 47, 61].

The pooled SMD for asthma knowledge ranged from 0.53 (95 % CI 0.03 to 1.02) for the CBA, 0.83 (95 % CI 0.63 to 1.03) for the QRCT, 1.08 (95 % CI 0.16 to 2.0) for six RCTs with a high degree of heterogeneity (I² = 97 %), to 2.25 (95 % CI -0.44 to 4.93) for three BAs with a high degree of heterogeneity as well (I² = 99 %) (Fig. 10).

The pooled SMD for medication compliance scores ranged from 0.24 (95 % CI -0.01 to 0.50) for three RCTs, 0.57 (95 % CI -0.13 to 1.26) for two BAs with a high

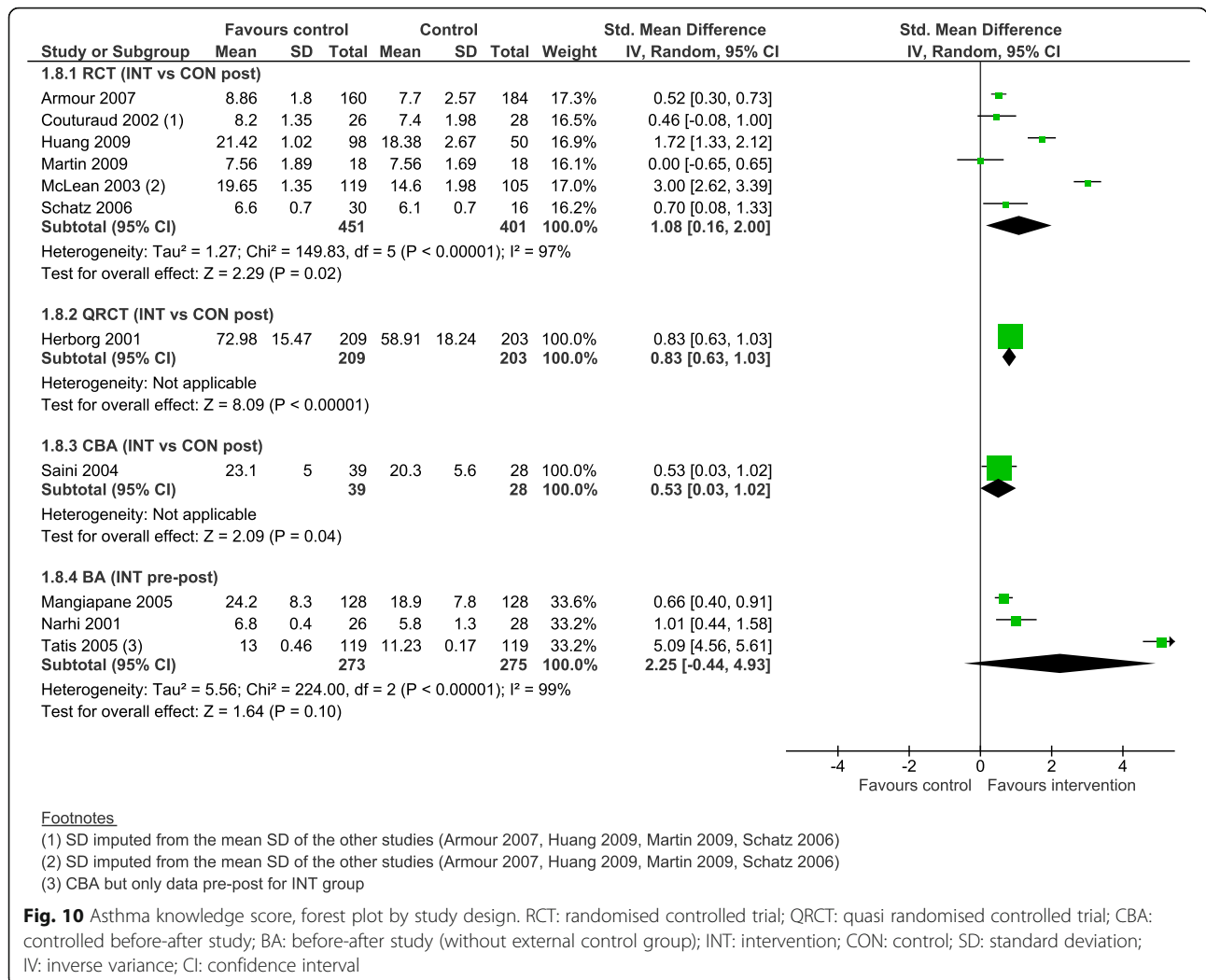


degree of heterogeneity ($I^2 = 83\%$), to 0.77 (95% CI 0.32 to 1.22) for the CBA (Fig. 11).

Discussion

Including study designs other than RCTs, QRCTs and CBA*s allowed the addition of 37 studies to the 20 studies included in the Cochrane review. In terms of study and intervention characteristics, the newly added studies allowed the consideration of programmes taking place in proportionally more countries outside of North America that included population-wide interventions with greater number of patients in a greater variety of settings and patient pools, and were of longer duration. In addition, patients in the studies of this augmented review suffered from less severe asthma. In terms of effectiveness, results from the meta-analyses confirmed that CDM programmes

were significantly favourable to patients. Indeed, they improved asthma-specific QoL, asthma severity scores and lung function across all designs, with the size of effect varying by study design: CBAs and BAs showing more often larger effects than RCTs. CDM interventions also significantly improved self-efficacy scores in CBAs and BAs, while the meta-analysis was inconclusive in RCTs. In addition, we were able to perform meta-analysis of healthcare use in this augmented review, which was not possible in the Cochrane review: while RCTs did not show significant improvement for healthcare use outcomes, BA showed lower likelihood of hospitalisations and unscheduled visits after CDM interventions. Finally, the augmented review permitted the consideration of additional outcomes: CDM interventions were associated with decreased likelihood of patients missing days off work or

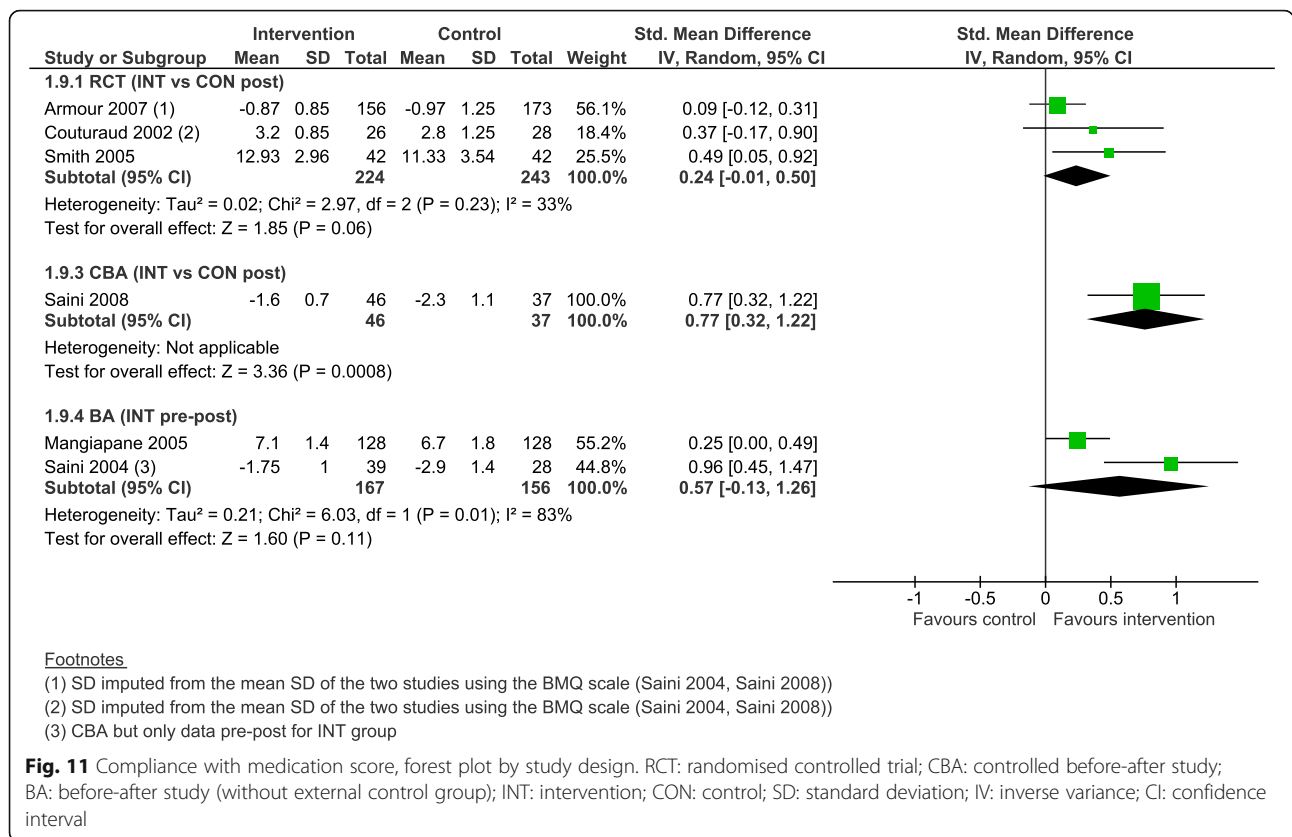


school in BAs, and increased likelihood of using an action plan in BAs, CBAs, and one XS.

Adding NRS and NCS to the original Cochrane review increased the applicability of the Cochrane evidence, as the variety of settings and profile of patients in the newly added studies represent probably better the general setting and target patient population of most asthma CDM programmes. Previous studies have already reported that patient populations selected for recruitment in RCTs in the respiratory field, and more specifically in asthma, represent only about 5 % of the patient population being treated by clinicians in everyday practice [90]. Although RCTs are important and necessary to establish the efficacy of new therapies and interventions, their usefulness can be limited when evaluating how complex interventions will perform in routine care in the real world [91, 92]. In fact, new guidance on conducting systematic reviews of effectiveness interventions encourages the inclusion of non-RCTs to allow for in-depth descriptions of study components and the context and process of

implementing the intervention [93]. A few years after that publication, a meta-review of study design criteria in systematic reviews of health systems interventions positively showed that only one third of reviews restricted study designs to RCTs [94].

Overall, evidence from all study designs was consistent in terms of the direction of the effect; because of the increased applicability, such results strengthen the conclusion of the Cochrane review that CDM programmes have a positive effect on quality of life and asthma severity, meaningful outcomes for the everyday life of patients with asthma. Adding non-randomised studies also allowed us to run new meta-analyses showing improvements associated with CDM programmes for five outcomes (hospitalisations, unscheduled visits, days off work, self-efficacy and action plan) that could not be performed in the Cochrane review. Despite the increased risk of bias, the results, which align with the hypothesized trends, suggest evidence of reduction of hospitalisations, unscheduled visits and days off work. Such results are encouraging in



the context of healthcare spending reductions. According to Schünemann and colleagues' terminology [95], the NRS and NCS evidence can be considered as complementary (i.e. NRS and NCS provide additional information on whether the intervention works in different populations) and sequential (i.e. information not (yet) obtained or available from RCTs).

When looking at the effect sizes of RCT, NRS and NCS, the proportion of outcomes reported by authors as improved in response to CDM was higher in the newly added studies compared with the studies in the Cochrane systematic review. The newly added studies (NRS and NCS) also showed both larger effect size than RCTs and larger confidence intervals, indicating uncertainty for the results in addition to high statistical heterogeneity. These results fuel the ongoing debate about the impact of study design and associated biases on study effect size. A number of reviews have been conducted comparing effect sizes and biases of RCTs with non-randomised studies and non-controlled studies. While some reviews found that lack of randomisation or inadequate randomisation was associated with selection bias, larger effects, smaller effects, or reversed direction of effects [14, 19, 96, 97], others found little to no difference in effect sizes between study designs or according to study quality [98, 99]. As suggested by Rockers and

colleagues, non-experiments can produce valid and causal effect estimates, in settings that are more natural than RCTs [92]. More research is clearly needed on the issue of study design, risk of bias assessment and effect size. A special emphasis should be put on sound methods for measuring and dealing with confounding bias in NRS studies and other biases in NCS, as well as valid methods for pooling NRS and NCS [100, 101].

Overall, randomised, non-randomised and non-controlled studies included in this augmented review were of moderate to low quality with regards to reporting, statistical and methodology standards. While risk of presenting uncertain results without knowing the direction or magnitude of the effect holds true for both non-randomised and randomised controlled trials, risk of bias and confounding is probably higher in non-randomised trials [97]. However, a study at high risk of bias does not necessarily mean the study results are actually biased. In the case of asthma CMD programmes, other authors conducting similar systematic reviews have reported similar low quality of studies [102, 103]. One reason for this low quality may be the lack of widely accepted methods for evaluating CDM programmes, which are typical complex interventions, built up from a number of interacting components, aiming to modify both providers and patients behaviours, targeting multiple organisational levels and groups, including a large

number and variety of outcomes and allowing a certain degree of flexibility (i.e. intervention tailored to patients) [93]. Such complex interventions are difficult to evaluate [104, 105], emphasizing the need for sound evaluation methods to evaluate routine practice in actual settings [106]. Recent guidance has been published to help authors in developing and evaluating complex interventions in general [93, 107] and CDM in particular [106, 108]. Guidelines to improve the completeness and precisions of reporting interventions and their effectiveness have also been published for a variety of study designs, such as the template for intervention description and replication (TIDieR) [109], SQUIRE 2.0 for quality improvement studies [110], the CONSORT statement for RCTs [111], and STROBE for cohort, case-control and cross-sectional studies [112]. Future CDM evaluations should follow these available guidelines to produce high-quality evidence that can then be synthesized in systematic reviews.

The main limitation of this review is that the initial search of the Cochrane review was restricted to quantitative studies, not including all types of available evidence on CDM programmes, such as evidence from implementation, qualitative and mixed methods research which could lead to a more comprehensive understanding of complex interventions.

Conclusions

Evidence from NRS and NCS complemented RCT evidence from the Cochrane review. In fact, adding NRS and NCS to the original Cochrane review both increased the directness of the evidence, as the variety of settings and profile of patients in the newly added studies probably better represent the general setting and target patient population of typical asthma CDM programmes, and also strengthened the message that CDM programmes have a positive effect on quality of life and asthma severity, which are meaningful outcomes for the everyday life of patients with asthma. The inclusion of study designs other than RCTs in systematic reviews investigating the effectiveness of healthcare interventions, especially when they are complex, is increasingly considered to allow for in-depth descriptions of study components and the context and process of implementing the intervention [93, 94, 97]. However, while NRS and NCS studies provide results from interventions in real-life settings that may be valuable to patients, healthcare providers, managers and policymakers, among others, the methodological quality of the studies remains suboptimal, calling for caution in effectiveness results' interpretation, as well as for improvements in CDM evaluation methods and reporting by health researchers.

Additional files

Additional file 1: Risk of bias tool. The extraction form used to assess the risk of bias of included studies. (PDF 55 kb)

Additional file 2: Supplementary Table: Key components of included studies. A table detailing key components of included studies. (PDF 99 kb)

Abbreviations

BA: Before-after; CBA: Controlled before-after; CDM: Chronic disease management; CI: Confidence interval; EPOC: Effective practice and organisation of care; FEV1: Forced expiratory volume in one second; ICS: Inhaled corticosteroids; ITS: Interrupted time series; MD: Mean difference; NCT: Non-controlled studies; NRS: Non-randomised studies; OR: Odds ratio; PEFR: Peak expiratory flow rate; QoL: Quality of life; QRCT: Quasi-randomised controlled trial; RCT: Randomised controlled trial; SMD: Standardised mean difference; XS: Cross-sectional

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Availability of data and materials

Not applicable (systematic review using data published in primary studies).

Authors' contributions

CA acquired the data, performed the data analyses and drafted the manuscript. BB revised the manuscript critically for important intellectual content. IPB conceived and designed the study, contributed to the acquisition of the data and participated in the drafting of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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