Can long-term regular physical activity improve health outcomes among adults with asthma—evidence from a systematic review and Bayesian meta-analysis

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Background: Evidence on the effects of regular physical activity (PA) on asthmatic adults is rather weak and inconsistent since previous studies were conducted based on the limited studies, various populations groups and single outcome. A systematic review (SR) and meta-analysis have a high level of evidence to comprehensively evaluate the effects of PA for adults with asthma based on the available data. Our study aims to provide an SR of available evidence regarding the effect of regular PA on asthma in adults.

Methods: A comprehensive search strategy was conducted using the PubMed, EMBASE, Cochrane Library, and Web of Science databases from their inception to October 2021. We identifying the eligible studies based on the PIOS principles, namely, populations (adults with asthma), interventions (regular PA), outcomes (quality of life or relapse-related outcomes), study design [randomized controlled trials (RCTs)]. A Bayesian-based meta-analysis was performed to pool available evidence. Quality assessment for individual studies was performed with the Cochrane risk of bias tool and the Newcastle-Ottawa Scale (NOS).

Results: A total of 22 publications (18 RCTs and 4 longitudinal studies) were identified, comprised of 85,392 individuals aged between 18 and 75 years old. Overall quality of the included studies was rated as low-to-moderated quality. We found that PA was effective in improving quality of life (QOL) [health related quality of life, (HRQoL) & Asthma Control Questionnaire, (ACQ): standard mean difference (SMD) =–0.80, 95% credible interval (CrI): –1.30 to –0.31; I^2=86.9%, $P_{heterogeneity}$<0.001], pulmonary function (FEV1/pred) [weighted mean difference (MD) =0.47, 95% CrI: 0.03 to 0.90; I^2=74.9%, $P_{heterogeneity}$<0.001], and maximal oxygen consumption (VO2max) (MD =1.18, 95% CrI: 0.87 to 1.48; I^2=17.0%, $P_{heterogeneity}$=0.31). Based on the longitudinal studies, the long-term high-level PA group had a lower risk of developing asthma compared with the low-level PA group [odds ratio (OR) =0.87, 95% CrI: 0.78 to 0.95; I^2=27.4%, $P_{heterogeneity}$=0.22)].

Discussion: Adults with asthma need to carried out regular PA in accordance with the recommendations, which will improve their QOL and pulmonary function, and moreover, long-term PA appears to be more beneficial for asthmatic patients. The quality and quantity of included studies might affect the interpretation.

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Introduction

As one of the most common chronic respiratory inflammatory diseases, asthma is characterized by variable symptoms of wheeze, breathlessness, shortness of breath, chest tightness, or cough, as well as variable expiratory airflow limitation, which occurs due to impaired epithelial barrier function and a dysregulated immune response. The prevalence of asthma has risen sharply over the past decades, reaching 8.5–11.2% in adults and influencing 1–18% of the population in different areas (1). It places a significant burden on families and the medical system, and poses a significant socioeconomic burden, thereby becoming a serious public health issue.

Reliever or controller medications are used among asthmatics for reducing exacerbations. Nevertheless, long-term use of medications may cause minor and serious adverse events (2-4). Moreover, most asthmatics on prescribed controller therapies do not adhere to them for several reasons such as forgetfulness and fear of side effects and costs (5). Considerable attention has recently been devoted to non-pharmacological treatments as alternative strategies for improving asthmatics' quality of life (QOL) and reducing disease risk (6).

Physical activity (PA) is defined by the World Health Organization as "any bodily movement produced by skeletal muscles that results in energy expenditure", and involves 4 core elements, namely frequency, intensity, duration, and modality (7). Regular moderate PA has been recommended as an important non-pharmacological intervention for reducing cardiovascular risk and improving QOL among people with asthma (8). Substantial evidence has indicated that PA exhibits a beneficial effect on asthma symptom control and lung function, particularly aerobic exercise (AE) (9,10). In particular, those with low active and high sedentary typology compared with their peers appeared to have a significant improvement in their asthma symptoms, cardiopulmonary fitness, and maximum oxygen uptake, as well as improved QOL without adverse effects (11-13). Several researchers have hypothesized the etiological relationship between low PA levels and incident asthma. For instance, PA has protective properties against asthma by reducing airway inflammation or positively affecting bronchiole patency (14), and this positive impact was also demonstrated in a mouse model of allergic asthma (15).

A prior study revealed that aerobic training could significantly reduce medication for asthmatic patients (16). Despite the recognized benefits of PA, controversies persist, and existing evidence remains equivocal (17,18). First, previous reviews regarding PA and asthma have demonstrated that some PA had beneficial effects on asthma patients while others showed no significant differences (17-19). For instance, a publication focusing on AE with limited included studies (11 publications) and outcomes (asthma control, lung function and airway inflammation) found a statistically significant improvement regarding asthma control [SMD: –0.48 (95% CI: –0.81 to –0.16)] (9), contradicting another review on the same outcome that demonstrated no statistically significant difference [SMD: –0.25 (95% CI: –0.51 to 0.02)] between the PA group and control group (CG) (6). This probably due to an inconsistent difference of study design, such as search sources, outcome measurement and definition of PA. Furthermore, numerous recent studies focusing on PA and asthma have been published with significantly larger datasets, requiring updated reliable evidence summaries (20,21). Second, although the Global Initiative for Asthma (GINA) has issued guidelines to encourage people with asthma to engage in regular PA for general health benefits, further specific details on using regular PA in treating asthmatic symptoms *per se* remain to be elucidated (8). In addition, PA is a diverse behavior that requires participants to engage in a wide range of alternative activities in their daily lives, whereas previous studies disregarded this point and included populations with varying phenotypes, which may result in different responses to PA, or focused exclusively on asthma control outcomes (1,12). Lastly, whether long-term regular PA is an effective asthma treatment for reducing symptoms and exacerbations remains to be determined, as asthma is an irreversible airway obstruction disease, and evidence from follow-up longitudinal studies examining the long-term effects of PA on asthma are required. A meta-analysis is a method for summarizing the findings of similar

studies, which can extend the sample size and increase the statistical effectiveness, especially when the findings of previous studies are inconsistent, meta-analysis has the ability to obtain the results based on a comprehensive analysis which would closer to the real life. Compared with the frequentist approach, the high sensitivity of Bayesian method can provide a flexibly modeling framework and outputting a more accurate results for the traditional meta-analysis. Therefore, we analyzed available evidence using a Bayesian modeling approach, which proposes more precise results than traditional frequency methods with its simple flexible prior assumptions (22), to examine the long-term effects of regular PA on QOL and other health outcomes in asthmatics patients based on trials and observational studies. We present the following article in accordance with the PRISMA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1170/rc) (23).

Methods

This meta-analysis was performed following the Cochrane Collaboration Handbook recommendations (24). No ethical approval or patient consent was required because all analyses were conducted based on previously published studies.

Search strategies and study selection

Without any language and publication date restrictions, we performed an exhaustive strategic literature search to identify relevant publications concerning the association between regular PA and QOL, as well as other health outcomes in asthmatic adults using the following databases: PubMed (via Medline), EMBASE, the Cochrane Library, Web of Science, PsycINFO (via Ovid), CINAHL, SPORTDiscus, and clinicaltrials.gov (search strategy performed for all databases were from their inception to October 2021). The search strategy was divided into 3 parts to meet the aims of the study using medical subject heading (MeSH) terms associated with keywords combined with Boolean operators. It included the following items: "asthma", "asthmatic", "wheeze", "adults", "physical activity", "aerobic exercise", "resistance training", "muscle-strengthening activities", "skeletal-strengthening activities", "balance activities", and "randomized controlled trials". All database-specific search queries can be found in Appendix 1.

We also conducted a recursive search to identify relevant publications by manually screening bibliography lists of

similar reviews and large-scale specialized conferences. Two independent investigators performed study selection, and any discrepancies which emerged during the process were discussed or resolved by consulting a third expert. Automatic deletion of duplicates was performed first, and irrelevant studies were removed based on their titles and abstracts. Subsequently, we analyzed the full texts of potentially eligible studies. Two independent investigators cross-checked selected citations to ensure their integrity and accuracy. All citations were downloaded and managed in EndNote X9 Software (Thompson ISI ResearchSoft, Clarivate Analytics, Philadelphia, USA).

Inclusion and exclusion criteria and data abstraction

The studies were included when they met the eligibility criteria as follows.

Populations
Participants were adults above 18 years old with mild-to-moderate or severe chronic asthma, regardless of whether they were diagnosed by a physician or self-reported using standard diagnostic interviews or exceeded a predefined threshold for asthma using a validated severity measurement.

Interventions
We included studies with PA interventions in adults with asthma. Acceptable exercise training included PA interventions performed at least twice weekly for at least 8 weeks, as defined by the American College of Sports Medicine Guidelines (25). The interventions included any type of PA, such as AE comprising jogging, swimming, cycling, and aerobic dance; anaerobic exercise (ANE), including weight lifting, sprinting, throwing, long jump, and tug-of-war; resistance training (RT), comprising push-ups, squats, sit-ups, dumbbells, and sandbags; or other PA modalities such as muscle-strengthening activities (MSA), skeletal-strengthening activities (SSA), and balance activities (BA). The above-mentioned PA was conducted with supervised and unsupervised interventions.

Comparators
Comparators included the CG along with diet intervention, education, and placebo groups.

Outcomes
The primary outcome was any measurement that assessed

QOL for asthmatic patients including various clinical measurement approaches which can evaluate the change in QOL (self or assessor-rated) from baseline to endpoint. The secondary outcome measurements were asthma control, pulmonary function, and other indicators for assessing asthma symptom severity.

Study design

Our study included any type of randomized controlled trials (RCTs) and longitudinal population-based studies, regardless of whether they were prospective or retrospective cohort studies, and regardless of race, country, or publication date. For detecting whether asthmatic adults would benefit from long-term PA, we additional included the observational studies. Studies were excluded if they met the following conditions: (I) participants were less than 18 years old or studies which could not distinguish participants 18 years old and below, and if most enrolled patients were substance withdrawal; (II) PAs whether combinatorial or multicomponent, were eliminated since they introduced confounding variables into our analyses; the definition of PA in study is vague, (III) full-texts or data could not be obtained for our analyses; (IV) studies were excluded if they were protocols or review studies; (V) outcomes were reported with biological indicators or other measures that could not produce the intersecting endpoint for our analyses, placebo or control group in any combination with any intervention.
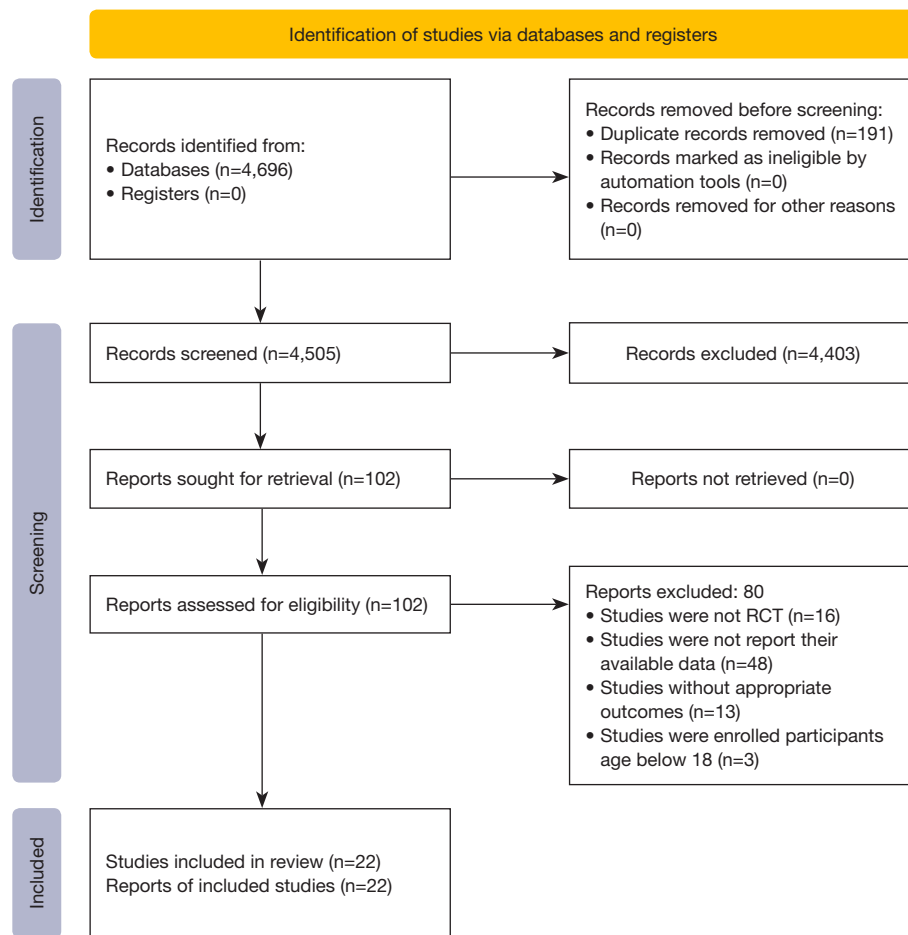
Outcome measurement and quality assessment

The following key information of the included studies was extracted into a pre-designed comprehensive Excel form: first author, publication year, origin, intervention duration/follow-up time, and study design, as well as the characteristics of participants such as age, sample size, and sex ratio. If the essential data were not reported in the original studies, they were obtained by contacting corresponding authors of potential studies.

Two reviewers independently evaluated the quality of the included RCTs based on the Cochrane risk of bias tool (24). RCTs were evaluated by the Cochrane risk of bias tool, which included 7 items, namely random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases, and items were judged as "high risk", "low risk", and "unclear risk".

The quality assessment of observational studies was performed using the Newcastle-Ottawa Scale (NOS), independently judged by 2 assessors. Three major separate items contributed to the overall NOS quality assessment tool: patient selection, comparability of the treatment and observation groups, and outcome assessment. Included studies with scores over or equal to 6 were considered to be of high quality, whereas those with a score below 7 were considered to be of low quality (26,27).

Statistical analyses

First, we conducted a traditional pairwise meta-analysis of included trials for each existing comparison (28). For outcomes presented as dichotomous variables, the odds ratio (OR) was applied to calculate the pooled effect sizes (ESs) for each study. For numerical variables, we extracted their mean difference and standard deviation (SD) of the change from baseline or transformed them into a standard format to ensure that our analyses were conducted smoothly. As the presence of ESs indicates a continuous outcome, weighted mean difference (WMD) or standard mean difference (SMD) were calculated for each comparison using group (relevant) means and SD from individual studies with a random effect model. The 95% credible interval (CrI) was calculated along with the above combined ESs as a measure of estimated uncertainty (29). The quantitative pooled analyses were conducted based on the fixed effect model (inverse variance), and the random effect model (I–V heterogeneity approach) was applied if heterogeneity was present (28). I^2 statistics were used to evaluate statistical heterogeneity, with estimated values of 25%, 50%, and 75% indicating mild, moderate, and high heterogeneity, respectively (30). The Bayesian statistical approach has a strong advantage over the traditional frequency approach in that the former approach not only provides a flexible and efficient modeling instrument by estimating posterior probability, but also controls various biases generated during the iteration process compared with the frequency method (22,31). Additionally, potential bias in small studies was evaluated using a comparison-adjusted funnel plot, which serves as an intuitive visual instrument for detecting the presence of any dominant types of potential bias, such as publication bias, selective reporting, or other biases. Quantitative Egger's test was performed to determine whether P values were less than 0.05 (32). A sequence of subgroup analyses was conducted to explain any observed heterogeneity or to explore statistically

Identification of studies via databases and registers

Identification

Records identified from:
• Databases (n=4,696)
• Registers (n=0)

→

Records removed before screening:
• Duplicate records removed (n=191)
• Records marked as ineligible by automation tools (n=0)
• Records removed for other reasons (n=0)

Screening

Records screened (n=4,505) → Records excluded (n=4,403)

Reports sought for retrieval (n=102) → Reports not retrieved (n=0)

Reports assessed for eligibility (n=102) →

Reports excluded: 80
• Studies were not RCT (n=16)
• Studies were not report their available data (n=48)
• Studies without appropriate outcomes (n=13)
• Studies were enrolled participants age below 18 (n=3)

Included

Studies included in review (n=22)
Reports of included studies (n=22)

Figure 1 Literature review flowchart. RCT, randomized controlled trial.

significant differences between studies. The variables of interest are as follows: quality of included studies (low and high), publication year (≥2010 and <2010), region (Europe, America, and other regions), indoor PA or outdoor PA (indoor and outdoor), whether under self-supervision (supervised and unsupervised), intervention duration (≥12 weeks and <12 weeks), total sample size (≥50 and <50), male-to-female ratio (≥1 and <1), and participant diagnosis (self-report and diagnosed with asthma by physician). All the above sequences of analyses were performed in STATA, version 14.0, using the code "winbugsfromststa" to debug WinBUGS software (Stata, Corp, College Station, TX, USA).

Results

Study selection and characteristics of the included studies

We obtained 4,696 studies from the database searches

(12 publications were identified through other sources), of which 191 duplicates were first excluded, while 4,403 were removed based on their titles and abstracts. Subsequently, the remaining 102 studies were eligible for full-text screening. A total of 80 publications were excluded for various reasons, as follows: 16 studies were presented as protocols, 48 did not provide their available data for our analyses, 13 had irrelevant outcomes, and 3 enrolled participants below 18 years old. Finally, 22 studies were included in our analyses, comprising 18 RCTs (33-50) and 4 longitudinal studies (51-54), and details of the study selection process are depicted in *Figure 1*.

All 22 included studies enrolled 85,392 individuals aged between 18 and 75 years, with 1,073 and 84,319 participants in RCTs and observational studies, respectively. There was a significantly lower proportion of male participants than female participants [males in RCTs: 173 (32.15%), males in longitudinal studies: 4,449 (5.28%)]. The intervention

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duration of trials ranged from 8 weeks to 12 months, with a median follow-up time of 9 years across the 4 included longitudinal studies. Participants were recruited primarily in South America (N=8, 44.4%) and Europe (N=4, 22.2%). All subjects enrolled in the included studies received the appropriate basic treatment and the majority of them had moderate to severe asthma. Ten of the 18 RCTs gave a clear description of the daily doses of inhaled corticosteroids (ICS) administered to the subjects. *Table 1* summarizes the demographic characteristics of the included studies.

Quality of the included studies

All 18 RCTs were evaluated as having a low risk of bias regarding random sequence generation. Thirteen out of 17 trials were rated as having a low risk of selection bias. Six studies were judged as having a low risk of performance bias, whereas 13 of the 18 studies were rated as having a high risk of detection bias. Regarding attrition bias, only 1 study was rated as having a high risk of bias, and of the remaining studies, 16 were rated as having a low risk of bias while 1 study had an unclear risk of bias. Concerning reporting bias, most studies (11/17, 64.71%) were judged as high quality with a low risk of bias. Figures S1,S2 provide detailed justifications for the risk of bias assessments of the included RCTs. For longitudinal studies, 3 studies were rated as high quality, scoring 7 points according to the NOS criteria. Figure S3 displays the detailed descriptions of the NOS assessment process.

Primary outcomes

QOL

Two trials used health-related quality of life (HRQOL) (121 participants) (45,46) while 8 trials used the asthma control questionnaire (ACQ) (600 participants) (33,36,40,41,44,48-50) as one of their endpoints to assess QOL among asthma patients. The results revealed that participants receiving PA were more likely to improve their QOL (SMD =−0.80, 95% CrI: −1.30 to −0.31; I^2=86.9%, $P_{heterogeneity}$<0.001) (*Table 2*). There were significant differences between the PA group and CG for the 4 domains of HRQOL [(physical limitation: SMD=−2.73, 95% CrI: −3.32 to −2.13; I^2=11.0%, $P_{heterogeneity}$=0.29), (symptom frequency: SMD =−2.20, 95% CrI: −2.65 to −1.74; I^2=0.0%, $P_{heterogeneity}$=0.94), (socioeconomic: SMD =−1.01, 95%

CrI: −2.02 to −0.01; I^2=76.2%, $P_{heterogeneity}$<0.05), (psychosocial: SMD =−2.32, 95% CrI: −2.79 to −1.86; I^2=0.0%, $P_{heterogeneity}$=0.81)] (*Table 2*). The funnel plot was not symmetrical, suggesting the existence of potential publication bias ($P_{Egger's\ test}$=0.648) (Figure S4).

Seven studies (590 participants) (33,40,41,43,44,47,48) reported their outcomes based on the asthma-related quality of life questionnaire (AQLQ), and the pooled results failed to reach statistical significance between the PA group and CG (MD =−0.03, 95% CrI: −0.61 to 0.54; I^2=87.9%, $P_{heterogeneity}$<0.001) (*Table 2*). No symmetry was observed in the funnel plot, indicating publication bias ($P_{Egger's\ test}$=0.783) (Figure S5). The same results were also found for the 4 domains of the AQLQ [(activity limitation: MD =0.16, 95% CrI: −0.67 to 1.00; I^2=93.3%, $P_{heterogeneity}$<0.001), (symptom: MD =0.39, 95% CrI: −0.37 to 1.14; I^2=91.9%, $P_{heterogeneity}$<0.001), (emotional function: MD =0.44, 95% CrI: −0.16 to 1.03; I^2=87.2%, $P_{heterogeneity}$<0.001), (environmental stimuli: MD =0.55, 95% CrI: −0.49 to 1.59; I^2=95.6%, $P_{heterogeneity}$<0.001)] (*Table 2*).

Secondary outcomes

Asthma control

Four studies (216 participants) (33,38,45,46) investigated the effectiveness of PA on asthma symptom free-days, without observing a significant difference (MD =0.93, 95% CrI: −0.39 to 2.25; I^2=94.2%, $P_{heterogeneity}$<0.001) (*Table 2*). The asymmetry of the funnel plot for asthma symptom free-day indicated publication bias ($P_{Egger's\ test}$=0.867) (Figure S6).

Pulmonary function
Forced expiratory volume in one second (FEV₁)
Ten trials (796 participants) (33-35,37,39,43-46,48,49) considered FEV_1 in liters as their primary outcome (MD=0.24, 95% CrI: −0.13 to 0.60; I^2=81.4%, $P_{heterogeneity}$<0.001), whereas 8 trials (381 participants) considered FEV_1 as a percentage of the predicted value (FEV_1/pred) (MD =0.47, 95% CrI: 0.03 to 0.90; I^2=74.9%, $P_{heterogeneity}$<0.001) (33,34,37,40-42,45,50) (*Table 2*). Significant publication bias was identified based on the above 2 outcomes as the funnel plots showed asymmetry [FEV_1 in liters: $P_{Egger's\ test}$=0.802, FEV_1/pred: $P_{Egger's\ test}$=0.741] (Figures S7,S8).
Forced vital capacity (FVC)
A random effect model was performed to estimate the pooled effect of FVC in liters (8 studies, 717 participants; MD =−0.02, 95% CrI: −0.70 to 0.65; I^2=93.5%,

Table 1 Demographic characteristics of included studies

Sources	Study design	PA type	Participants sample		Proportion of female (%)	Age (years), mean ± SD/range		Whether supervision	Therapeutic course/length of follow-up	Region	Outcomes
			PA	CG		PA	CG				
Cochrane, 1990	RCT	Varied aerobic exercises, including cycling, jogging, and "aerobics"	18	18	61.10	28±7	28±8	Some sessions	3 months	UK	FEV_1, FEV_1/pred, VO_2max
Farid, 2005	RCT	A course of aerobic exercise	18	18	55.60	27	29	Unclear	8 weeks	Iran	FEV_1, FVC/pred, FEV_1/FVC
Gonalves, 2008	RCT	Treadmill training, education and breathing exercises	10	10	65.00	34.6 (21.0–47.0)	34.6 (21.0–47.0)	Yes	12 weeks	Brazil	HRQoL, HRQoL (4 sub-items), ASFD, FeNO
Mendes, 2010	RCT	Unspecified aerobic exercise training, breathing exercises and educational programme	50	51	73.30	39 (22–47.9)	39.5 (23.5–47.0)	Yes	3 months	Brazil	HRQoL, HRQoL (4 sub-items), ASFD, FEV_1, FEV_1/pred, FVC, FVC/pred, FEV_1/FVC
Mendes, 2011	RCT	Unspecified aerobic exercise training, breathing exercises and educational programme	27	24	41.20	37.9 (25.7–47.3)	36.0 (22.0–47.5)	Yes	3 months	Brazil	FEV_1, FEV_1/pred, FVC, FVC/pred, FEV_1/FVC, FeNO, VO_2max
Boyd, 2012	RCT	Walking	6	8	92.90	53 [38–62]	54 [33–78]	No	12 weeks	UK	ACQ, FEV_1/pred
Scott, 2013	RCT	Gym and intermittent personal training sessions and a diet intervention	13	15	53.60	33.9±11.5	44.7±14.7	Once a week	12 weeks	Australian	AQLQ, ACQ, FEV_1, FVC, FEV_1/FVC, FeNO
França-Pinto, 2015	RCT	Treadmill training and breathing exercises	22	21	48.80	40±11	44±99	Yes	12 weeks	Brazil	AQLQ, AQLQ (4 sub-items), ASFD, FEV_1, FEV_1/pred, FeNO, VO_2max

Table 1 (*continued*)

Table 1 (*continued*)

Sources	Study design	PA type	Participants sample		Proportion of female (%)	Age (years), mean ± SD/range		Whether supervision	Therapeutic course/length of follow-up	Region	Outcomes
			PA	CG		PA	CG				
Toennesen, 2018	RCT	Indoor cycling	29	34	76.20	43.7±13.9	38.2±12.7	Yes	8 weeks	Denmark	AQLQ, ACQ, FEV_1pred, FVC/pred, FeNO, VO_2max
Freitas, 2017	RCT	Unspecified aerobic exercise training and hypocaloric diet	26	25	98.00	45.9±7.7	48.5±9.6	No	3 months	Brazil	AQLQ (4 sub-items), ACQ, FEV_1, FVC, FeNO
Refaat, 2015	RCT	Exercise training	38	30	45.60	35.8±1.7	38±5.3	Yes	3 months	Kuwait	AQLQ, AQLQ (4 sub-items), FEV_1, FVC
Turner, 2011	RCT	Exercise training	19	15	55.90	65.3±10.8	71.0±9.7	Yes	3 months	Australia	AQLQ (4 sub-items), ACQ
Shaw, 2011	RCT	Aerobic exercise	22	22	63.60	21.95±3.84	21.90±3.89	Yes	8 weeks	South Africa	FEV_1, FVC, FEV_1/FVC
Coelho, 2018	RCT	Physical activity + usual care	20	17	86.50	45±19	47±14	No	3 months	Brazil	AQLQ, ACQ, FEV_1/pred, FVC/pred, FEV_1/FVC
Freitas, 2018	RCT	A treadmill interspersed with either bike or elliptical machine workouts	26	26	96.20	45.9±7.7	48.5±9.6	The exercise program included two sessions of supervised aerobic and resistance exercises	3 months	Brazil	ASFD
Ma, 2015	RCT	Moderate-intensity physical activity	165	165	70.60	47.5±12.6	47.7±12.1	Ongoing supervision	12 months	US	AQLQ, AQLQ (4 sub-items), ACQ, FEV_1, FVC, FEV_1/FVC

Table 1 (*continued*)

Table 1 (*continued*)

Sources	Study design	PA type	Participants sample PA	Participants sample CG	Proportion of female (%)	Age (years), mean ± SD/range PA	Age (years), mean ± SD/range CG	Whether supervision	Therapeutic course/length of follow-up	Region	Outcomes
Meyer, 2015	RCT	Walking, endurance and circuit training, cardiopulmonary exercise	13	8	61.90	54±11	59±9	Once weekly supervised sessions	12 months	Germany	AQLQ, AQLQ (4 sub-items)
Shaw, 2010	RCT	Weekly supervised aerobic exercise	22	22	63.60	21.95±3.87	21.90±3.89	three times weekly supervised	8 weeks	Republic of South Africa	FEV_1, FVC, VO_2max
Beckett, 2001	LS	MPA	4,547		54.90	18–30		Unclear	10 years	US	Incidence
Benet, 2011	LS	Recreational physical activity habits (walking, cycling, gardening, home do-it-yourself activities, sports, and climbing stairs)	51,080		Women	40–65		Unclear	9 years	France	Incidence
Huovinen, 2003	LS	A series of PA	9,671		54.00	25–52		Unclear	9 years	Finland	Incidence
Lucke, 2007	LS	A series of PA	1,9021		Women	18–75		Unclear	5–7 years	Australia	Incidence

ACQ, Asthma Control Questionnaire; AQLQ, Asthma-related quality of life questionnaire; AQLQ (4 sub-items), AQLQ-Activity limitation domain, AQLQ-Symptoms domain, AQLQ-Emotional function domain, AQLQ-Environmental stimuli domain; ASFD, asthma symptom-free days; CG, control group; FEV_1, forced expiratory volume in one second (L); FEV_1/pred, FEV_1 as a percentage of the predicted value; FVC, forced vital capacity (L); FVC/pred, FVC as a percentage of the predicted value; HRQoL, health related quality of life; HRQoL (4 sub-items), HRQoL-Physical limitation, HRQoL-Symptom frequency, HRQoL-Socioeconomic, HRQoL-Psychosocial; LS, longitudinal study; MPA, moderate PA; PA, physical activity; RCT, randomized controlled trial; UK, the United Kingdom; US, the United States of America; VO_2max, maximal oxygen uptake.

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Table 2 Primary results based on various outcomes and subgroup analyses

Meta-analyses outcomes	Meta-analyses variables	No. of studies	No. of patients		Pool effect size	Heterogeneity	
			PA	CG		I^2 (%)	P
RCTs[a]		18	544	529			
Primary outcomes							
Quality of life	HRQoL & ACQ	10	360	361	−0.80 (−1.30 to −0.31)	86.90	<0.001
	HRQoL-Physical limitation	2	60	61	−2.73 (−3.32 to −2.13)	11.00	0.29
	HRQoL-Symptom frequency	2	60	61	−2.20 (−2.65 to −1.74)	0.00	0.94
	HRQoL-Socioeconomic	2	60	61	−1.01 (−2.02 to −0.01)	76.20	<0.05
	HRQoL-Psychosocial	2	60	61	−2.32 (−2.79 to −1.86)	0.00	0.81
	AQLQ	7	300	290	−0.03 (−0.61 to 0.54)	87.90	<0.001
	AQLQ-Activity limitation domain	6	283	264	0.16 (−0.67 to 1.00)	93.30	<0.001
	AQLQ-Symptoms domain	6	283	264	0.39 (−0.37 to 1.14)	91.90	<0.001
	AQLQ-Emotional function domain	6	283	264	0.44 (−0.16 to 1.03)	87.20	<0.001
	AQLQ-Environmental stimuli domain	6	283	264	0.55 (−0.49 to 1.59)	95.60	<0.001
Secondary outcomes							
Asthma control	Asthma symptom free-day	4	108	108	0.93 (−0.39 to 2.25)	94.20	<0.001
Pulmonary function	FEV_1	10	403	393	0.24 (−0.13 to 0.60)	81.40	<0.001
	FEV_1/pred	8	190	191	0.47 (0.03 to 0.90)	74.90	<0.001
	FVC	8	363	354	−0.02 (−0.70 to 0.65)	93.50	<0.05
	FVC/pred	5	144	144	0.39 (−0.05 to 0.82)	67.90	<0.001
	FEV_1/FVC	7	315	312	−0.03 (−0.41 to 0.35)	76.20	<0.001
Airway inflammation	FeNO	6	127	129	0.58 (−0.90 to 2.06)	96.00	<0.001
Exercise tolerance	VO_2Max	5	118	119	1.18 (0.87 to 1.48)	17.00	0.31
Longitudinal study[b]							
High level PA *vs.* low level PA		7	30,470	34,260	0.87 (0.77 to 0.98)	27.40%	0.22

Table 2 (*continued*)

Table 2 (*continued*)

Meta-analyses outcomes	Meta-analyses variables	No. of studies	No. of patients		Pool effect size	Heterogeneity	
			PA	CG		I^2 (%)	P
Subgroup analysis based on the primary outcome of quality of life[c]							
Quality of included studies	Overall	10	360	361	−0.80 (−1.30 to −0.31)	86.90	<0.001
	Low bias	9	354	353	−0.91 (−1.07 to −0.75)	88.20	<0.001
	High bias	1	6	8	−0.41 (−1.48 to 0.66)	−	−
Region	Overall	10	360	361	−0.80 (−1.30 to −0.31)	86.90	<0.001
	Europe and America	3	200	207	−0.95 (−1.15 to −0.74)	0.00	0.47
	Other regions	7	160	154	−0.83 (−1.08 to −0.58)	91.00	<0.001
Publication year	Overall	10	360	361	−0.80 (−1.30 to −0.31)	86.90	<0.001
	Above and equal 2010	1	10	10	−2.89 (−4.18 to −1.61)	−	−
	Below 2010	9	350	351	−0.87 (−1.03 to −0.71)	86.60	<0.001
Total sample size	Overall	10	360	361	−0.80 (−1.30 to −0.31)		
	Above or equal 50	6	90	86	−0.23 (−0.54 to 0.07)	74.10	<0.001
	Below 50	4	270	275	−1.14 (−1.32 to −0.95)	88.00	<0.001
Male to female ratio	Overall	10	360	361	−0.80 (−1.30 to −0.31)	86.90	<0.001
	Above or equal 1	10	360	361	−0.90 (−1.06 to −0.74)	−	−
	Below 1	0	−	−	−	−	−
Indoor or outdoor	Overall	10	360	361	−0.80 (−1.30 to −0.31)	86.90	<0.001
	Indoor	8	189	188	−0.82 (−1.04 to −0.60)	89.50	<0.001
	Outdoor	2	171	173	−0.97 (−1.20 to −0.75)	9.90	0.29
Self-supervision	Overall	10	360	361	−0.80 (−1.30 to −0.31)	86.90	<0.001
	Yes	6	295	296	−1.02 (−1.20 to −0.84)	90.80	<0.001
	No or session	4	65	65	−0.41 (−0.76 to 0.06)	40.70	0.17
Intervention durations	Overall	10	360	361	−0.80 (−1.30 to −0.31)	86.90	<0.001
	Above or equal 12 weeks	9	331	327	−0.91 (−1.07 to −0.74)	88.40	<0.001
	Below 12 weeks	1	29	34	−0.79 (−1.31 to −0.28)	86.90	<0.001

If studies reported with more than two categories of different PA levels, they were converted into two groups, namely high level PA and low level PA while the later group was used as the reference category. Pool effect size: [a], pooled WMDs/SMDs (95% CrI); [b], pooled ORs (95% CrI); [c], pooled SMDs (95% CrI). ACQ, Asthma Control Questionnaire; AQLQ, asthma-related quality of life questionnaire; AQLQ (4 sub-items), AQLQ-Activity limitation domain, AQLQ-Symptoms domain, AQLQ-Emotional function domain, AQLQ-Environmental stimuli domain; ASFD, asthma symptom-free days; CI, confidence interval; CG, control group; FEV$_1$, forced expiratory volume in one second (L); FEV$_1$/pred, FEV$_1$ as a percentage of the predicted value; FeNO, fractional exhaled nitric oxide; FVC, Forced vital capacity (L); FVC/pred, FVC as a percentage of the predicted value; HRQoL, Health related quality of life; HRQoL (4 sub-items), HRQoL-Physical limitation, HRQoL-Symptom frequency, HRQoL-Socioeconomic, HRQoL-Psychosocial; LS, longitudinal study; MPA, moderate PA; OR, odds ratio; PA, physical activity; RCT, randomized controlled trial; SMD, standard mean differences; UK, the United Kingdom; US, the United States of America; VO$_2$max, Maximal oxygen uptake; WMD, weighted mean differences.

$P_{heterogeneity}<0.001$) (35,37,39,43-45,48,49) and FVC as a percentage of the predicted value (FVC/pred) (5 studies, 288 participants; MD =0.39, 95% CrI: –0.05 to 0.82; $I^2=67.9\%$, $P_{heterogeneity}<0.001$) (37,40-42,45) (*Table 2*). The funnel plot for the above outcomes appeared asymmetrical, indicating publication bias [FVC in liters: $P_{Egger's test}=0.842$, FVC/pred: $P_{Egger's test}=0.141$] (Figures S9,S10).

FEV1/FVC

Seven studies (627 participants) examined the outcome of FEV_1/FVC, and no significant change was found between the 2 groups (MD =–0.03, 95% CrI: –0.41 to 0.35; $I^2=76.2\%$, $P_{heterogeneity}<0.001$) (37,39,40,42,44,45,48) (*Table 2*). Bilateral asymmetry on the funnel plot was observed ($P_{Egger's test}=0.013$) (Figure S11).

Airway inflammation

Fraction of exhaled nitric oxide (FeNO)

Six studies comprising 256 participants reported on the FeNO. There were no significant differences in FeNO (MD =0.58, 95% CrI: –0.90 to 2.06; $I^2=96.0\%$, $P_{heterogeneity}<0.001$) (33,37,41,44,46,49) (*Table 2*). The funnel plot and Egger's test were employed to evaluate publication bias with the relevant estimates ($P_{Egger's test}=0.013$) (Figure S12).

Exercise tolerance

Maximal oxygen consumption (VO₂max)

Five studies (237 participants) examined the effects of PA on VO_2max and discovered a significant improvement between the 2 groups (MD =1.18, 95% CrI: 0.87 to 1.48; $I^2=17.0\%$, $P_{heterogeneity}=0.31$) (33-35,37,41) (*Table 2*). A highly symmetrical funnel plot was obtained, indicating the absence of publication bias, and Egger's test (P=0.117) was consistent with the funnel plot result (Figure S13).

Observational studies

If studies reported more than 2 categories of different PA levels, they were converted into 2 groups, namely high level PA and low level PA, and the latter group was used as the reference category. Four longitudinal studies (84,319 participants) were splitted into 7 studies (64,730 participants) for presenting their PA level with more than 2 groups (48-51). The pooled ES (OR) was 0.87 (95% CrI: 0.77 to 0.98), with mild heterogeneity ($I^2=27.4\%$, P=0.22) (*Table 2*). Symmetry of the funnel plot was observed ($P_{Egger's test}=0.992$) (Figure S14).

Subgroup analyses

Based on the primary outcome of QOL, the subgroup analyses were conducted with different variables of interest, and most of them were yielded consistency that without significantly statistical differences between subgroup items. Nevertheless, when the items of total sample size and self-supervision were taken into consideration, the total participants below 50 (MD =–1.14, 95% CrI: –1.32 to –0.95) saw a notable improvement compared with the CG (MD =–0.23, 95% CrI: –0.54 to 0.07). The same result was found for participants under self-supervision (MD =–1.02, 95% CrI: –1.20 to –0.84) compared with group without or with part of supervision (MD =–0.41, 95% CrI: –0.76 to 0.06) (*Table 2*).

Discussion

To the best of our knowledge, this study is the first meta-analysis to provide an exhaustive overview of the effectiveness of PA in adults with asthma by simultaneously incorporating both trials and observational studies. Based on the 22 studies, comprising 18 RCTs and 4 longitudinal studies, our findings confirmed that regular PA could improve the QOL and other health outcomes among adult patients, and has also been linked to maintaining long-term PA.

There is poor evidence to endorse one form of PA over another, even from the latest guideline issued in 2021 (8). Our findings establish a link between increased regular PA and favorable outcomes, including higher QOL (HRQOL and ACQ), better lung function (FEV_1/pred), improved VO_2max, and long-term effects. As a critical index for characterizing individuals and assessing the effectiveness of interventions, the HRQOL scale is a widely used tool consisting of 4 domains, namely physical limitation, symptom frequency, socioeconomic conditions, and psychosocial health. It can evaluate QOL among asthmatic patients that can be captured by biological or clinical indicators. When SMD was pooled with HRQOL and ACQ, we detected significant differences between the PA group and CG (SMD =–0.80, 95% CrI: –1.30 to –0.31). The same results were also obtained for the 4 sub-items of HRQOL, although only 2 included studies assessed these items. While a substantial body of evidence already demonstrated that asthmatic patients could benefit from regular PA, the same efficacy was also observed in patients

with exercise-induced asthma (55-57), as asthmatics' variable symptoms such as wheeze and shortness of breath are regularly triggered by exercise (58). Furthermore, asthmatics were shown to develop anxiety about exercise-induced bronchoconstriction (EIB) (59-61), which is why some often intuitively or purposely adopt a sedentary lifestyle over an active one. Although exercise is an important cause of airway obstruction, which can eventually develop into asthma, the maintenance of medications such as ICS-formoterol can generally be reduced to maintain symptom control in EIB (62). Additionally, a short warm-up pre-exercise can be introduced for controlling exercise-related symptoms, or a short-acting beta agonist (SABA) reliever (62) can be taken whenever a low dose of ICS (63) is taken before or during exercise.

Our study also found that when asthmatic individuals performed PA, their pulmonary function outcome significantly improved (FEV_1/pred). This outcome is critical when evaluating health outcomes for asthmatics patients, as peripheral airway involvement and functional status are closely related to pathophysiology, disease progression, and clinical manifestations of asthma (64), although they are not the gold-standard airflow limitation measurements (65). Long-term beneficial effects of high-level PA have also been shown (OR: 0.87, 95% CrI: 0.77 to 0.98), with a lower risk of developing asthma than the low-level PA group. Although the number of longitudinal studies we identified was small (N=4), the total accrued number of subjects was considerable (N=84,319). A reverse causal relationship should also be considered to explain why asthmatic patients have lower PA rates. Several factors contribute to this, including poor education, fear for asthma symptoms, or inadequately regulated asthma (66).

Any PA performed during daily life such as household activities, recreation, transportation, sports, and other leisure-time activities should be encouraged, as they have been shown to benefit not only asthma-related outcomes but also other dimensions of health-related endpoints (cardiorespiratory and muscular fitness) in asthmatic patients (67,68), particularly severe asthma and specific asthma populations (69,70). Notably, PA combined with pharmacological interventions was more effective than PA alone, and this requires further investigation. Other remaining issues should also be investigated, including the treatment's side effects and patient acceptability of asthma self-management (71,72). In particular, for obese asthmatic patients, a weight-reduction program incorporating aerobic and strength exercises is more effective for symptom control than a weight reduction program alone (49). Further research should focus on objectively investigating assessment technology for measuring PA, such as an accelerometer, which is a wearable device that enables continuous and precise monitoring of the multiaxial accelerations of body movement in patients, offering a greater degree of reliability than traditional self-report questionnaires (73).

Strengths and limitations

To summarize, our study contributes to the latest evidence by providing an informative summary of the evidence regarding how regular PA may help asthmatic patients to improve their QOL and control asthma. This guide may assist policymakers, clinicians, or caregivers in making choices and navigates the direction of clinical decision making, thereby facilitating future research and clinical application. As far as we know, this is the first attempt to summarize intervention trials and observational follow-up studies to evaluate the relationship between regular PA and asthma-related outcomes among adults. Potential studies were retrieved and further retrieved through screening the references of similar studies and by manual searches during the study selection process in case of the omission of relevant studies.

This study has several limitations that must be acknowledged. First, all results were based on a relatively limited number of included studies, leading to insufficient evidence in our analysis. Additionally, the methodological shortcomings of the 18 RCTs may jeopardize the study's overall quality. The issues of heterogeneity, imprecision, inconsistency between included studies, and further risk of bias of individual studies are mainly reflected in outcome assessment blinding and selective bias items. Moreover, a language bias was generated due to non-English language databased were search. We also included both RCTs and cohort studies while such two different type studies can generate heterogenous or even conflicting results which may cause possible bias to our findings. Finally, several included studies enrolled asthmatic patients with comorbidities such as obesity, which may introduce bias to our findings (37,52). Considering the above limitations, the findings of our study should be interpreted with caution.

Conclusions

Despite some limitations and uncertainties, our findings

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demonstrate the benefits of regular PA in terms of health-related outcomes for asthmatic patients and their long-term consequences. In the future, well-designed research addressing the precise association between PA and asthmatic patients is encouraged.

Acknowledgments

Footnote

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(English Language Editor: C. Betlazar-Maseh)

Appendix 1 Search strategies

PubMed

#1   "Exercise"[Mesh]

#2   Search (Physical Activity [Title/Abstract]) OR (Activities, Physical [Title/Abstract]) OR (Physical Activities [Title/Abstract]) OR (Exercise, Physical [Title/Abstract]) OR (Exercises, Physical [Title/Abstract]) OR (Physical Exercise [Title/Abstract]) OR (Physical Exercises [Title/Abstract]) OR (Acute Exercise [Title/Abstract]) OR (Acute Exercises [Title/Abstract]) OR (Exercise, Acute [Title/Abstract]) OR (Exercises, Acute [Title/Abstract]) OR (Exercise, Isometric [Title/Abstract]) OR (Exercises, Isometric [Title/Abstract]) OR (Isometric Exercises[Title/Abstract]) OR (Exercise, Aerobic [Title/Abstract]) OR (Aerobic Exercise [Title/Abstract]) OR (Exercises, Aerobic [Title/Abstract]) OR (Exercise Trainings [Title/Abstract]) OR (Training, Exercise [Title/Abstract]) OR (Trainings, Exercise [Title/Abstract])

#3   "Asthma"[Mesh]

#4   ((Asthmas[Title/Abstract]) OR (Bronchial Asthma[Title/Abstract])) OR (Asthma, Bronchial[Title/Abstract])

#5   "Asthma, Occupational"[Mesh]

#6   ((Asthmas, Occupational[Title/Abstract]) OR (Occupational Asthma[Title/Abstract])) OR (Occupational Asthmas[Title/Abstract])

#7   "Asthma, Exercise-Induced"[Mesh]

#8   (((((((((((Asthma, Exercise Induced[Title/Abstract]) OR (Exercise-Induced Asthma[Title/Abstract])) OR (Asthmas, Exercise-Induced[Title/Abstract])) OR (Exercise Induced Asthma[Title/Abstract])) OR (Exercise-Induced Asthmas[Title/Abstract])) OR (Bronchospasm, Exercise-Induced[Title/Abstract])) OR (Bronchospasm, Exercise Induced[Title/Abstract])) OR (Bronchospasms, Exercise-Induced[Title/Abstract])) OR (Exercise-Induced Bronchospasms[Title/Abstract])) OR (Exercise-Induced Bronchospasm[Title/Abstract])) OR (Exercise Induced Bronchospasm[Title/Abstract])

#9   ("Exercise"[Mesh]) OR (Search (Physical Activity [Title/Abstract]) OR (Activities, Physical [Title/Abstract]) OR (Physical Activities [Title/Abstract]) OR (Exercise, Physical [Title/Abstract]) OR (Exercises, Physical [Title/Abstract]) OR (Physical Exercise [Title/Abstract]) OR (Physical Exercises [Title/Abstract]) OR (Acute Exercise [Title/Abstract]) OR (Acute Exercises [Title/Abstract]) OR (Exercise, Acute [Title/Abstract]) OR (Exercises, Acute [Title/Abstract]) OR (Exercise, Isometric [Title/Abstract]) OR (Exercises, Isometric [Title/Abstract]) OR (Isometric Exercises[Title/Abstract]) OR (Exercise, Aerobic [Title/Abstract]) OR (Aerobic Exercise [Title/Abstract]) OR (Exercises, Aerobic [Title/Abstract]) OR (Exercise Trainings [Title/Abstract]) OR (Training, Exercise [Title/Abstract]) OR (Trainings, Exercise [Title/Abstract]))

#10   ((((("Asthma"[Mesh]) OR (((Asthmas[Title/Abstract]) OR (Bronchial Asthma[Title/Abstract])) OR (Asthma, Bronchial[Title/Abstract]))) OR ("Asthma, Occupational"[Mesh])) OR (((Asthmas, Occupational[Title/Abstract]) OR (Occupational Asthma[Title/Abstract])) OR (Occupational Asthmas[Title/Abstract]))) OR ("Asthma, Exercise-Induced"[Mesh])) OR (((((((((((Asthma, Exercise Induced[Title/Abstract]) OR (Exercise-Induced Asthma[Title/Abstract])) OR (Asthmas, Exercise-Induced[Title/Abstract])) OR (Exercise Induced Asthma[Title/Abstract])) OR (Exercise-Induced Asthmas[Title/Abstract])) OR (Bronchospasm, Exercise-Induced[Title/Abstract])) OR (Bronchospasm, Exercise Induced[Title/Abstract])) OR (Bronchospasms, Exercise-Induced[Title/Abstract])) OR (Exercise-Induced Bronchospasms[Title/Abstract])) OR (Exercise-Induced Bronchospasm[Title/Abstract])) OR (Exercise Induced Bronchospasm[Title/Abstract]))

#11   ((("Exercise"[Mesh]) OR (Search (Physical Activity [Title/Abstract]) OR (Activities, Physical [Title/Abstract]) OR (Physical Activities [Title/Abstract]) OR (Exercise, Physical [Title/Abstract]) OR (Exercises, Physical [Title/Abstract]) OR (Physical Exercise [Title/Abstract]) OR (Physical Exercises [Title/Abstract]) OR (Acute Exercise [Title/Abstract]) OR (Acute Exercises [Title/Abstract]) OR (Exercise, Acute [Title/Abstract]) OR (Exercises, Acute [Title/Abstract]) OR (Exercise, Isometric [Title/Abstract]) OR (Exercises, Isometric [Title/Abstract]) OR (Isometric Exercises[Title/Abstract]) OR (Exercise, Aerobic [Title/Abstract]) OR (Aerobic Exercise [Title/Abstract]) OR (Exercises, Aerobic [Title/Abstract]) OR (Exercise Trainings [Title/Abstract]) OR (Training, Exercise [Title/Abstract]) OR (Trainings, Exercise [Title/Abstract]))) AND ((((((("Asthma"[Mesh]) OR (((Asthmas[Title/Abstract]) OR (Bronchial Asthma[Title/Abstract])) OR (Asthma, Bronchial[Title/Abstract]))) OR ("Asthma, Occupational"[Mesh])) OR (((Asthmas,

Occupational[Title/Abstract]) OR (Occupational Asthma[Title/Abstract])) OR (Occupational Asthmas[Title/Abstract]))) OR ("Asthma, Exercise-Induced"[Mesh])) OR ((((((((((Asthma, Exercise Induced[Title/Abstract]) OR (Exercise-Induced Asthma[Title/Abstract])) OR (Asthmas, Exercise-Induced[Title/Abstract])) OR (Exercise Induced Asthma[Title/Abstract])) OR (Exercise-Induced Asthmas[Title/Abstract])) OR (Bronchospasm, Exercise-Induced[Title/Abstract])) OR (Bronchospasm, Exercise Induced[Title/Abstract])) OR (Bronchospasms, Exercise-Induced[Title/Abstract])) OR (Exercise-Induced Bronchospasms[Title/Abstract])) OR (Exercise-Induced Bronchospasm[Title/Abstract])) OR (Exercise Induced Bronchospasm[Title/Abstract])))) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals [mh] NOT (humans [mh] AND animals[mh])))

#12 (((("Exercise"[Mesh]) OR (Search (Physical Activity [Title/Abstract]) OR (Activities, Physical [Title/Abstract]) OR (Physical Activities [Title/Abstract]) OR (Exercise, Physical [Title/Abstract]) OR (Exercises, Physical [Title/Abstract]) OR (Physical Exercise [Title/Abstract]) OR (Physical Exercises [Title/Abstract]) OR (Acute Exercise [Title/Abstract]) OR (Acute Exercises [Title/Abstract]) OR (Exercise, Acute [Title/Abstract]) OR (Exercises, Acute [Title/Abstract]) OR (Exercise, Isometric [Title/Abstract]) OR (Exercises, Isometric [Title/Abstract]) OR (Isometric Exercises[Title/Abstract]) OR (Exercise, Aerobic [Title/Abstract]) OR (Aerobic Exercise [Title/Abstract]) OR (Exercises, Aerobic [Title/Abstract]) OR (Exercise Trainings [Title/Abstract]) OR (Training, Exercise [Title/Abstract]) OR (Trainings, Exercise [Title/Abstract]))) AND ((((((("Asthma"[Mesh]) OR (((Asthmas[Title/Abstract]) OR (Bronchial Asthma[Title/Abstract])) OR (Asthma, Bronchial[Title/Abstract]))) OR ("Asthma, Occupational"[Mesh])) OR (((Asthmas, Occupational[Title/Abstract]) OR (Occupational Asthma[Title/Abstract])) OR (Occupational Asthmas[Title/Abstract]))) OR ("Asthma, Exercise-Induced"[Mesh])) OR ((((((((((Asthma, Exercise Induced[Title/Abstract]) OR (Exercise-Induced Asthma[Title/Abstract])) OR (Asthmas, Exercise-Induced[Title/Abstract])) OR (Exercise Induced Asthma[Title/Abstract])) OR (Exercise-Induced Asthmas[Title/Abstract])) OR (Bronchospasm, Exercise-Induced[Title/Abstract])) OR (Bronchospasm, Exercise Induced[Title/Abstract])) OR (Bronchospasms, Exercise-Induced[Title/Abstract])) OR (Exercise-Induced Bronchospasms[Title/Abstract])) OR (Exercise-Induced Bronchospasm[Title/Abstract])) OR (Exercise Induced Bronchospasm[Title/Abstract])))) AND (cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR retrospective studies[mesh:noexp] OR cohort[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB])
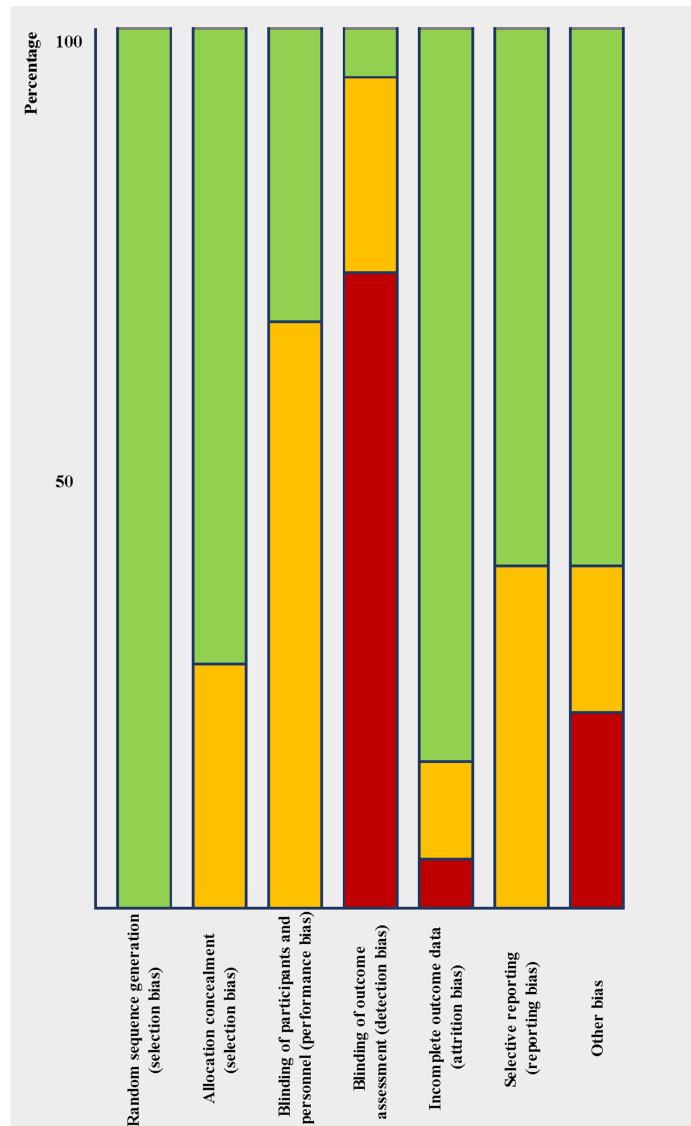
Embase

#1 'exercise'/exp

#2 'physical activity':ab,ti OR 'activities, physical':ab,ti OR 'physical activities':ab,ti OR 'exercise, physical':ab,ti OR 'exercises, physical':ab,ti OR 'physical exercise':ab,ti OR 'physical exercises':ab,ti OR 'acute exercise':ab,ti OR 'acute exercises':ab,ti OR 'exercise, acute':ab,ti OR 'exercises, acute':ab,ti OR 'exercise, isometric':ab,ti OR 'exercises, isometric':ab,ti OR 'isometric exercises':ab,ti OR 'exercise, aerobic':ab,ti OR 'exercise trainings':ab,ti OR 'training, exercise':ab,ti OR 'trainings, exercise':ab,ti

#3 'asthma'/exp

#4 'asthmas':ab,ti OR 'bronchial asthma':ab,ti OR 'asthma, bronchial':ab,ti OR 'asthmas, occupational':ab,ti OR 'occupational asthmas':ab,ti OR 'asthma, exercise induced':ab,ti OR 'exercise induced asthma':ab,ti OR 'bronchospasm, exercise-induced':ab,ti OR 'bronchospasm, exercise induced':ab,ti OR 'bronchospasms, exercise-induced':ab,ti OR 'exercise-induced bronchospasm':ab,ti OR 'exercise induced bronchospasm':ab,ti

#5 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti

#6 'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR cohort*:ab,ti

#7 #1 OR #2

#8 #3 OR #4

#9 #5 AND #7 AND #8

#10 #6 AND #7 AND #8

Web of Science

TS=(Asthmas OR Bronchial Asthma OR Asthma, Bronchial OR Asthmas, Occupational OR Occupational Asthmas OR Asthma, Exercise Induced OR Exercise Induced Asthma OR Bronchospasm, Exercise-Induced OR Bronchospasm, Exercise Induced OR Bronchospasm, Exercise Induced OR Bronchospasms, Exercise-Induced OR Exercise-Induced Bronchospasm OR Exercise Induced Bronchospasm) AND TS=(Physical Activity OR Activities, Physical OR Physical Activities OR Asthmas, Occupational OR Physical Exercise OR Acute Exercise OR Acute Exercises OR Exercise, Acute OR Exercises, Acute OR Exercise, Isometric OR Exercise, Isometric OR Exercises, Isometric OR Isometric Exercises OR Exercise, Aerobic OR Aerobic Exercise OR Exercises, Aerobic OR Exercise Trainings Training, Exercise Trainings, Exercise) AND TS=(clinical trial* OR research design OR comparative stud* OR evaluation stud* OR controlled trial* OR follow-up stud* OR prospective stud* OR random* OR placebo* OR single blind* OR double blind*)

Publications	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cochrane, 1990	L	L	U	U	L	U	H
Farid, 2005	L	L	U	U	L	U	U
Gonçalves, 2008	L	U	U	U	L	U	L
Mendes, 2010	L	U	U	U	L	L	L
Mendes, 2011	L	U	U	H	L	L	L
Boyd, 2012	L	U	U	H	L	U	H
Scott, 2012	L	L	U	H	L	L	L
França-Pinto, 2014	L	L	U	H	L	L	L
Toennesen, 2017	L	L	L	H	L	L	L
Freitas, 2016	L	L	L	H	L	L	L
Refaat, 2015	L	U	U	H	U	U	H
Turner, 2011	L	L	L	H	L	L	U
Shaw, 2011	L	L	L	H	U	U	U
Coelho, 2017	L	L	U	H	L	L	L
Freitas, 2018	L	L	L	H	H	U	L
Ma, 2015	L	L	L	H	L	L	L
Meyer, 2015	L	L	U	L	L	L	L
Shawa, 2009	U	L	U	H	L	L	H

Low risk / Unclear risk / High risk

**Figure S1** Risk of bias for individual quality.

Figure S2 Risk of bias for summary quality. Green part, low risk; yellow part, unclear risk; red part, high risk.

Methodological Quality of the Selected Studies According to the NOS

Study	Selection				Comparability		Exposure	
	Representativeness of the exposed cohort	Selection of the none exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Beckett, 2001	★	★	★	★	★	★	★	N/A
Benet, 2011	★	N/A	★	★	★★	★	★	N/A
Huovinen, 2003	★	★	N/A	★	★★	★	★	N/A
Lucke, 2007	★	★	N/A	★	★	★	★	N/A

Figure S3 Newcastle-Ottawa Scale for Quality of the included studies. This table identifies "high" quality choices with a "star." A study can be awarded a maximum of 1 star for each numbered item within the Selection and Exposure categories. A maximum of 2 stars can be given for Comparability. ★, yes; N/A, not applicable.
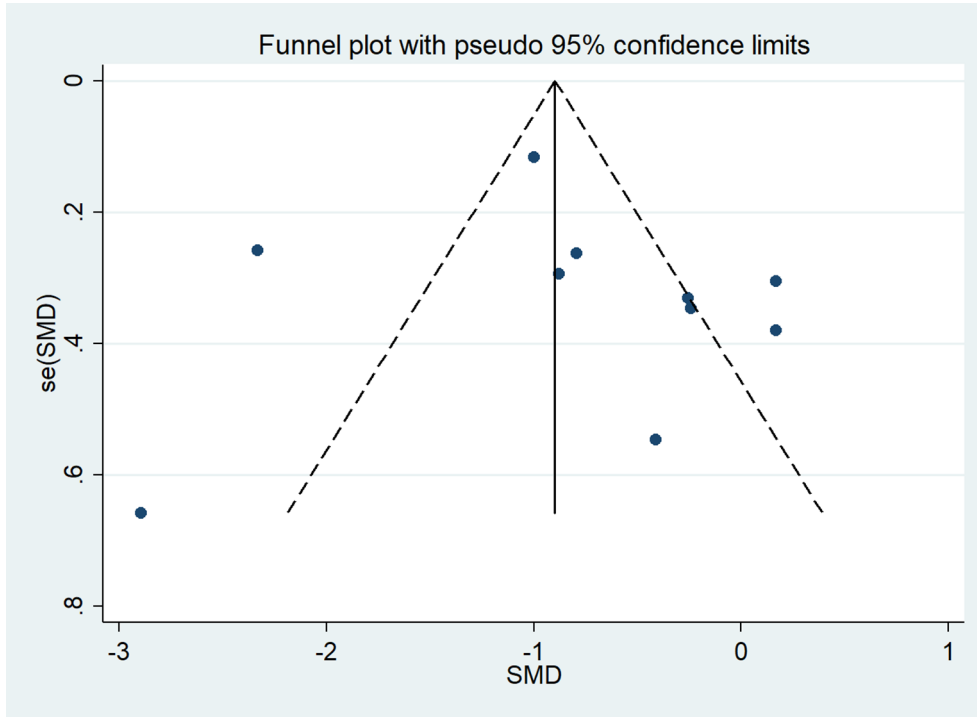
Figure S4 HRQOL plus ACG funnel plot. ACQ, Asthma Control Questionnaire; HRQoL, Health related quality of life; SMD, Standard mean differences.
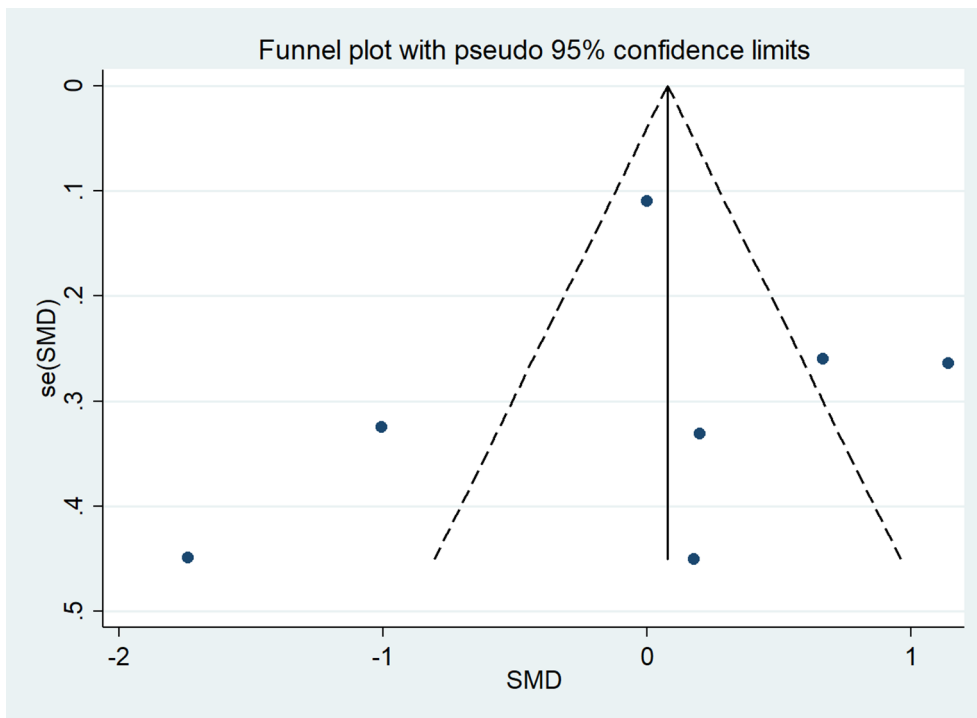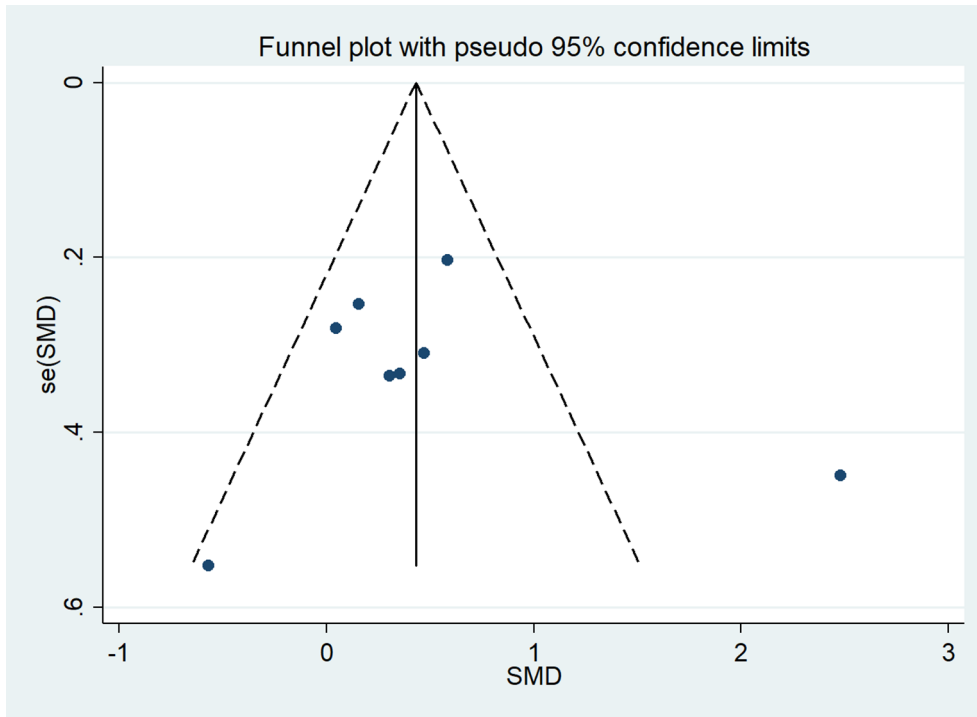

Figure S5 AQLQ funnel plot. AQLQ, asthma-related quality of life questionnaire; SMD, standard mean differences.
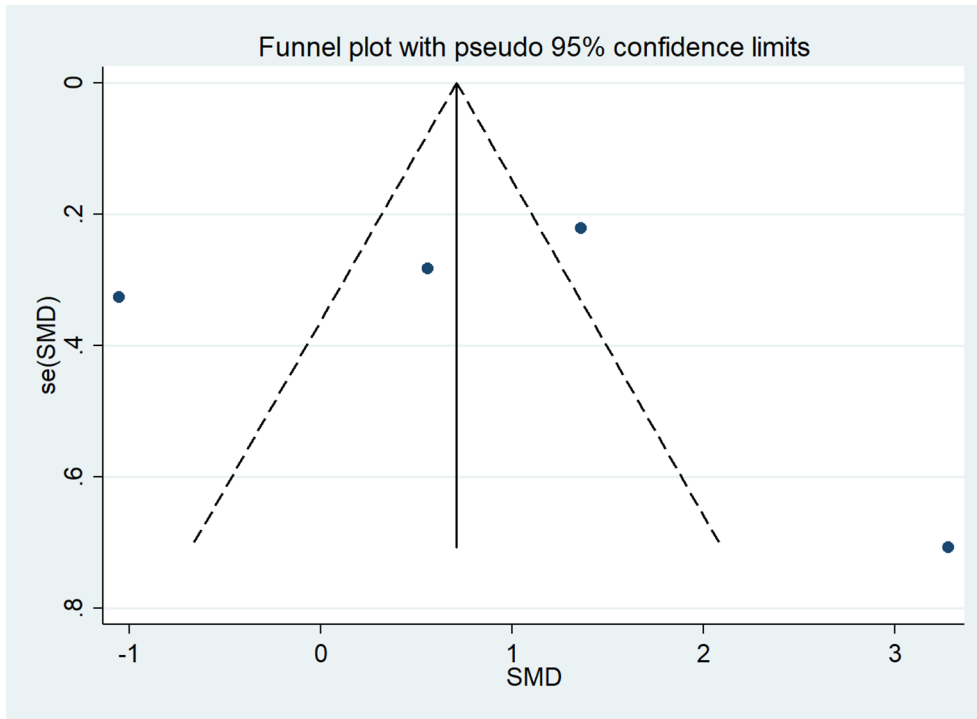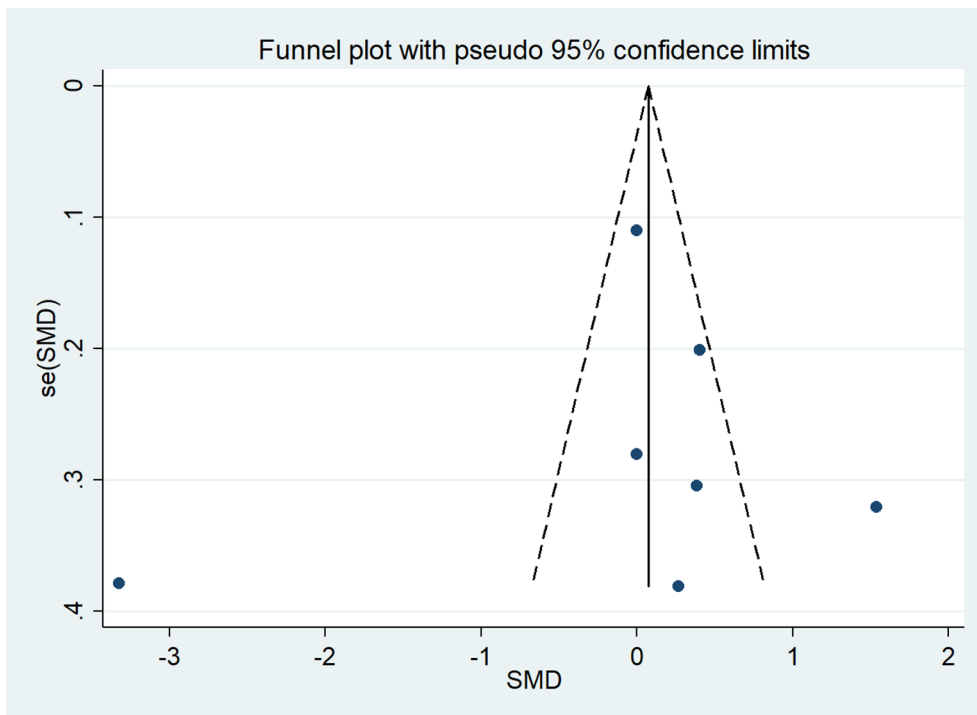
Figure S6 Asthma free symptom funnel plot. SMD, standard mean differences.
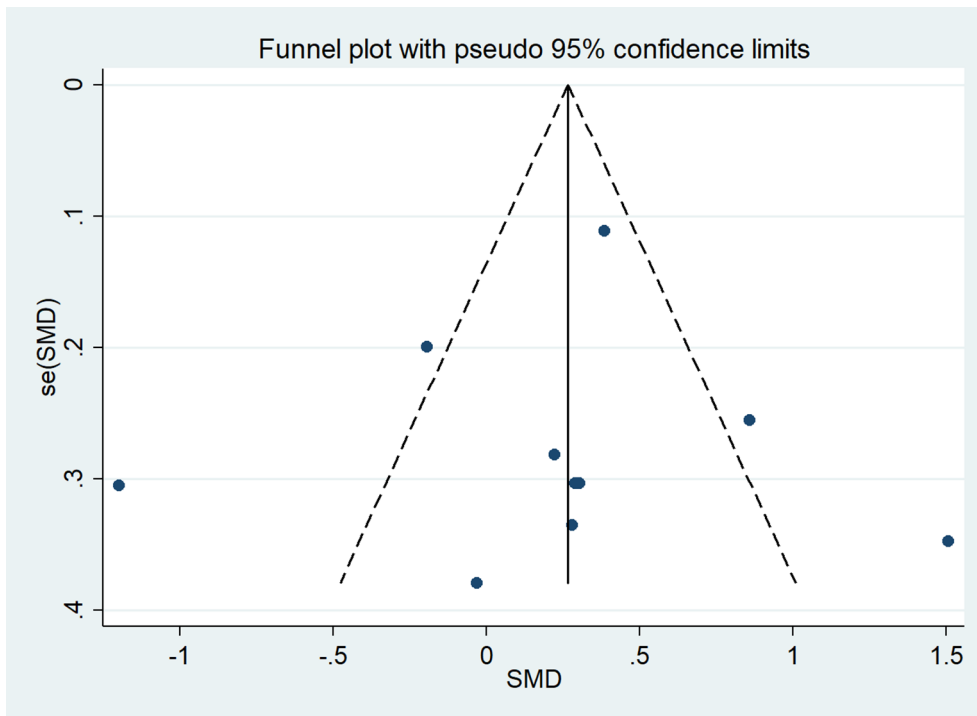
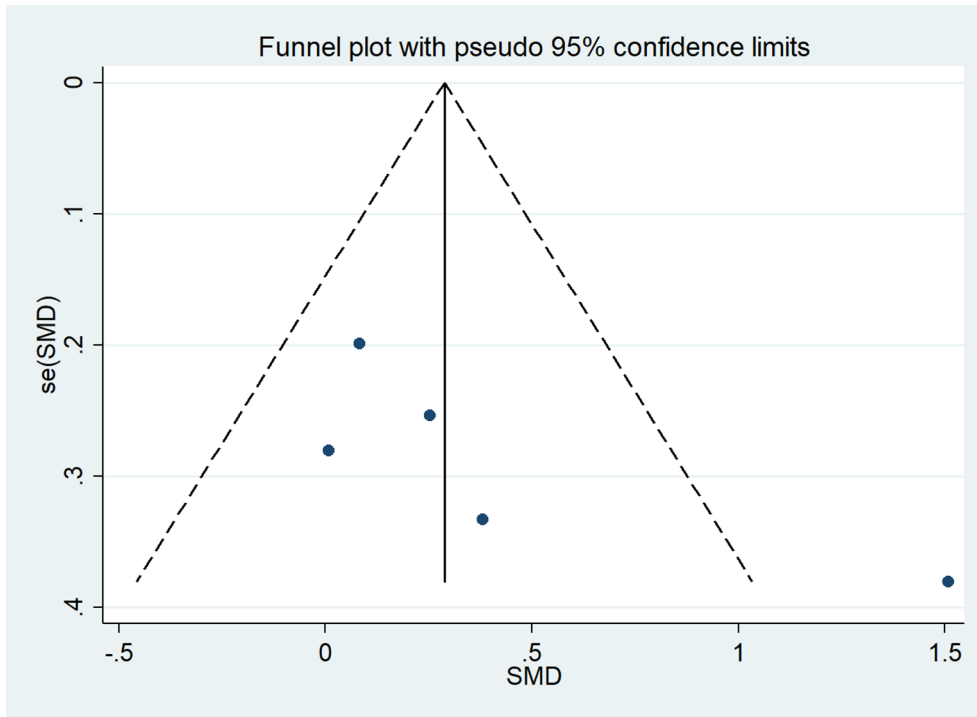**Figure S7** FEV₁ funnel plot. FEV₁, forced expiratory volume in one second (L); SMD, standard mean differences.

https://dx.doi.org/10.21037/atm-22-1170

Figure S8 FEV$_1$%, pred funnel plot. FEV$_1$/pred, FEV$_1$ as a percentage of the predicted value; SMD, standard mean differences.

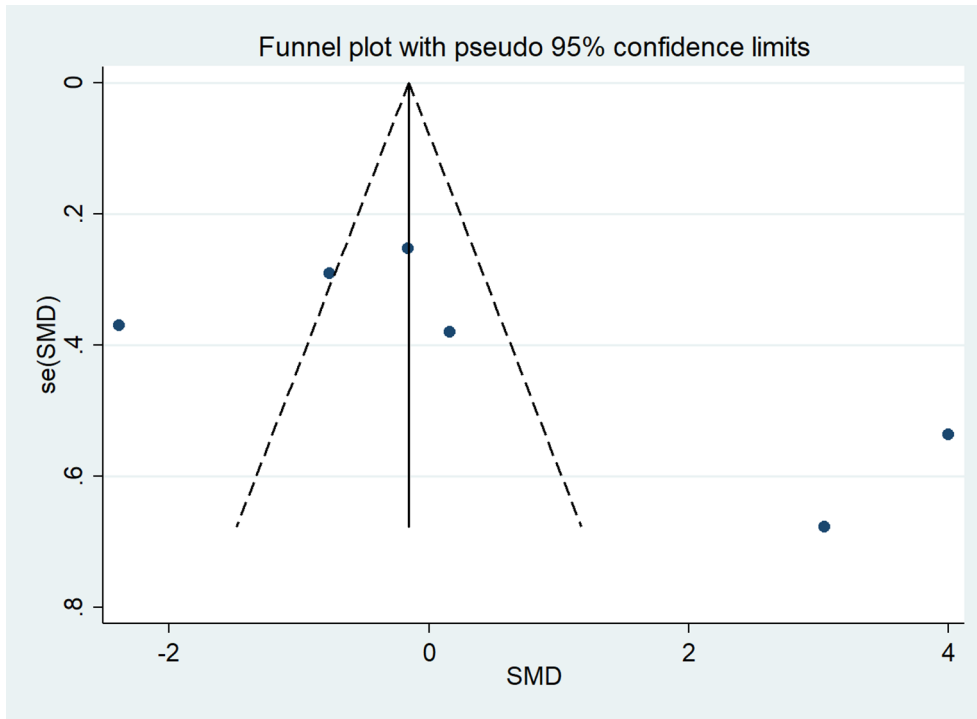**Figure S9** FVC funnel plot. FVC, forced vital capacity (L); SMD, standard mean differences.
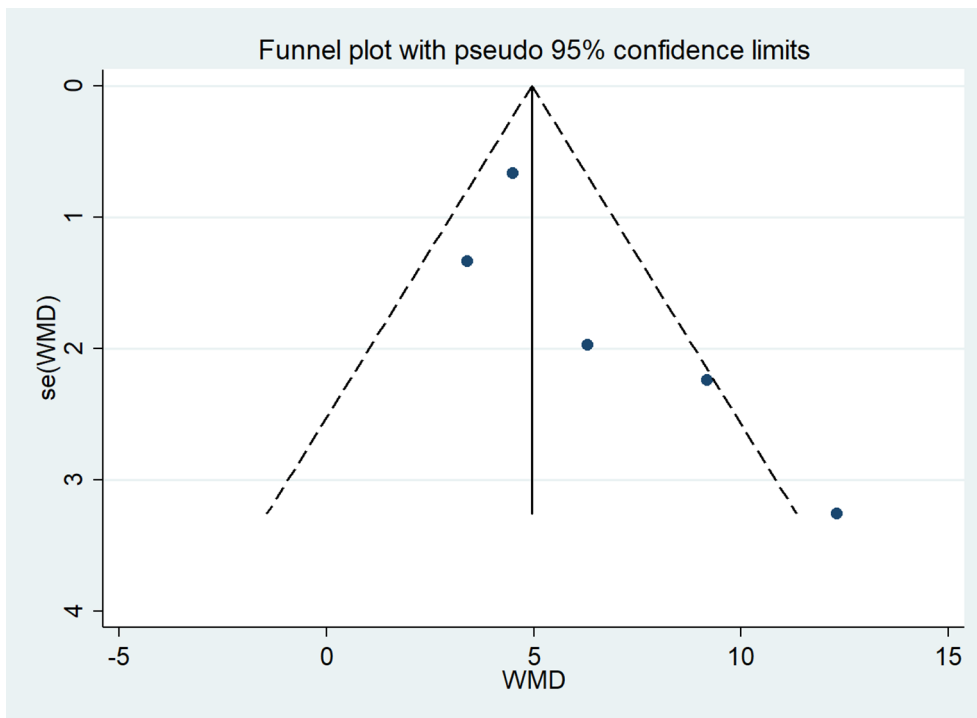
Figure S10 FVC%, pred funnel plot. FVC/pred, FVC as a percentage of the predicted value; SMD, Standard mean differences.
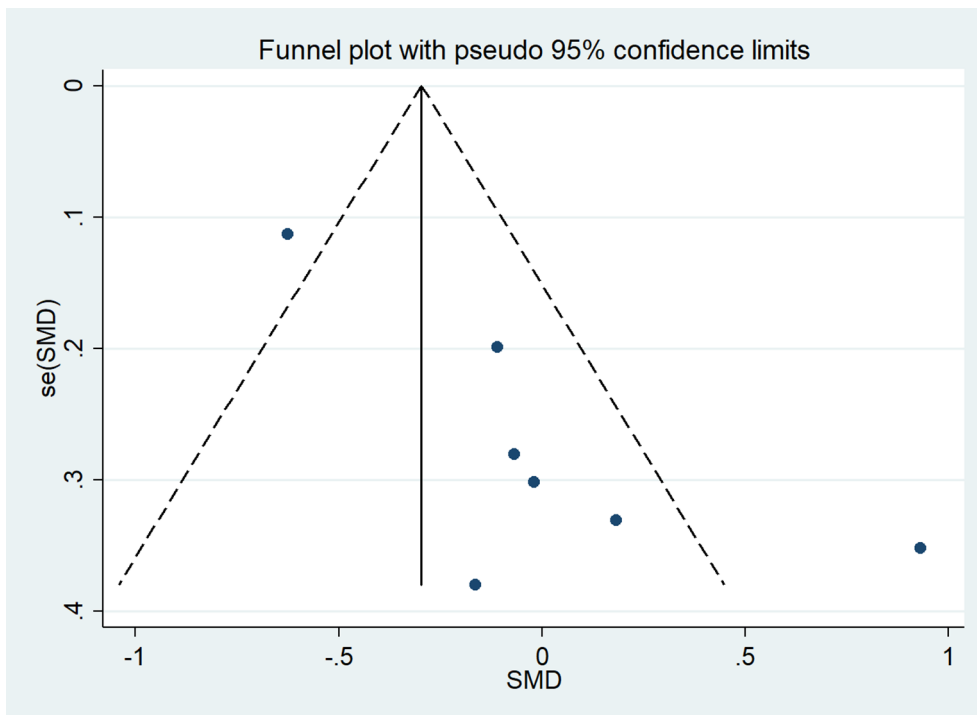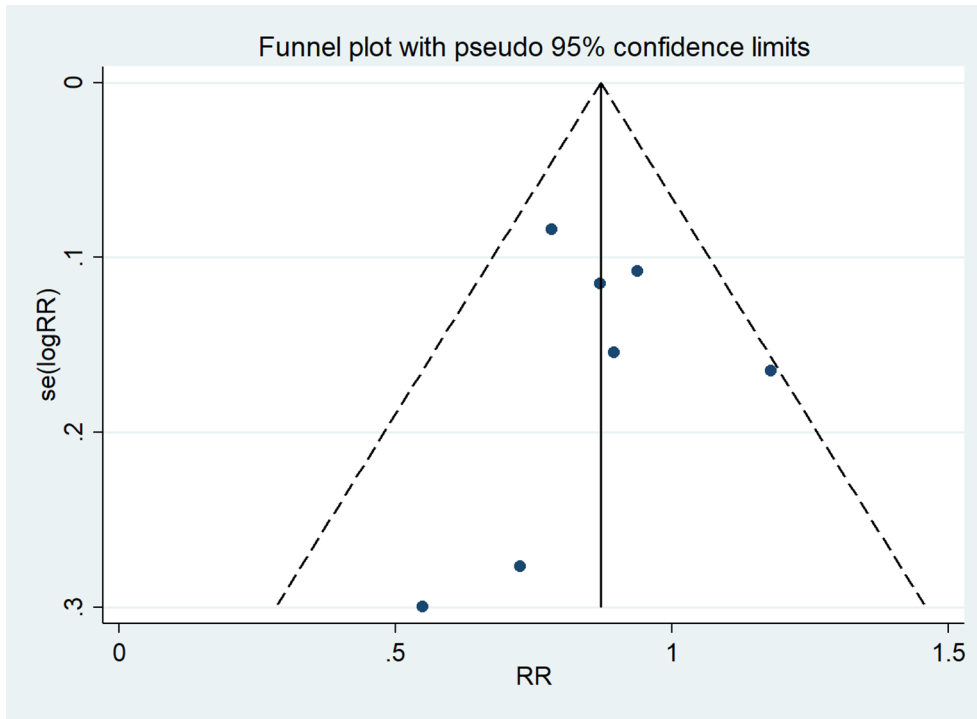

Figure S11 FEV$_1$/FVC funnel plot. FEV$_1$, forced expiratory volume in one second (L); FVC, forced vital capacity (L); SMD, standard mean differences.

Figure S12 FeNO funnel plot. FeNO, fractional exhaled nitric oxide; SMD, standard mean differences.

Figure S13 VO$_2$Max funnel plot. VO$_2$max, maximal oxygen uptake; WMD, weighted mean differences.

Figure S14 Observational studies funnel plot. RR risk ratio.