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Comparative Effectiveness of Breathing Exercises and/or Retraining Techniques in the Treatment of Asthma

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://www.effectivehealthcare.ahrq.gov/index.cfm/what-is-comparative-effectiveness-research1/.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (http://www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Comparative Effectiveness of Breathing Exercises and/or Retraining Techniques in the Treatment of Asthma

Structured Abstract

Objectives. To examine evidence for whether breathing exercises and retraining techniques lead to improvements in asthma symptoms, reductions in asthma medication use, improved quality of life, or improved pulmonary function in asthma sufferers.

Data Sources. MEDLINE; PsycInfo; EMBASE; Cumulative Index to Nursing and Allied Health Literature; Physiotherapy Evidence Database; Cochrane Central Register of Controlled Trials; AltHealthWatch; Allied and Complementary Medicine; Manual, Alternative and Natural Therapy Index System from 1990 through July 28, 2011. Searches were supplemented with manual searching of reference lists and grey literature, including regulatory documents, conference abstracts, and clinical trial registries.

Review Methods. Analytic framework, key questions, and review protocol were developed with input from key informants and technical experts. Two independent reviewers screened identified abstracts predefined inclusion/exclusion criteria. Two investigators reviewed full-text articles and independently quality-rated those meeting inclusion/exclusion criteria. Data from fair- and good-quality trials were abstracted into standardized forms and checked by another investigator. We summarized data qualitatively and, where possible, used random effects meta-analysis to quantitatively pool similar trials.

Results. We identified four types of interventions: hyperventilation reduction breathing techniques, yoga breathing techniques, inspiratory muscle training (IMT), and other nonhyperventilation reduction breathing techniques. We found the most robust body of evidence for hyperventilation reduction breathing techniques, including the only large-scale trial (n=345). Hyperventilation reduction interventions (particularly those with 5 hours or more of patient contact) achieved significant improvement in asthma symptoms and reductions in reliever medication use, but did not improve pulmonary function. These trials also were more applicable to the US setting than trials examining other intervention approaches, although applicability was still limited since none were conducted in the US. Yoga breathing techniques improved pulmonary function in addition to reducing asthma symptoms. Evidence for IMT and other breathing retraining techniques was limited to small, heterogeneous trials best characterized as pilot studies providing insufficient evidence to conclude that these are or are not effective. Trials most likely to show benefit included treatment components in addition to breathing training; provided more hours of interventionist contact; and did not include relaxation or breathing training in the comparison groups. The only harms of breathing retraining techniques identified were minor annoyances associated with mouth-taping.

Conclusions. Behavioral approaches that include hyperventilation reduction or yoga breathing techniques can improve asthma symptoms or reduce reliever medication use over 6 to 12 months

in adults with poorly controlled asthma and have no known harmful effects. However, available evidence is limited in its strength and applicability to the US.

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Executive Summary

Background

In 2009, an estimated 8.2 percent of Americans had current asthma (9.6% of children and 7.7% of adults), which is complicated by the fact that the prevalence of asthma has increased substantially in recent years.[1,2] In 2007, asthma accounted for 456,000 hospitalizations and over 3,447 deaths.[3]

The goal of asthma treatment is to achieve asthma control, as evidenced by normal or near normal pulmonary function, maintenance of normal activity levels, and minimal need for short-acting beta$_2$-agonist inhalers for "quick-relief" of asthma symptoms (≤ twice per week).[4] Persistent asthma treatment includes the use of long-term control medications (most commonly inhaled corticosteroids [ICS]) to reduce airway inflammation and quick-relief medications for acute exacerbations.

While the benefits of asthma treatment generally outweigh the potential risks, these medications can be associated with adverse effects.[5,6] Additionally, some asthma patients have concerns about asthma medications and some patients would likely prefer to minimize their use of medication if alternative treatments were available.[7,8]

A number of nonpharmacologic methods for asthma management involve breathing retraining. Some of these are predicated on the theory that asthma is related to hyperventilation, such as the Buteyko and Papworth methods. These treatments seek to reduce hyperventilation by encouraging shallow or slow nasal breathing, breath-holding at the end of expiration, and minimizing sighs and yawns and related breathing patterns that are sometimes characterized as "over-breathing."[9] Non-hyperventilation methods include yoga breathing techniques and other physiotherapy methods. Treatment based on yoga theory generally encourages slowing and regularizing the breath by prolonging the expiratory phase, enhancing abdominal/diaphragmatic breathing, and imposing resistance on both inspiration and exhalation.[10] Other physiotherapy methods may use elements consistent with these traditions to reduce the rate of breathing; control the depth, flow, or timing of breathing; and prescribe exercises that increase inspiratory muscle strength.

Objectives

The current review examines the effect of breathing retraining methods on asthma symptomatology, medication use, quality of life, and pulmonary function in both adults and children. We also examine adverse effects of these techniques. The analytic framework we developed to guide our review is shown in Figure 1. The key questions for this review were:

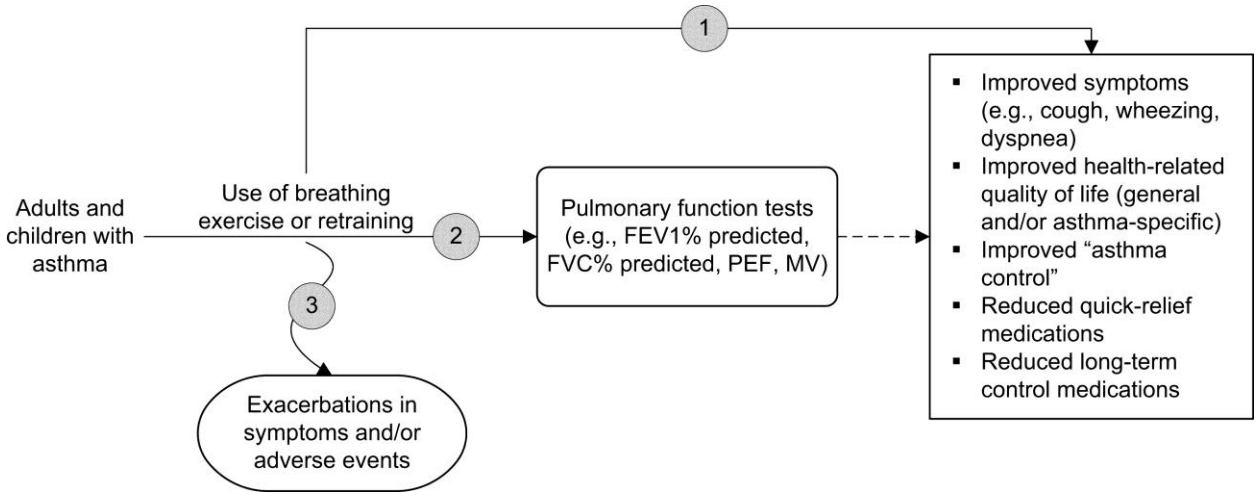
1. In adults and children 5 years of age and older with asthma, does the use of breathing exercises and/or retraining techniques* improve health outcomes, including: symptoms (e.g., cough, wheezing, dyspnea); health-related quality of life (general and/or asthma-specific); acute asthma exacerbations; reduced use of quick-relief medications or reduced use of long-term control medications, when compared with usual care and/or other breathing techniques alone or in combination with other intervention strategies?

    a. Does the efficacy and/or effectiveness of breathing techniques for asthma health outcomes differ between different subgroups (e.g., adults/children; males/females; different races or ethnicities; smokers/nonsmokers; various types and severities of asthma; and/or different coexisting conditions)?
    b. Does the efficacy and/or effectiveness of breathing techniques for asthma health outcomes differ according to variations in implementation (e.g., trainer experience) and/or nonbreathing components of the intervention (e.g., anxiety management)?
2. In adults and children 5 years of age and older with asthma, does the use of breathing exercises and/or retraining techniques improve pulmonary function or other similar intermediate outcomes when compared with usual care and/or other breathing techniques alone or in combination with other intervention strategies?
    a. Does the efficacy and/or effectiveness of breathing techniques for other asthma outcomes differ between different subgroups (e.g., adults/children; males/females; different races or ethnicities; smokers/nonsmokers; various types and severities of asthma; and/or different coexisting conditions)?
    b. Does the efficacy and/or effectiveness of breathing techniques for other asthma outcomes differ according to variations in implementation (e.g., trainer experience) and/or nonbreathing components of the intervention (e.g., anxiety management)?
3. What is the nature and frequency of serious adverse effects of treatment with breathing exercises and/or retraining techniques, including increased frequency of acute asthma exacerbations?
    a. Do the safety or adverse effects of treatment with breathing techniques differ between different subgroups (e.g., adults/children; males/females; different races or ethnicities; smokers/nonsmokers; various types and severities of asthma; and/or different coexisting conditions)?

*For example: the Buteyko breathing technique; inspiratory muscle training; breathing physical therapy including paced and pursed lip breathing exercises; the Papworth Method; biofeedback- and technology-assisted breathing retraining; and yoga breathing exercises.

Analytic Framework

Figure 1. Analytic framework



Abbreviations: FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; MV: minute volume; PEF: peak expiratory flow

Methods

The Oregon Evidence-based Practice Center drafted a topic refinement document with proposed key questions after consulting with key informants. The public was invited to comment on the key questions during a 4-week period. After reviewing the public commentary, the final key questions were approved by the Agency for Healthcare Research and Quality and the review commenced.

We engaged a technical expert panel (TEP) that included five individuals who specialize in asthma management from the fields of Family Medicine, Community Health and Nursing, Psychology, Physical Therapy, and Pediatrics to provide input during the project. The TEP was established to ensure the scientific rigor, reliability, and methodological soundness of the research. The TEP provided reactions to the methods protocol and provided input on substantive issues related to specific studies and/or outcomes

A research librarian performed comprehensive literature searches in MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Physiotherapy Evidence Database (PEDro), Cochrane Central Register of Controlled Trials (CCRCT), AltHealthWatch, Allied and Complementary Medicine (AMED), and Manual, Alternative and Natural Therapy Index System (MANTIS) from 1990 through July, 2011. We supplemented these searches with manual searching of reference lists contained in all included articles and in relevant review articles. Grey literature searches were also performed by the research librarian.

We included English-language trials of breathing retraining techniques that included participants aged 5 years or older; reported at 4 week post-baseline or later asthma symptoms, asthma medication use, quality of life, functioning, or pulmonary function. Trials had to include a control group or comparison with another breathing training technique. For the question of harms, we would also have included large observational studies as well as trials if we had found any. We had no restriction on geographic location. We did not include trials that used relaxation techniques as a comparator.

Two independent reviewers assigned ratings of "good", "fair", or "poor" quality to each trial. Discrepancies were resolved by discussion or consultation with the larger review team. Trials given a final rating of "poor" quality were excluded. We used the following major elements to assign quality ratings:

- the presence of adequate randomization methods (use of computer-generated random number tables or other process considered truly random)
- allocation concealment
- similarity of groups at baseline
- the specification of eligibility criteria
- reliable and valid measurement of baseline asthma status (optimal assessment included use of pulmonary function testing to confirm reversible component)
- retention (retention of 90 percent or more overall was considered good; 60 to 89 percent was adequate, and less than 60 percent was considered a fatal flaw; differential attrition of 10 to 19 percentage points was considered potentially problematic and 20 percentage points or more was considered a fatal flaw)
- time until followup (6 months or more was preferable, fewer than 6 weeks was potentially problematic)
- equal, reliable, and valid measurements
- blinding of outcome assessors
- appropriate analyses (e.g., analyzing all participants in the treatment group to which they were initially assigned, use of conservative data substitution [preferably multiple imputation, imputation based random effects regression or similar models, or use of baseline values] when retention was below 90 percent, adjustment for potential confounders, no use of statistical tests that were inappropriate for the type of data analyzed)

Generally, a good-quality study met all major criteria, though it was possible to get a "good" rating if an item was not reported (so could not be assessed) if the rest of the methods were judged to be "good." A fair-quality study did not meet all criteria, but was judged to have no flaw so serious that it invalidated its results. A poor-quality study contained a serious flaw in design, analysis, or execution, such as differential attrition as described above, or some other flaw judged to be so serious as to cast doubt on the validity of the results, such as large baseline group differences that were not or could not be adjusted for in an analysis, no information about followup and assumption of 100 percent followup was not tenable, or where insufficient information was provided to determine the risk of bias.

We abstracted data from all included studies with a quality rating of "fair" or "good" into a standard evidence table. Data were abstracted by one reviewer. A second reviewer checked by these data. Authors were contacted to clarify methods and results if needed. Discrepancies were resolved by discussion or consultation with other team members. Major elements abstracted included study location; study design; recruitment setting and approach; inclusion/exclusion criteria; demographic and health characteristics of the sample including baseline asthma; description of the intervention and control arms; any co-intervention components (e.g., advise about diet, relaxation training); compliance with treatment; sample retention; asthma outcomes, including symptoms, quality of life, medication use, and pulmonary function tests; and adverse events. To assess applicability, we used data abstracted on the population studied, the intervention and comparator, the outcomes measured, settings, and timing of assessments to

identify specific issues that may limit the applicability of individual studies or the body of evidence to US health care settings, as recommended in the *Methods Guide*.[11]

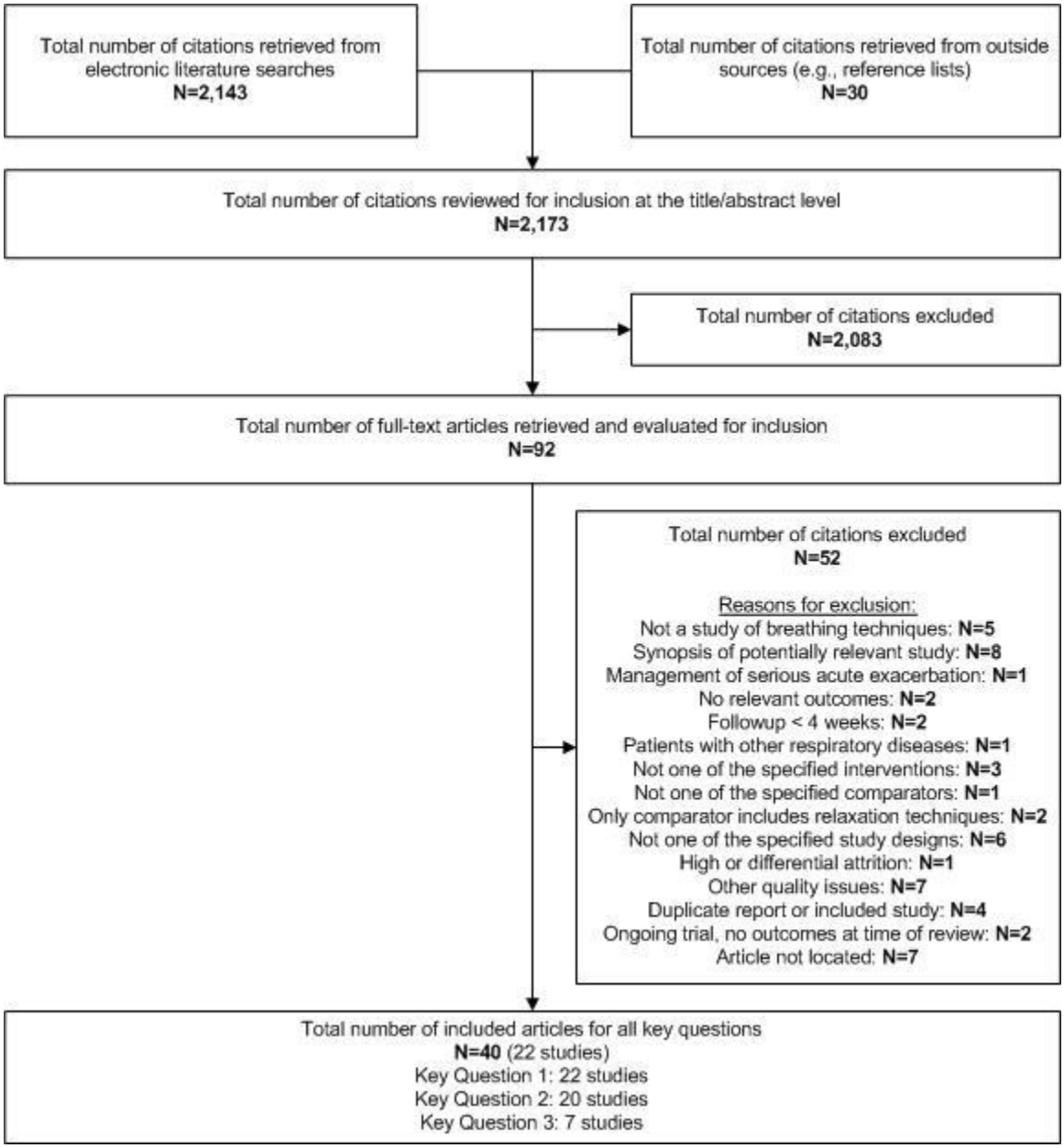
We summarized all included studies in narrative form as well as in summary tables that present the important features of the study populations, design, intervention, outcomes, and results. We divided comparisons into five groups based on the primary intervention focus and control group: (1) interventions focused on hyperventilation reduction breathing training vs. control, (2) yoga breathing methods vs. control, (3) inspiratory muscle training (IMT) vs. control, (4) breathing approaches that did not focus on hyperventilation reduction vs. control, and (5) hyperventilation reduction vs. nonhyperventilation reduction breathing training approaches. We discuss outcomes separately for each of the five groups. To facilitate comparison of effect sizes across studies reporting different outcomes, we calculated a standardized effect size (Hedges g). Random effects meta-analyses were conducted where there were at least three trials within a group. Meta-analyses were always conducted within groups because of the high degree of clinical and methodological heterogeneity across groups. We used Stata 11.2® for all effect size calculations and meta-analyses (Stata Corp, College Station, TX).

We graded the strength of evidence for primary outcomes using the standard process of the EPCs,[12] assigning grades in four domains: (1) risk of bias (low, medium, high), (2) consistency (consistent [no inconsistency present], inconsistent, unknown or not applicable), (3) directness (direct, indirect), and (4) precision (precise, imprecise). Risk of bias is the degree to which the included studies for a given outcome or comparison has a high likelihood of adequate protection against bias. Consistency refers to the degree to which reported effect sizes from included studies appear to have the same direction and magnitude of effect. When only a single study was included, consistency could not be judged. Directness relates to whether the evidence links the interventions directly to health outcomes. Precision refers to the degree of certainty surrounding an effect estimate with respect to a given outcome.

Results

The literature search yielded 2,173 citations. After reviewing abstracts, 92 articles were retained for possible inclusions and full text of the articles was examined (Figure 2). After screening their full texts, 22 studies were judged to have met the inclusion criteria (published in 40 articles).[13-34] All studies were randomized controlled trials (RCTs) except one, which was a randomized crossover trial.[14] We excluded the remaining 52 full-text articles. The primary reasons for exclusion included not being a study on breathing techniques, not providing primary data, not using one of the specified study designs, and being rated as poor quality.

Figure 2. Literature flow diagram



All trials were conducted in people with symptomatic, mostly stable asthma. Some trials were limited to people with a certain level of beta-agonist use suggesting their asthma was not well controlled. Most trials confirmed reversibility of respiratory symptoms through pulmonary function testing. Trials primarily included adults; only one trial of IMT children (ages 8 to 12)[28] and only four other trials included people younger than 16 years of age.[13,16,19,21]

Allocation was described as concealed in only 32 percent of the trials. Asthma symptoms, medication use, and quality of life were almost always based on self-report, and only 41 percent of the trials reported that outcomes assessment were conducted blindly. Lack of blinding may be especially problematic for pulmonary function testing, which is effort-dependent and involves coaching on the part of the assessors to get an optimal performance. Lack of blinding may also

be problematic for self-reported outcomes, where social desirability could introduce bias. Most trials were small, with 68 percent including only 30 or fewer participants per treatment arm. Only a single trial included more than 100 participants per treatment arm.[19] Trials were also inconsistent in the degree to which they ensured the sample was limited to people with asthma: 42 percent did not report the use of pulmonary function testing to confirm asthma diagnosis, and 39 percent did not describe excluding participants with other respiratory disorders or people at high risk for other respiratory disorders (e.g., smokers).

Key Question 1

Hyperventilation Reduction Breathing Retraining vs. Control Group

Seven trials (n=1,055) tested a hyperventilation reduction technique versus a control and generally suggested that hyperventilation reduction approaches may improve asthma symptoms and reduce reliever medication use, but do not affect pulmonary function (Table 1).[14,15,17-20,22] Four trials were fairly intensive and involved at least five hours of comprehensive instruction and/or guided practice with the breathing technique.[15,17-19] The group included the only large-scale trial in the review,[19] which reported reductions in asthma symptoms and reliever medication use at 6-month followup, but was hampered by lower retention in the control groups (82% and 73%) than the Buteyko group (90%). Two trials involved less-intensive interventions, but still attempted somewhat comprehensive breathing retraining approaches.[14,20,22] One additional study examined only a single, focused aspect of the Buteyko breathing technique, mouth-taping at night in a randomized cross-over trial.[14] All four of the most intensive and comprehensive interventions reported improvements in asthma symptoms at 6- to 12- months of followup.[15,17-19] The lower-intensity trials did not find improvements in asthma symptoms after 1 to 6 months.[14,20,22]

Four of these trials reported sufficient data to be included in the meta-analysis, including three of the four more intensive trials and the pooled standardized estimate of -1.39 (95% confidence interval [CI], -2.61 to -0.17, I^2=97.1%), suggesting a large effect on asthma symptoms.[17-19,22] Similarly, three[15,19,20] of the five trials reporting reliever medication use showed reductions, generally of 1.5 to 2.5 puffs per day.[14,15,19,20,22] Quality of life results were only reported in four trials,[14,15,20,22] and two of them showed greater improvements with hyperventilation reduction breathing retraining than control groups.[20,22] Hyperventilation reduction approaches did not improve pulmonary function in the five trials that reported this outcome (pooled standardized estimate=0.18, 95% CI, 0.00 to 0.37, k=5, I^2=18.4%).[15,17-19,22]

All trials were rated fair quality. The three lower-intensity trials had only 1-month of followup for all or most outcomes[14,20,22] and only two of the RCTs randomized more than 50 participants per group.[19,22] Two suffered from fairly high attrition[15,22] and three had greater attrition in the intervention group by at least ten percentage points at one or more followups.[15,18,22] Allocation concealment was reported in only three trials,[17,19,22] and outcomes assessment was clearly blinded in only four of the trials.[14,15,17,19]

Applicability of these trials was moderate at best. All trials were conducted in health care settings outside of the United States, but all in English-speaking, developed countries.

Yoga Breathing vs. Control

The five trials (n=360) that compared yoga with a control group generally showed improvements in asthma symptoms, with the most intensive programs also showing improvements in pulmonary function (Table 1).[23-27] Four of the five trials reported reductions in asthma symptoms, although data could not be pooled due to lack of necessary data in several cases.[23,24,26,27] Medication use was rarely reported, and quality of life was only reported in three of the trials, but did show improvement in two of them (standardized pooled estimate for all three trials=0.66, 95% CI, 0.21 to 1.10, I^2=59.3%).[24,26,27] All trials reported forced expiratory volume in 1 second (FEV_1) and three trials showed greater improvement in those participating in the yoga intervention.[23,26,27] All trials were rated fair quality, and three had substantial quality issues that limit our confidence in results.[23,24,26] Three of the trials were extremely intensive and conducted in India, with minimal applicability for the US health care system, and two of them had significant methodological issues.[23,26] Two trials included substantial additional components beyond yoga breathing techniques, making isolation of the breathing component impossible.[24,27] The trial with the greatest applicability to the US health care system showed no group differences on any measure.[25]

Inspiratory Muscle Training vs. Control

Evidence was insufficient to draw conclusions about the effect of IMT on asthma in five small trials (n=169) (Table 1).[28-32] Three of the trials were conducted by a single investigator,[30-32] and all trials involved 25 or fewer participants per group, varied substantially in populations, intensity, and approach, and all but one[30] had substantial quality issues. Trials had low applicability to the US health care system.

Nonhyperventilation Reduction Breathing Techniques vs. Control

Three trials (n=186) compared a nonhyperventilation reduction breathing technique with a control group and generally showed few group differences in asthma symptoms, medication use, or pulmonary function (Table 1).[15,33,34] One trial consisted of "established physiotherapy methods" including a focus on slow diaphragmatic breathing, compared with general asthma education plus the opportunity to have a one-on-one asthma review.[34] The second trial examined the use of biofeedback targeting heart rate variability (HRV), as well as training in pursed-lip abdominal breathing with prolonged exhalation.[33] This trial had three different control groups: biofeedback targeting only HRV, placebo biofeedback involving placebo "subliminal suggestions designed to help asthma," and a waiting list. The final trial compared the use of a device to modify breathing to achieve an inspiration-to-expiration cycle of 1:2, with a sham device that did not modify breathing.[15] All three trials were rated as "fair" quality.

Hyperventilation Reduction Breathing Techniques vs. Other Breathing Techniques

Only medication outcomes showed group differences in the four RCTs (n=285) comparing the use of breathing techniques targeting hyperventilation reduction with other breathing techniques, and all favored hyperventilation reduction techniques (Table 1).[13,15,16,21] One trial showed very large reductions in reliever medication use among high medication users: participants in the hyperventilation group went from using approximately nine to 10 puffs of

beta-agonist per day to approximately one puff every other day, compared with less than one puff per day reduction in the abdominal breathing group.[13] Another trial showed reductions in both the hyperventilation reduction and nonhyperventilation reduction breathing retraining in asthma symptoms and medication use.[21] This was the best-quality trial included in the review; the only minor flaws were retention of less than 90 percent and small sample size.

Key Question 1a

The trials were heterogeneous on too many factors to be able to look across studies to asses the impact of population characteristics on effect size. However, two trials did report subgroup analyses examining differential effects of treatment by different characteristics.[14,22] Subgroup analyses were not described as being planned *a priori*, but are clinically logical subgroups the interventions may be expected to target specifically. The United Kingdom trial comparing Papworth-style intervention with asthma education found that results were consistent between those who scored in the "disordered breathing" range on the Nijmegen questionnaire and those who did not.[22] Similarly, the trial of nighttime mouth-taping did not find larger effect among the subgroup of people who were rated as being "mouth breathers" at baseline.[14]

Key Question 1b

Interventions that included components beyond breathing retraining[15,18,24,27] were likely to show a benefit more than interventions that isolated one aspect of breathing retraining (e.g., prolonged exhalation,[15,33] mouth taping,[14] strengthening inspiratory muscles[30-32]). In addition, trials that matched intensity between treatment groups appear less likely to reduce reliever medication use, though this effect was not seen for other outcomes. Finally, trials that compared breathing retraining with either another breathing technique or an intervention likely to induce relaxation or a reduced state of autonomic arousal were less likely to show group differences on asthma symptoms and quality of life than when compared with control groups that did not include either of these components.

Key Question 2

Hyperventilation Reduction Breathing Retraining vs. Control Group

Hyperventilation reduction techniques did not affect pulmonary function (Table 1). All seven trials reported one or more pulmonary function outcomes, primarily FEV_1, forced vital capacity, and peak expiratory flow (PEF).[14,15,17-20,22] Group differences were only found in one trial and only in the comparison with one of the two control groups.[19] Three trials measured end-tidal carbon dioxide (CO_2), [17,18,22] which is a specific target of interventions to reduce hyperventilation, but only one found group differences, reported at 4, 12, and 26 weeks.[17] Breathing rate was reduced in two of these trials, which suggests that participants did modify their breathing in the way they were instructed, but that modification did not always alter the CO_2 levels as hypothesized by the Buteyko method proponents.[17,18]

Yoga Breathing vs. Control

Neither of the US-based trials improved pulmonary function outcomes,[24,25] despite the positive effects on other outcomes for the comprehensive naturopathic treatment program (Table 1).[24] Intensive yoga training in India, however, resulted in substantial improvements in

pulmonary function,[23,26,27] with the largest effect sizes seen in the trials with the greatest methodological limitations.[23,26]

Inspiratory Muscle Training vs. Control

Three of the four trials reporting pulmonary function found greater improvement in FEV_1 or PEF in participants who underwent IMT than those who did not (Table 1).[28-30] These data, however, are best considered exploratory pilot trials, given their heterogeneity in methods and populations, small size, and quality issues.

Other Nonhyperventilation Reduction Approach vs. Control

Spirometry results did not change over time in either the trial of prolonged exhalation using a training device[15] or in any of the treatment groups in the biofeedback trial (Table 1).[33] The remaining trial in this group did not report pulmonary function testing.[34]

Hyperventilation Reduction Breathing Techniques vs. Other Breathing Techniques

All four trials in this group reported change in FEV_1 (Table 1).[13,15,16,21] No trial found group differences, and there was little change within any of the groups in any trials. Only one trial reported PEF, and this trial found no group differences.[13] Other measures of pulmonary function similarly showed no group differences, including end-tidal CO_2,[13,21] provocative dose of methacholine causing 20 percent reduction in FEV_1,[15] and forced vital capacity.[21]

Key Question 2a

The best-quality trial of yoga conducted in India showing large benefits of treatment reported that participants with exercise-sensitive asthma showed a greater improvement on FEV_1 than those whose asthma was not sensitive to exercise.[27] No other trials reported subgroup analyses for any pulmonary function outcomes, and there was no evidence that this subgroup analysis was planned *a priori* or that it was a clinically important subgroup expected to differentially benefit from this intervention.

Key Question 2b

Benefits were more likely to be seen if the control group did not involve breathing training of any kind or relaxation techniques (42% positive vs. 14% positive with breathing/relaxation comparison group). These data are preliminary, however, and are only valid for hypothesis generation and do not account for effect size.

Key Question 3

Seven trials reported on adverse events including five trials that examined a hyperventilation reduction approach compared with either a control or another breathing retraining approach.[14,16,18,20,21,24,25] The trial of mouth-taping reported some minor adverse events such as causing sore lips, causing a feeling of suffocation, or disturbing sleep. All other trials reported either no adverse events at all, or no adverse events related judged to be related to the breathing retraining.

Table 1: Strength of Evidence

Outcome	Group	Number of studies	Risk of bias	Consistency	Directness	Precision	Strength of evidence	Comments
Key Question 1: asthma symptoms (global symptom severity or control, specific symptoms, exacerbations)	Hyperventilation reduction breathing technique versus control	7	Medium	Consistent	Direct	Imprecise	Moderate	Range of effects in 6 comprehensive interventions none to large, 4 of 6 reported benefit; 1 narrowly-focused trial showed no benefit for mouth-taping
	Yoga breathing technique versus control	5	Medium-High	Consistent	Direct	Imprecise	Low	4 of 5 trials report benefit, three with substantial quality concerns
	IMT versus control	2	Medium-High	Consistent	Direct	Imprecise	Insufficient	2 small trials with different populations and methods, both show benefit, one with high risk of bias
	Non-hyperventilation reduction breathing technique versus control	3	Medium	Consistent	Direct	Imprecise	Low	No benefit in trials using biofeedback or breathing device, mixed results in 1 trial of physiotherapy
	Hyperventilation reduction breathing technique versus nonhyperventilation reduction breathing technique	4	Medium	Consistent	Direct	Imprecise	Low	No trial found a benefit of one approach over another; both groups improved in 2 trials, neither group improved in 2 trials
Key Question 1: medication use (reliever)	Hyperventilation reduction breathing technique versus control	5	Medium	Consistent	Direct	Imprecise	Low	3 trials found reduction in reliever medication and 2 lowest-intensity trials did not.
	Yoga breathing technique versus control	2	Medium	Inconsistent	Direct	Imprecise	Insufficient	2 trials with substantial differences in intensity, location, and population and reported contradictory results
	IMT versus control	4	High	Consistent	Direct	Imprecise	Insufficient	4 trials, 3 by one author, 3 with high risk of bias, all show benefit on some measure at some time point

Outcome	Group	Number of studies	Risk of bias	Consistency	Directness	Precision	Strength of evidence	Comments
	Nonhyperventilation reduction breathing technique versus control	2	Medium	Consistent	Direct	Imprecise	Low	No benefit of treatment for any medication outcome in three trials
	Hyperventilation reduction breathing technique versus nonhyperventilation reduction breathing technique	3	Medium	Consistent	Direct	Imprecise	Low	Greater reduction in use with hyperventilation reduction breathing training in 2 of 3 cases, both groups improved in 1 trial
Key Question 1: medication use (controller)	Hyperventilation reduction breathing technique versus control	4	Medium	Inconsistent	Direct	Imprecise	Low	1 of 3 found large benefit, but raw data NR
	Yoga breathing technique versus control	1	High	N/A	Direct	Imprecise	Insufficient	1 trial with high risk of bias showed benefit of yoga
	IMT versus control	0	N/A	N/A	N/A	N/A	Insufficient	0 trials
	Nonhyperventilation reduction breathing technique versus control	3	Medium	Consistent	Direct	Imprecise	Low	No benefit of treatment for any medication outcome in three trials
	Hyperventilation reduction breathing technique versus nonhyperventilation reduction breathing technique	4	Medium	Inconsistent	Direct	Imprecise	Low	No differences in effectiveness in 3 of 4 cases
Key Question 1: quality of life	Hyperventilation reduction breathing technique versus control	4	Medium	Consistent	Direct	Imprecise	Low	Benefit found in 2 of 4
	Yoga breathing technique versus control	3	Medium	Consistent	Direct	Imprecise	Low	3 trials with mixed results, large effect seen in trial with shortest followup
	IMT versus control	0	N/A	N/A	N/A	N/A	Insufficient	0 trials
	Nonhyperventilation reduction breathing technique versus control	2	Medium	Inconsistent	Direct	Imprecise	Insufficient	2 trials with mixed results

Outcome	Group	Number of studies	Risk of bias	Consistency	Directness	Precision	Strength of evidence	Comments
	Hyperventilation reduction breathing technique versus nonhyperventilation reduction breathing technique	4	Medium	Consistent	Direct	Imprecise	Low	No differences in effectiveness in all cases, both groups improved in 1 trial
Key Question 1: Functioning or mental health	Hyperventilation reduction breathing technique versus control	4	Medium	Consistent	Direct	Imprecise	Low	2 of 2 found small benefit for anxiety and depression, 2 of 2 found mixed results for functioning
	Yoga breathing technique versus control	1	High	N/A	Direct	Imprecise	Insufficient	1 trial with substantial nonyoga components showed benefit
	IMT versus control	2	High	Consistent	Direct	Imprecise	Insufficient	2 trials with high risk of bias showing benefit, one in children, one in adults
	Nonhyperventilation reduction breathing technique versus control	1	Medium	N/A	Direct	Imprecise	Insufficient	1 trial with mixed results, benefit primarily seen on role limitations due to physical problems, not other subscales
	Hyperventilation reduction breathing technique versus nonhyperventilation reduction breathing technique	1	Medium	N/A	Direct	Imprecise	Insufficient	Single study showing greater benefit of Buteyko breathing training than yoga breathing training via device on some functioning subscales
Key Question 2: pulmonary function (FEV_1)	Hyperventilation reduction breathing technique versus control	5	Medium	Consistent	Indirect	Imprecise	Low	Small or no benefit found in all trials
	Yoga breathing technique versus control	5	Medium-High	Consistent	Indirect	Imprecise	Low	3 of 5 show benefit of yoga, all 3 high-intensity interventions, 2 with large effects
	IMT versus control	3	High	Inconsistent	Indirect	Imprecise	Insufficient	2 of 3 trials, two with high risk of bias
	Nonhyperventilation reduction breathing technique versus control	2	Medium	Consistent	Indirect	Imprecise	Insufficient	2 trials with different treatment approaches showing no benefit of treatment

Outcome	Group	Number of studies	Risk of bias	Consistency	Directness	Precision	Strength of evidence	Comments
	Hyperventilation reduction breathing technique versus nonhyperventilation reduction breathing technique	4	Medium	Consistent	Indirect	Imprecise	Low	No benefit for FEV_1 in any trials
Key Question 2: pulmonary function (PEF)	Hyperventilation reduction breathing technique versus control	3	Medium	Consistent	Indirect	Imprecise	Low	No benefit found in any trial
	Yoga breathing technique versus control	4	Medium-High	Consistent	Indirect	Imprecise	Moderate	3 of 4 show benefit of yoga, all 3 high-intensity interventions, 2 with large effects
	IMT versus control	1	High	N/A	Indirect	Imprecise	Insufficient	Single trial with large effect, high risk of bias
	Nonhyperventilation reduction breathing technique versus control	0	N/A	N/A	Indirect	N/A	Insufficient	0 trials
	Hyperventilation reduction breathing technique versus nonhyperventilation reduction breathing technique	1	High	N/A	Indirect	Imprecise	Insufficient	1 trial showing no benefit in either group
Key Question 3: harms	Hyperventilation reduction breathing technique versus control	3	Medium	Consistent	Direct	Imprecise	Low	None found adverse effects related to the intervention, one listed minor annoyances associated with mouth-taping
	Yoga breathing technique versus control	2	Medium	Consistent	Direct	Imprecise	Low	No adverse effects related to yoga
	IMT versus control	0	N/A	N/A	N/A	N/A	Insufficient	0 trials
	Nonhyperventilation reduction breathing technique versus control	0	N/A	N/A	N/A	N/A	Insufficient	0 trials

Outcome	Group	Number of studies	Risk of bias	Consistency	Directness	Precision	Strength of evidence	Comments
	Hyperventilation reduction breathing technique versus nonhyperventilation reduction breathing technique	2	Medium	Consistent	Direct	Imprecise	Low	No adverse effects related to interventions

Abbreviations: FEV_1: forced expiratory volume in 1 second; IMT: inspiratory muscle training; N/A: not applicable; PEF: peak expiratory flow

Discussion

The body of evidence suggests that selected intensive behavioral approaches that include breathing retraining or exercises may improve asthma symptoms or reduce reliever medication use in adults with poorly controlled asthma. However, the overall body of evidence primarily consisted of small, methodologically limited trials with widely heterogeneous samples, settings, and treatment approaches, and incomplete and inconsistent outcome reporting. Also, primary outcomes (symptom reduction and reliever medication use) were self-reported, making them susceptible to social desirability bias. Hyperventilation reduction techniques provided the strongest evidence for improvement in asthma symptoms and reliever medication use, including the only large-scale trial,[19] and the applicability to US health care systems was the best (although still limited, since to trials were conducted in the US). When seen, reduction in asthma symptoms were likely clinically significant: standardized effect sizes were frequently greater than 0.80, which is considered a large effect, and scale scores for symptoms and quality of life often changed in an amount associated with clinically significant differences. Reductions in reliever medication use were generally in the 1.5 to 2.5 puffs per day range, which were likely of clinical significance as well. However, this technique did not improve pulmonary function.

Intensive yoga breathing training, on the other hand, did improve pulmonary function in addition to improving symptoms in three trials of intensive yoga breathing training conducted in India.[23,26,27] Quality issues in these trials, however, limit confidence in results, and applicability to US health care systems was very low.

Evidence for IMT and other breathing retraining techniques were limited to small, heterogeneous trials best characterized as pilot studies that do not provide sufficient evidence to conclude that they are effective. There were only five IMT trials, three of which were conducted by the same researcher and all but one had substantial methodological limitations. The three nonhyperventilation reductions used three very different approaches and were either narrowly focused on one aspect of breathing retraining, or provided less than 1.5 hours of contact with instructors. Only one of these trials reported improvement in asthma-related measures and improvements disappeared between the 4-week and 26-week assessments.

Despite the relatively positive results for hyperventilation reduction techniques and yoga breathing, improvements could not be definitively attributed to the use of the specific techniques. Subjective assessment of asthma symptoms is responsive to placebo interventions (e.g., sham acupuncture or a placebo inhaler), and participants in hyperventilation-reduction interventions were instructed to delay use of reliever medication.[35] Rather than directly improving asthma, trials might have helped participants eliminate overuse of reliever medications, which is still an important positive outcome. Some trials attempted to control of the enthusiastic advocacy of the treatment modality by including comparison groups that involved other, plausible breathing retraining. However, it is difficult to say whether the treatment providers were comparable in their espousal of the effectiveness of their techniques.

A subset of articles in a Cochrane review on psychological treatments for asthma suggests that relaxation methods may reduce reliever medication use, and breathing retraining techniques may similarly benefit participants by reducing levels of anxiety and/or autonomic arousal.[36] Thus, these factors may have been sufficient to lead to improved asthma symptoms and reduced reliever medication use in some cases.

In summary, there are a number of possible explanations for the improvements in asthma outcomes reported in the trials in this review, including the placebo effect, lowered autonomic

arousal through relaxation or reduced anxiety, deliberate delayed use of reliever medication, lifestyle changes (diet, stress management, nutritional supplements), bias in outcome measurement, or the specific breathing techniques that were the focus of this review. It is very difficult to isolate critical treatment elements in complex interventions, and use of some elements in isolation may underestimate their importance if the components are dependent on each other or interact with each other, or if individuals vary in the degree to which specific components are necessary or sufficient to gain improvements. Thus, critical intervention components often cannot be elucidated, particularly in a relatively poor and heterogeneous body of research.

In most cases, the strength of evidence was insufficient or low. The evidence that hyperventilation reduction breathing techniques can reduce asthma symptoms and reliever medication use was judged moderate, as was evidence that yoga breathing techniques can improve pulmonary function.

The trials in this review generally had low applicability to US healthcare, primarily due to the settings in which the trials took place. Only three of the trials were conducted in the US.[24,25,33] Trials of hyperventilation reduction techniques had the best applicability, being conducted in healthcare settings in developed, English-speaking (but nonUS) countries. These trials generally used certified Buteyko practitioners and the availability of certified Buteyko practitioners in the US is unknown.

The yoga and IMT trials had particularly low applicability, as they were conducted primarily in India, Brazil, South Africa, and Israel, which are countries with substantial cultural and/or economic differences from the US. Some yoga and IMT trials were even further limited in their applicability to the general US population by limiting samples to males[23] or females only,[31] vegetarians within a fairly narrow age range,[23] people with six months of yoga experience and not using medications[26] and children with untreated asthma.[28] In some of these trials, the standard of usual care appeared to be different from the current US standard of care due to nonuse of controller medications[23,26] or poor success in managing asthma.[28]

There were several limitations and potential limitations to our review, both in our approach to the review and in the evidence base. In terms of our approach, potential limitations include the fact that we did not include non-English publications, that we excluded “poor”quality publications, that we excluded trials that used relaxation training as a comparison group, that we relied on personal communication with authors for some data, and that we were unable to locate seven publications that could possibly have been eligible for inclusion in the review. These are counterbalanced by some strengths of our report, including extensive grey-literature searching, examination of English abstracts of non-English trials, and efforts to contact authors in order to include all possible eligible English-language trials, in addition to extensive input from experts during protocol development, rigorous adherence to inclusion/exclusion rules, and conservative use of meta-analysis.

The evidence was limited in a number of ways. There were no trials rated as “good” quality and a number of trials could barely be considered “fair” quality. There was only one trial that could be considered large, and more than half of the trials included 25 or fewer participants per treatment group. Outcome reporting was very heterogeneous and inconsistent, with important outcomes missing in many trials, and outcomes assessment was not consistently blinded. In addition, there was little consistency of asthma-related terms used in these trials, and terms were sometimes used vaguely or differently, making it difficult to characterize interventions.

Additional evidence would improve our understanding for all intervention types. Future trials should detail breathing retraining techniques, as described by Bruton,[37] and these trials

should include outcomes of asthma symptoms, reliever medication use, quality of life, and pulmonary function at minimum. In addition, controller medication use should always be described. Best practices regarding randomization, blinding, and followup are also crucial to any further research in this area. For hyperventilation reduction techniques, top priorities for future research include replication of results of the large, good-quality trial with intensity-matched comparator, trials that attempt to isolate the necessity or efficacy of specific components of treatment, and trials focused on hyperventilation reduction techniques in children. A well-designed and executed replication of a high-intensity yoga breathing approach in the US, without additional nonyoga components would be an important next step for the use of yoga in asthma.

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Introduction

Condition Definition

Asthma is a chronic disorder of the airways characterized by the complex and variable interaction of underlying inflammation, bronchial hyper-responsiveness, and airway obstruction.[1] Asthma's principal symptoms result primarily from bronchoconstriction and a resulting reduction in airflow. These symptoms include shortness of breath, cough, wheezing, and chest pain or tightness. The associated reduction in airflow is usually reversible spontaneously or with treatment.[1] The specific clinical manifestations and severity of asthma can vary among and within susceptible individuals. Asthma further varies in its chronicity, cellular pathophysiology, triggers, and responsiveness to medication. It may be persistent or intermittent, mild to severe, exercise-associated, or aspirin-sensitive.[1] This variability in clinical patterns is not entirely understood, but is influenced by the complex interplay of inflammation, airway hyper-responsiveness, airway obstruction, and host-environment factors.

Prevalence and Disease Burden

In 2009, the estimated prevalence of asthma in the United States was 8.2 percent, representing 24.6 million adults and children. The prevalence was 9.6 percent among children and 7.7 percent among adults.[2]

The prevalence of asthma has increased substantially during the past 30 years. While it is difficult to compare exact prevalence figures over this period due to changes in surveillance methods, it appears that the prevalence has roughly doubled in most age, sex, and race subgroups.[3] Asthma is also more common among certain ethnic and racial groups, with Puerto Ricans, African Americans, American Indians, and Alaska Natives.[4] In addition, the prevalence of asthma is highest among people of low socioeconomic status.[4]

When poorly controlled, asthma is associated with increased health care use, decreased quality of life, and significant activity limitations.[5,6] In 2006, asthma accounted for 456,000 hospitalizations and 3,447 deaths in the United States.[2] The morbidity associated with asthma adds to the costs incurred by both patients and health care organizations. In the United States, the projected annual cost (direct and indirect) of asthma in 2010 was estimated to be over $20 billion.[3]

Etiology and Natural History of Asthma

Our knowledge of the pathogenesis of asthma has evolved over the past 25 years from a primary focus on bronchospasm to an understanding of the role of airway inflammation. We currently describe these processes along a continuum that includes severe persistent disease resulting from airway remodeling due to chronic inflammation.[1] The onset of asthma can occur at any age and the disease may or may not persist.[7] While causes of childhood asthma are not well-understood, we do know that children who develop asthma are more likely to have mothers with asthma, have increased airway resistance, have allergic sensitization by age three,[8] are atopic (especially if the atopy is accompanied by high levels of exposure to perennial allergens early in life).[9] Although the definitive etiology or etiologies of adult-onset asthma have not been identified, it is estimated to be work-related in 11 to 50 percent of cases, depending on age and sex.[10] Additionally, some evidence supports various other risk factors for new-onset asthma in

adulthood, including atopic sensitization and airway hyperresponsiveness in childhood, rhinitis, low socioeconomic status, family history of asthma, smoking (former and current), and female sex.[7]

The clinical course of asthma is largely unpredictable and is widely variable. The progression of asthma appears to vary in different age groups, as measured by pulmonary function.[1] In children, deficits in pulmonary-function growth appear to generally occur by the age of 6 years, and primarily in those whose symptoms began before the age of 3 years. In adults, there is evidence that pulmonary function may progressively decline, but the implications of this decline for the development of fixed airflow obstruction are not understood.[1]

Diagnosis and Assessment of Asthma

Diagnosing and assessing asthma requires clinical judgment based on medical history, physical examination, and pulmonary function testing.[1] Guidelines from an expert panel recommend that before establishing a diagnosis of asthma a clinician should determine that: (a) episodic symptoms of airflow obstruction or airway hyperresponsiveness are present; (b) airflow obstruction is at least partially reversible; and (c) alternate diagnoses are excluded.[1] Because other diagnoses cannot be reliably excluded by medical history and physical examination, and because patients' vary considerably in their ability to perceive of airflow obstruction, an objective assessment of pulmonary function is necessary for an asthma diagnosis. While peak expiratory flow (PEF) meters are useful for monitoring the disease, spirometry is more reliable and recommended for establishing the diagnosis.[1] Guidelines recommend assessing forced expiratory volume for 1 (FEV_1) or 6 seconds and/or forced vital capacity (FVC, the total volume of air that can be forcibly exhaled after maximal inhalation) before and after use of a short-acting bronchodilator. Maximal patient effort during spirometry testing is crucial for accurate assessment. A skilled technician who can uphold American Thoracic Society (ATS) performance guidelines is also required.[11]

Airway obstruction is considered reversible if there is an increase in FEV_1 of more than 200 milliliters and 12 percent from baseline after two to four puffs of albuterol. In patients who are not taking long-term control medications (e.g., inhaled corticosteroids [ICS]) an FEV_1 below 60 percent of predicted (based on age and sex) is categorized as "severe" asthma, 60 to 80 percent of predicted is "moderate," and above 80 percent is "mild."

Distinguishing severity of underlying disease from current control is important in characterizing asthma. Asthma severity is the intrinsic intensity of the disease. Asthma control is the degree to which symptoms and functional limitations are minimized (e.g., a person may have severe underlying disease that is well controlled). Severity is assessed before introduction of long-term controller medications such as inhaled corticosteroids. Once therapy is initiated, asthma control is monitored and treatment modifications are based on degree of control.

Treatment of Asthma

As our understanding of the critical role played by inflammation in the pathophysiology has increased, so has the number of therapies targeting this inflammatory process. In addition to short-acting $beta_2$-agonist (SABA) drugs for quick-relief of acute exacerbations, pharmacologic treatment of persistent asthma often entails the use of anti-inflammatory medications for long-term control — most commonly ICS, but also including drugs that target various inflammatory cell types, such as leukotriene modifiers. (see Table 1 for an overview of medications recommended for use in treating asthma).[1]

The goal of treatment is to achieve asthma control, as evidenced by normal or near normal pulmonary function, maintenance of normal activity levels, and minimal need for SABA inhalers for "quick-relief" of asthma symptoms (≤ twice per week).[1] Asthma treatment is often multi-focal and tailored to the individual's characteristics, including disease pattern and severity, treatment response, and side effects. Current US guidelines recommend four essential components for effectively managing asthma symptoms effective asthma management: assessing and monitoring the disease, self-management education, controlling environmental and co-morbid conditions, and adequate pharmacologic therapy. Although treatment seeks to improve asthma control, treatment does not appear to affect the underlying severity of the asthma, at least in adults.[1]

Table 1. Commonly used long-term and quick-relief medications to treat asthma

Medi-cation	Drug class	Product(s)	Indications	Mechanism	Potential adverse effects
Long-term control medi-cations	Inhaled cortico-steroids	Beclometha-sone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone furoate, triamcinolone acetonide	Long-term prevention of symptoms; suppression, control and reversal of inflammation. Reduced need for oral corticosteroids.	Anti-inflammatory, blocks late reaction to allergen and reduces airway hyper-responsiveness and inhibits cytokine production, adhesion protein activation and inflammatory cell migration and activation... Reverse beta$_2$-receptor down regulation by inhibiting microvascular leakage.	Cough, dysphonia, oral thrush (candidiasis). Systemic effects may occur with high doses (e.g., adrenal suppression, osteoporosis, skin thinning, and easy bruising). Suppression of growth velocity seen in children taking low to medium doses (transient effect).
	Systemic cortico-steroids	Methyl-prednisolone, prednisolone, prednisone	For short-term "burst" control and for long-term prevention of symptoms in severe persistent asthma.	Same as ICS.	Short term use: reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, hypertension, mood alteration, peptic ulcer, rarely aseptic necrosis. Long-term use: adrenal axis suppression, dermal thinning, growth suppression, hypertension, diabetes, Cushing's syndrome, muscle weakness, cataracts, impaired immune function (rare).
	Cromolyn sodium and nedocromil	NA	Long-term prevention of symptoms of mild persistent asthma. Preventive treatment prior to exercise or allergen exposure.	Anti-inflammatory, blocks early and late reaction to allergen, interferes with chloride channel function, and stabilizes mast cell membranes and inhibits activation and release of mediators from eosinophils and epithelial cells. Inhibits acute response to exercise, cold dry air and sulfuric dioxide.	Cough and irritation, unpleasant taste for nedocromil.

Medi-cation	Drug class	Product(s)	Indications	Mechanism	Potential adverse effects
	Immuno-modulators	Omalizumab	Long-term control and prevention of symptoms in moderate to severe persistent allergic asthmatics poorly controlled by ICS.	Prevention IgE binging to high-affinity receptors on basophils and mast cells. Decrease mast cell mediator from allergen exposure. Decrease number of high-affinity receptors in basophils and submucosal cells.	Pain and bruising at injection site, anaphylaxis, and malignant neoplasms (unclear relationship).
	Leukotriene receptor antagonists	Montelukast tablets and granules, zafirlukast tablets	Long-term control and prevention of symptoms in mild persistent asthma patients aged ≥ 12 years.	Leukotriene receptor antagonists, selective competitive inhibition of $CysLT_1$ receptor.	No specific AEs reported for montelukast except Churg-Strauss (rare). Reversible hepatitis and rare irreversible hepatic failure (liver transplant and death) for zafirlukast.
	5-Lipo-oxygenase inhibitor	Zileuton tables	Long-term control and prevention of symptoms in mild persistent asthma patients aged ≥ 12 years	Inhibits production of leukotrienes from arachidonic acid	Elevation of liver enzymes and limited case reports of reversible hepatitis and hyperbilirubinemia.
	Long-acting $beta_2$-agonists	Inhaled formoterol and salmeterol; albuterol sustained-release tablets	Long-term prevention of symptoms in addition to ICS. Prevention of exercise-induced broncho-spasm.	Bronchodilation, smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP producing functional antagonism of bronchoconstriction.	Tachycardia, skeletal muscle tremor, hypokalemia, prolongation of QT_c interval in overdose. Diminished bronchoprotective effects. Potential risk of uncommon, severe, life-threatening or fatal exacerbation.
	Methyl-xanthines	Theophylline sustained-release tablets and capsules	Long-term control and prevention of symptoms in mild persistent asthma or as adjunctive with ICS in moderate or persistent asthma.	Bronchodilation, smooth muscle relaxation from phosphodiesterase inhabitation and possible adenosine antagonism. May affect eosinoic infiltration to bronchial mucosa as well as decrease in epithelial T-lymphocyte. Increase diaphragm contractility and mucociliary clearance.	Insomnia, gastric upset, ulcer aggravation or reflux, hyperactivity (children), urination difficulties (elderly men with prostatism). Dose-related acute toxicities (e.g., tachycardia, nausea, CNS stimulation, hyperkalemia SVT, seizures, vomiting, headache, hematemesis, and hyperglycemia).

Medi-cation	Drug class	Product(s)	Indications	Mechanism	Potential adverse effects
Quick-relief medi-cations	Short-acting beta$_2$-agonists	Inhaled albuterol, levalbuterol and pirbuterol	Relief of acute symptoms and preventive treatment for exercise-induced bronchospasm prior to exercise.	Bronchodilation binds to the beta$_2$-adrenergic receptor producing smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP producing functional antagonism of bronchoconstriction.	Tachycardia, skeletal muscle tremor, lactic acid increase, headache, hyperglycemia. Patients with cardiovascular conditions may have adverse cardiovascular reactions.
	Anti-cholinergics	Ipratropium bromide	Relief of acute broncho-spasm.	Bronchodilation, competitive inhibition of muscarinic cholinergic receptors. Reduced intrinsic vagal tone of airways may block reflex bronchoconstriction secondary to irritants or to reflux eosinophils. May decrease mucous gland secretion.	Dry mouth, wheezing, and blurred vision if sprayed in eyes.
	Cortico-steroids	Methylpredniso lone, prednisolone, prednisone	Prevent progression, reverse inflammation, speed recovery, and reduce relapse rate in exacerbations.	Same as ICS.	Reversible abnormalities in glucose metabolism, increased appetite, fluid retention, facial flushing, weight gain, hypertension, mood alteration, peptic ulcer, aseptic necrosis (rare).

Adapted from the National Asthma Education and Prevention Program's Prevention Guidelines for the Diagnosis and Management of Asthma (Figures 3-22 and 3-23)[1]

Abbreviations: AE: adverse effect; AMP: adeno monophosphate; CNS: central nervous system; ICS: inhaled corticosteroids; SVT: supraventricular tachycardia

Despite clinical practice guidance on self-management education and medication use, many patients with asthma appear to adhere poorly to such recommendations.[12,13] Studies have found that adults with asthma and the parents of children with asthma have concerns about regular use of medication, including fears of long-term dependence and side effects associated with inhaled and oral steroids.[14,15] While side effects for ICS are rare, these medications can be associated a number of possible side effects, including slowed growth in children. However, effects on growth are small, appear to be seen primarily in the first months of treatment, are generally nonprogressive, and may be reversible. It is worth noting that poorly controlled asthma can also delay growth in children. At high doses and with long-term use, ICS use can be associated with adrenal suppression, osteoporosis in adults, skin thinning/easy bruising, and possibly the increased risk of developing cataracts in adults and glaucoma in adults with a family history of glaucoma.[1] In addition, according to the product information insert for QVAR® 40 micrograms (mcg) and 80 mcg, long-term effects of chronic ICS use are still not fully known, including effects on the immunologic processes in the mouth, pharynx, trachea, and lung.[16] Possible side effects of SABAs include headache, musculoskeletal pain, tachycardia, and other cardiovascular effects. In addition, there have been rare reports of serious, even fatal, asthma exacerbations associated with overuse of SABAs, particularly older versions of these medications (isoproterenol and fenoterol).[17]

A variety of complementary and/or alternative therapies have been advocated for the control of asthma given its spectrum of severity and causes as well as concerns about long-term medication use. These include breathing exercises, herbal remedies, homeopathy, acupuncture, relaxation therapies, and manual therapy (e.g., chiropractic techniques, massage). Breathing retraining exercises are among the complementary and alternative treatments most frequently used by people with asthma, and are purported to have virtually no adverse effects.[14,18,19] Breathing retraining is generally assumed to be complementary to guideline-based care, with the primary goals of improving asthma control and reducing the use of medications, particularly SABAs. Some specific breathing retaining approaches include the Buteyko breathing technique, yoga-based approaches, technology-assisted approaches, and physical therapy techniques.

Buteyko and other methods based on hyperventilation reduction and CO_2 regulation

The Buteyko breathing technique, developed by Konstantin Buteyko, is based on the theory that chronic hyperventilation in people with asthma leads to decreased carbon dioxide (CO_2) in the blood (hypocapnia), which constricts the airways. Buteyko developed a breathing method to increase the amount of CO_2 in the blood. This method involves controlled shallow breathing through the nose only, with breath-holding at the end of the exhalation. The length of time a person is able to hold their breath at the end of an exhalation indicates the extent of hyperventilation, with longer periods of breath-holding indicating less hyperventilation.[20] Buteyko practitioners train users to eliminate or minimize big sighs, yawns, and gasps, which they consider "overbreathing." This method requires commitment on the part of users, which usually takes considerable practice to master and improves with time. When experiencing asthma symptoms, Buteyko users are encouraged to utilize breathing the technique for 5-10 minutes before using a bronchodilator to relieve symptoms. Buteyko practitioners encourage the use of porous tape to hold the lips together at night for those who tend to breathe through their mouths at night. The British Thoracic Society guideline developers concluded that evidence supported consideration for the use of the Buteyko breathing technique to control the symptoms of asthma.[21]

Other clinicians have used approaches not specifically identified as Buteyko breathing training, but are consistent with Buteyko methods and/or integrate Buteyko methods. For example, the Papworth method involves instruction in slow (e.g., 8 breaths per minute), steady diaphragmatic breathing through the nose, with a pause at the end of each breath and elimination of big sighs and other overbreathing. In addition, they work with patients to learn to use relaxed, controlled breathing while talking and engaging in daily activities.[22,23]

The evidence supporting the hyperventilation theory of the pathophysiology of asthma is mixed. One study showed that people with asthma have lower end-tidal CO_2 levels (i.e., blood levels of CO_2 at the end of exhalation) than those without asthma.[24] Research by ven den Elshout and colleagues appears consistent with Buteyko's theory by demonstrating that inducing a reduction in end-tidal CO_2 levels increased airway resistance in people with asthma and a history of bronchial hyperresponsiveness to histamine, but did not change airway resistance in matched controls without asthma. When hypercapnia (high level of CO_2 in the blood) was induced in the same study, airway resistance decreased in both patients with asthma and controls.[25] Another study, however, found that longer breath-holding time was associated with a reduction in end-tidal CO_2, which is counter to Buteyko' s theory.[26]

Yoga-based approaches

The breathing techniques used in yoga are different from hyperventilation reduction methods. Particular breathing techniques, known as *pranayama*, are integral to virtually all yoga traditions. While these traditions vary in the specific use of breathing techniques, they generally involve slowing and regularizing the breath by prolonging the expiratory phase, enhancing abdominal/diaphragmatic breathing, and imposing resistance to both inspiration and exhalation.[27] The prolonged expiratory phase is assumed to promote mental and physical relaxation. Increased respiratory resistance, which can be achieved through manually blocking one nostril or by using the tongue and other mouth muscles to narrow breathing passages, is thought to promote efficient alveolar gas exchange (resulting in an increase in alveolar CO_2) and, in asthma patients, to help reduce hyperinflation of the lungs. Like hyperventilation reduction methods, yoga practitioners usually advocate the use nasal breathing rather than mouth breathing, and both approaches appear to have the effect of slowing the passage of air in and out of the lungs. It is unclear if the two approaches have similar physiologic effects.

Physical therapy techniques and inspiratory muscle training

Slow-paced respiration provides users with an external stimulus to encourage a specific (slow) breathing rate. Slower breathing rates have been associated with lower stress response (as measured by skin resistance, finger pulse volume, and self-reported anxiety in the face of anticipated stressors). Slow-paced respiration is typically combined with abdominal breathing to reduce panic attacks, and thus may be of help to the extent that asthma is triggered by stress or anxiety.[28] Biofeedback has been used to target stress response through reduced autonomic arousal, and has also been used to target airway resistance and the relaxation of the muscles used for breathing directly.[28] In addition, efforts may be made to strengthen inspiratory and/or expiratory muscles to help reduce perception of dyspnoea and aid in overcoming airway resistance and avoiding hyperinflation due to insufficient expiratory strength.

Scope and Purpose

The original public nomination made by a Buteyko practitioner and physiotherapist requested a review focused specifically on the effectiveness of the Buteyko method for reducing bronchodilator and inhaled steroid use and improving the health status of adults and children with asthma. After input from experts and consulting the literature, we expanded the topic to also address the breathing retraining approaches described above. Thus, the objective of this review is to synthesize the data on the effectiveness and comparative effectiveness of a variety of breathing retraining techniques in the management of asthma in adults and children 5 years of age or older.

Key Questions

Three systematically reviewed key questions are addressed in this report. These questions address the impact of breathing exercises on health outcomes and pulmonary function in addition to the harms related to breathing exercises in the treatment of asthma.

1. In adults and children 5 years of age and older with asthma, does the use of breathing exercises and/or retraining techniques* improve health outcomes, including: symptoms (e.g., cough, wheezing, dyspnea); health-related quality of life (general and/or asthma-specific); acute asthma exacerbations; reduced use of quick-relief medications or

reduced use of long-term control medications, when compared with usual care and/or other breathing techniques alone or in combination with other intervention strategies?

   a. Does the efficacy and/or effectiveness of breathing techniques for asthma health outcomes differ between different subgroups (e.g., adults/children; males/females; different races or ethnicities; smokers/nonsmokers; various types and severities of asthma; and/or different coexisting conditions)?
   b. Does the efficacy and/or effectiveness of breathing techniques for asthma health outcomes differ according to variations in implementation (e.g., trainer experience) and/or nonbreathing components of the intervention (e.g., anxiety management)?

2. In adults and children 5 years of age and older with asthma, does the use of breathing exercises and/or retraining techniques improve pulmonary function or other similar intermediate outcomes when compared with usual care and/or other breathing techniques alone or in combination with other intervention strategies?
   a. Does the efficacy and/or effectiveness of breathing techniques for other asthma outcomes differ between different subgroups (e.g., adults/children; males/females; different races or ethnicities; smokers/nonsmokers; various types and severities of asthma; and/or different coexisting conditions)?
   b. Does the efficacy and/or effectiveness of breathing techniques for other asthma outcomes differ according to variations in implementation (e.g., trainer experience) and/or nonbreathing components of the intervention (e.g., anxiety management)?

3. What is the nature and frequency of serious adverse effects of treatment with breathing exercises and/or retraining techniques, including increased frequency of acute asthma exacerbations?
   a. Do the safety or adverse effects of treatment with breathing techniques differ between different subgroups (e.g., adults/children; males/females; different races or ethnicities; smokers/nonsmokers; various types and severities of asthma; and/or different coexisting conditions)?

*For example: the Buteyko breathing technique; inspiratory muscle training; breathing physical therapy including paced and pursed lip breathing exercises; the Papworth Method; biofeedback- and technology-assisted breathing retraining; and yoga breathing exercises.

Methods

AHRQ requested a comparative effectiveness review on the effectiveness of breathing exercises and/or retraining for the treatment of asthma as part of its Effective Health Care (EHC) program. The Oregon EPC established a team and a protocol to develop the evidence report.

Topic Development and Refinement

The topic for this report was nominated through a public process. The Scientific Resource Center (SRC) for the AHRQ Effective Health Care Program compiled information about this topic to evaluate its priority for comparative effectiveness review. This information was evaluated and discussed by staff of the Effective Health Care Program and was approved for a full review.[29]

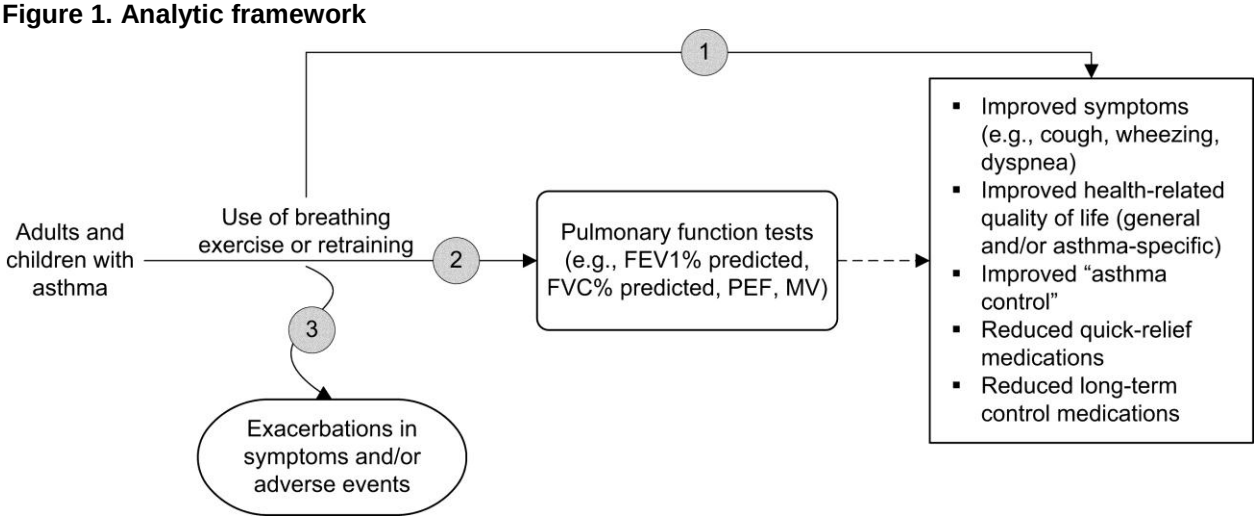
The Oregon EPC drafted a topic refinement document with proposed key questions after consulting with seven key informants. Key informants included western allopathic and alternative medical providers and representatives of patient advocacy groups. The alternative medical practitioners covered the areas of Buteyko Breathing Technique, yoga breathing techniques, and the Papworth breathing retraining method.

The key questions were posted on AHRQ's website for public comment in August and September of 2010 for 4 weeks and revised as needed. We then drafted a protocol for the comparative effectiveness review and recruited a technical expert panel (TEP) to provide high-level content and methodological expertise throughout the review. The TEP was comprised of five individuals who specialize in asthma management from the fields of Family Medicine, Community Health and Nursing, Psychology, Physical Therapy, and Pediatrics. The TEP was set up to ensure the scientific rigor, reliability, and methodological soundness of the research. The TEP commented on the review protocol and on various components of the in-process review. They also offered advice on substantive issues related to specific studies and/or outcomes.

Analytic Framework

The analytic framework for evaluating the comparative effectiveness of breathing exercises and/or retraining for the treatment of asthma is shown in Figure 1. In general, the figure illustrates how the use of breathing exercises or retraining may result in intermediate outcomes (e.g., forced expiratory volume in 1 second (FEV_1) or PEF, and/or ultimate heath outcomes (e.g., improved symptom severity and quality of life). The figure also depicts the possibility of adverse events occurring after treatment. We did not systematically review the association between pulmonary function test results and asthma symptoms, along with other health outcomes.

Figure 1. Analytic framework



Abbreviations: FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; MV: minute volume; PEF: peak expiratory flow

Literature Search Strategy

A research librarian performed comprehensive literature searches in the following databases:

- MEDLINE accessed via PubMed
- PsycInfo
- EMBASE
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)
- Physiotherapy Evidence Database (PEDro)
- Cochrane Central Register of Controlled Trials (CCRCT)
- AltHealthWatch
- Allied and Complementary Medicine (AMED)
- Manual, Alternative and Natural Therapy Index System (MANTIS)

Appendix A outlines our search terms for each database. These searches were used to locate relevant studies related to all three key questions. All searches were executed first in January 2011 and updated through July 28, 2011.

Searches were restricted to English-language literature and to the time period of 1990 to July 28, 2011. We did not have translation services available to review non-English papers, and our TEP agreed that the majority of the relevant literature would be published in English or have been translated into English. However, because the Buteyko methods were developed in Russia, there may be relevant early research published only in Russian. We retained the abstracts for non-English studies with English abstracts that appeared to fit our inclusion criteria (aside from the language). Titles and abstracts of these studies are presented in Appendix B.

Searches of these databases were supplemented with manual searching of reference lists contained in all included articles and in relevant review articles. Grey literature searches were also performed by the research librarian. For the purposes of this review, grey literature referred

to any information that is not controlled by commercial publishing and included regulatory documents (e.g., U.S. Food and Drug Administration Medical and Statistical Reviews and Authorized Medicines for the European Union); clinical trial registry entries (e.g.,ClinicalTrials.gov, the World Health Organization International Trials Registry Platform (ICTRP), and Current Controlled Trials (ISRCTN Register); and conference abstracts (e.g., CSA's Conference Papers Index, Scopus conference papers, ProceedingsFirst, and PapersFirst). Upon receipt of the grey literature search results, we reviewed abstracts and/or full-text results according to the methods described below. We matched abstracts to any published studies and reviewed them in conjunction with the full text of these studies. In addition, a Scientific Information Packet (SIP) was requested from one relevant organization that produces materials and educational trainings for one intervention of relevance to this review (Buteyko Institute of Breathing & Health, Manuka, Australia). However, we did not receive a SIP.

The results of our searches were downloaded and imported into version 11.0.1 of Reference Manager® (Thomson Reuters, New York, NY), a bibliographic management database. We manually scanned for duplicates. Reference Manager was used to track the search results at the levels of title/abstract review and article inclusion/exclusion.

Process for Study Selection

A two-step process was used for study selection. First, two members of the research team independently reviewed each title and abstract (if available) to determine if an article met the broad inclusion/exclusion criteria for study design, population, and intervention (Table 2). Each title/abstract was coded as: potentially included, excluded, or background. Next, we retrieved full-text articles for all potentially included studies, including those that were questionable or unclear at the abstract stage. Two reviewers independently assessed each full-text article using a standard form that detailed the predetermined inclusion and exclusion criteria. Disagreements were resolved through discussion.

Table 2. Inclusion and exclusion criteria

Category	Inclusion criteria	Exclusion criteria
Population	• Humans, all races, ethnicities, cultural groups • Adults aged ≥ 18 years with asthma of any type and severity, symptomatic or using asthma medication • Children ≥ 5 years with asthma of any type and severity, symptomatic or using asthma medication • Asthma diagnosis by medical practitioner (self-report of physician diagnosis acceptable)	• Children < 5 years • Individuals with comorbid chronic obstructive pulmonary disease, emphysema, chronic bronchitis or any other chronic disease that affects pulmonary function (e.g., heart disease, thyroid disease)

Category	Inclusion criteria	Exclusion criteria
Interventions	Interventions in which breathing retraining/exercises are a primary component. Such exercises include: • Buteyko breathing technique (including those focused only on mouth taping • Inspiratory muscle training • Expiratory muscle training • Diaphragmatic breathing techniques • Breathing physical therapy (e.g., paced and pursed lip breathing exercises) • Papworth method • Biofeedback- and other technology-assisted breathing retraining • Yoga breathing exercises • Other breathing exercises	• Interventions that do not focus primarily on asthma • Interventions whereby breathing techniques are not a primary treatment • In-hospital management of acute exacerbations • Physical fitness training • Alexander Technique
Comparator	• Other breathing techniques alone or in combination with other intervention strategies • Usual care as standard for the setting (e.g., asthma self-management education, control of environmental factors, pharmacologic therapy) • Technology-supported placebo device • Attention controls (receiving similar time and attention as the intervention group on another topic unrelated to breathing retraining) • Wait-list controls • No treatment offered (outside care is assumed)	• Other alternative or complementary methods that are potentially efficacious for asthma and are not focused on breathing retraining [e.g., relaxation techniques (e.g., progressive muscle relaxation), acupuncture, herbal therapies, chiropractic] • Physical activity or exercise

Category	Inclusion criteria	Exclusion criteria
Outcomes	Key Question 1: • Symptoms (e.g., cough, wheezing, dyspnea, nocturnal symptoms) • Health-related quality of life (general and/or asthma-specific) • Asthma control (e.g., acute exacerbations, hospitalizations for asthma, urgent or emergent clinic or hospital visits for asthma (including unscheduled doctor visits), nocturnal control, missed school/work, daily activity tolerance or restrictions) • Exercise tolerance (e.g., 6-minute walk, shuttle run) • Quick-relief medication use (e.g., short-acting beta$_2$-agonists, anticholinergics) • Long-term control medications (e.g., inhaled corticosteroids, long-acting immunomodulators) Key Question 2: • Pulmonary function tests: FEV_1 % predicted; FVC % predicted; PEF; MV, exhaled nitric oxide, methylcholine challenge and/or responsiveness, sputum eosinophil markers of inflammation, other measures of CO_2, other spirometry measures Key Question 3: • Increased asthma symptoms or acute asthma exacerbations • Adverse reactions to therapies • Reduction in/negative influences on quality of life	• Costs • During or post-exercise breathlessness or pulmonary function (considered too highly correlated with fitness)
Time Period	1990 to present	Before 1990
Setting	All settings	Not applicable
Study geography	All locations	
Publication language	English	All other languages

Category	Inclusion criteria	Exclusion criteria
Study design	Key Questions 1, 2 and 3: • Randomized controlled trials • Controlled clinical trials • Comparative observational studies (prospective and retrospective cohort studies; case-control studies); including only those controlling for medication use and health care use with long-term (≥ 6 month) outcomes, with some validity of case ascertainment or in those with broadly representative samples Key Questions 1a and 2a: • Randomized controlled trials • Controlled clinical trials • Comparative observational studies (prospective and retrospective cohort studies; case-control studies); including cohort of patients who have undergone breathing retraining, reliably divided into subgroups of interest, adequately powered to detect differences in outcomes between groups, and adequately controlling for confounders Key Questions 1b and 2b: • Randomized controlled trials • Controlled clinical trials	Key Questions 1, 2 and 3: • Editorials, letters, nonsystematic literature reviews • Noncomparative observational studies (e.g., case-series, case reports, cross-sectional studies) • Comparative observations trials not meeting all inclusion criteria Key Questions 1a and 2a: • Editorials, letters, nonsystematic literature reviews • Noncomparative observational studies (e.g., case-series, case reports, cross-sectional studies) • Comparative observations trials not meeting all inclusion criteria Key Questions 1b and 2b: • Editorials, letters, nonsystematic literature reviews • Observational studies
Intervention duration	All	Not applicable
Follow-up duration	≥ 4 weeks post intervention	< 4 weeks post intervention
Sample size	N ≥ 10	N < 10

Abbreviations: CO_2: carbon dioxide; FEV_1: forced expiratory flow in 1 second; FVC: forced vital capacity; MV: minute volume; PEF: peak expiratory flow

Data Abstraction and Data Management

We abstracted data from all included studies with a quality rating of "fair" or "good" (see section below on individual study quality assessment) into a standard evidence table. One investigator abstracted the data and a second checked the data. Discrepancies regarding data abstraction were resolved by re-review, discussion, and comments from others. The following information was obtained from each study, where available: author identification; year of publication; study location; study design; recruitment setting and approach; inclusion/exclusion criteria; demographic and health characteristics of the sample including baseline asthma; description of the intervention and control arms; any co-intervention components (e.g., advise about diet, relaxation training); compliance with treatment; and sample retention. Outcomes included: asthma symptoms; medication and health care use; quality of life and functioning; pulmonary function; and adverse outcomes. We also recorded the instruments used to measure each outcome, where available. We contacted authors of included studies if clarification of methods (e.g., randomization methods) or results (e.g., providing missing data or verifying the data) was needed.

Individual Study Quality Assessment

We used predefined criteria developed by the U.S. Preventive Services Task Force to assess the methodological quality of included studies.[30] Two independent reviewers assigned a quality rating of the internal validity for each study. Disagreements were resolved by discussion and consensus. A rating of "good," "fair," or "poor" was assigned using the predefined criteria for studies meeting inclusion criteria. For randomized controlled trials (RCTs), specific areas assessed included:

- The presence of adequate randomization methods (use of computer-generated random number tables or other process considered truly random);
- Allocation concealment;
- Similarity of groups at baseline;
- The specification of eligibility criteria;
- Reliable and valid diagnosis or asthma (optimal assessment included use of pulmonary function testing to confirm reversible component);
- Retention (retention of 90 percent or more overall was considered good; 60 to 89 percent was adequate, and less than 60 percent was considered a fatal flaw; differential attrition of 10 to 19 percentage points was considered potentially problematic and 20 percentage points or more was considered a fatal flaw);
- Time to followup (6 months or more was preferable, fewer than 6 weeks was potentially problematic)
- Equal, reliable and valid measurements;
- Blinding of outcome assessors; and
- Appropriate analyses (e.g., analyzing all participants in the treatment group to which they were initially assigned, use of conservative data substitution [preferably multiple imputation, imputation based random effects regression or similar models, or use of baseline values] when retention was below 90 percent, adjustment for potential confounders, no use of statistical tests that were inappropriate for the type of data analyzed).

All of these items were used to evaluate the risk of bias. Generally, a good-quality study met all major criteria, though it was possible to get a "good" rating if an item was not reported (so could not be assessed) if the rest of the methods were judged to be "good." A fair-quality study did not meet all criteria, but was judged to have no flaw so serious that it invalidated its results. A poor-quality study contained a serious flaw in design, analysis, or execution, such as differential attrition as described above, or some other flaw judged to be so serious as to cast doubt on the validity of the results. Examples of serious flaws include very large baseline group differences that were not or could not be adjusted for in an analysis, no information about followup and assumption of 100% followup was not teneable, or insufficient information was provided to determine the risk of bias.

We did not include studies rated as poor-quality in this review.

Data Synthesis

We summarized all included studies in narrative form as well as in summary tables that present the important features of the study populations, design, intervention, outcomes, and results. We divided comparisons into five groups based on the primary intervention focus and control group: (1) interventions focused on hyperventilation reduction breathing training vs.

control, (2) yoga breathing methods vs. control, (3) inspiratory muscle training (IMT) vs. control, (4) breathing approaches that did not focus on hyperventilation reduction vs. control, and (5) hyperventilation reduction vs. nonhyperventilation reduction breathing training approaches. Outcomes are discussed separately for each of the five groups.

To facilitate comparison of effect sizes across studies reporting different outcomes, when possible we calculated a standardized effect size (Hedges g) using Stata 11.2® (Stata Corp, College Station, TX) where sufficient data were available for calculation. In calculating standardized effect sizes for asthma symptom outcomes, all scores were coded so that a higher score indicated more symptoms (worse outcome). For quality of life measures, all scores were coded so that a higher score indicated higher quality of life (better outcome). Random effects meta-analyses were conducted where there were at least three trials within a group. Meta-analyses were always conducted within groups because of the high degree of clinical and methodological heterogeneity across group. Heterogeneity was evaluated using the I^2 statistic. When trials reported multiple followup assessment, we pooled data from the assessment that was closest to the followup time reported by the other trials in the analysis. For trials with more than one control arm, we included the control group most similar in intensity to the intervention group that was included in the meta-analysis, thus choosing intensity-matched comparators wherever possible. We did not perform funnel plots or Egger's test of small study effects to assess for publication bias because of the small number of trials included in each meta-analysis.

In a separate exploratory qualitative analysis, we stratified all trials (regardless of group) by a series of study characteristics of interest and examined the proportion of trials reporting positive results in trials with and without the pertinent characteristic. Characteristics examined included study quality rating (substantial quality concerns vs. average quality concerns), whether the comparator included a breathing or relaxation component, whether the intervention involved the use of a device, and whether the two groups being compared involved the same number of hours of contact and homework. We examined outcomes, including: asthma symptoms, reliever medication use, quality of life, and pulmonary function.

Grading the Strength of Evidence

We graded the strength of evidence for primary outcomes using the standard process of the EPCs as outlined in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[31] Specifically, we assessed the strength of evidence for the major outcomes in each of the Key Questions. These outcomes included: (1) asthma symptoms and control, (2) asthma medication use, (3) quality of life and function for Key Question 1; and 4) pulmonary function test results for Key Question 2. The grade of evidence was based on four major domains: (1) risk of bias (low, medium, high), (2) consistency (no inconsistency present, inconsistency present, unknown or not applicable), (3) directness (direct, indirect), and (4) precision (precise, imprecise). Risk of bias is the degree to which the included studies for a given outcome or comparison has a high likelihood of adequate protection against bias. We evaluated risk of bias considering both study design and aggregate quality of the studies. Consistency refers to the degree to which reported effect sizes from included studies appear to have the same direction and magnitude of effect. We assessed the sign of the effect sizes (i.e., effects have the same direction) and whether the range of effect sizes was narrow. When only a single study was included, consistency could not be judged. Directness relates to whether the evidence links the interventions directly to health outcomes. For a comparison of two treatments, directness implies

that head-to-head trials measure the most important outcomes. Precision refers to the degree of certainty surrounding an effect estimate with respect to a given outcome.

We assigned an overall strength of evidence grade based on the ratings for these four individual domains for each key outcome, and for each comparison of interest. The overall strength of evidence was rated using four basic grades (as described in the AHRQ *Methods Guide*): high, moderate, low, and insufficient (Table 3).[31] We rated the evidence as insufficient when no studies were available for an outcome or comparison of interest. Ratings were assigned based on our judgment of the likelihood that the evidence reflected the true effect for the major comparisons of interest.

Table 3. Strength of evidence grades and definitions

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence is unavailable or does not permit a conclusion

Applicability

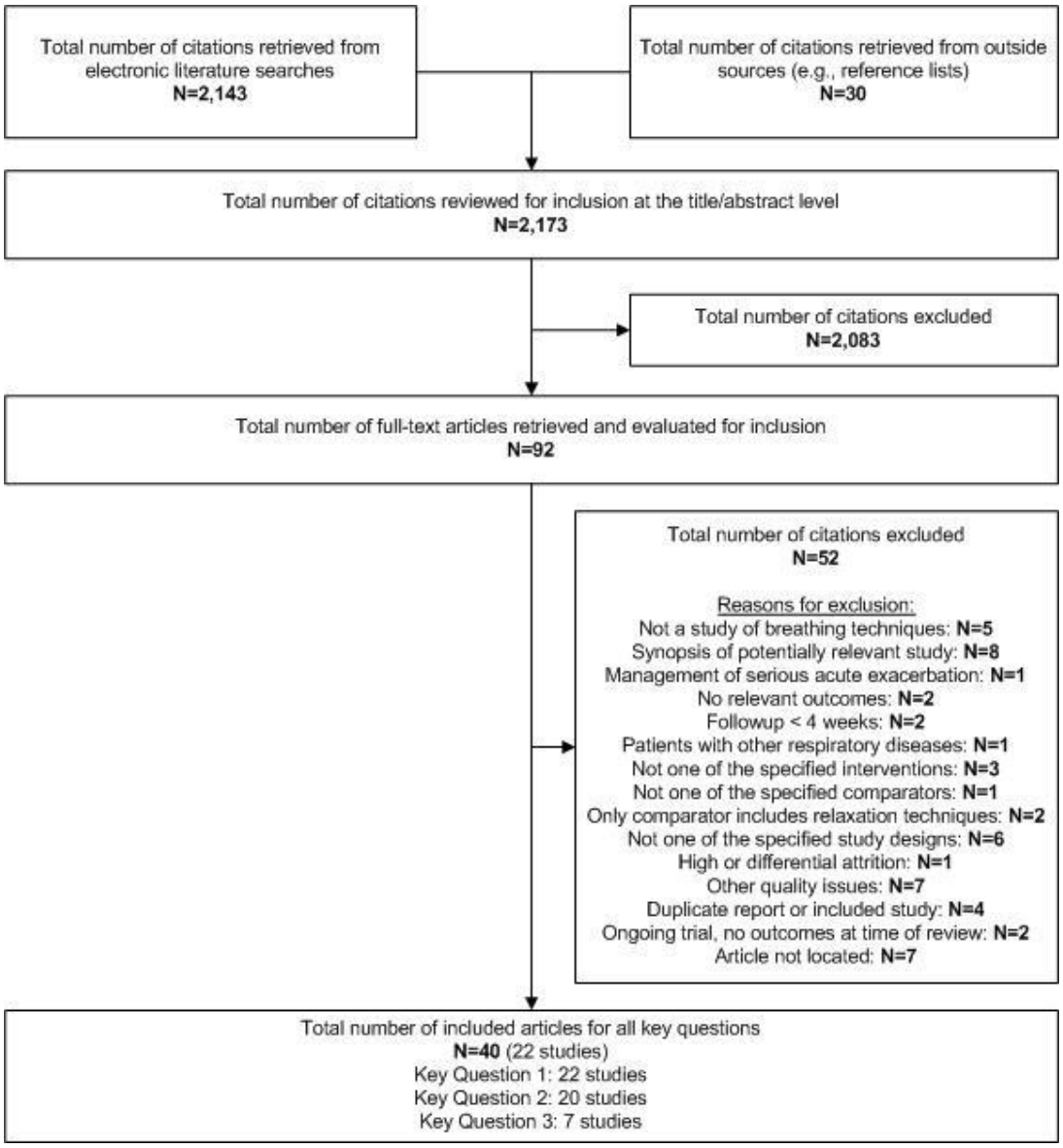
To assess applicability, we used data abstracted on the population studied, the intervention and comparator, the outcomes measured, settings (including cultural context), and timing of assessments to identify specific issues that may limit the applicability of individual studies or the body of evidence to US health care settings, as recommended in the *Methods Guide*.[32] We used these data to evaluate applicability, paying special attention to study eligibility criteria, recruitment strategies, baseline demographic features (e.g., age, smoking status, and comorbid conditions) and the intervention characteristics (whether there were multiple interventionists, level/degree of training among interventionists, whether there was a clearly defined protocol).

Results

Literature Search

Our literature search yielded 2,173 citations. From these, we provisionally accepted 92 articles for review based on abstracts and titles (Figure 2). After screening their full texts, 22 studies,[33-54] published in 40 articles,[33-72] were judged to have met the inclusion criteria (Appendix C). All of these studies were RCTs except one, which was a randomized crossover trial.[34] The remaining 52 full-text articles were excluded (Appendix D). The primary reasons for exclusion included not studying breathing techniques, not providing primary data, not having a specified study design, and being rated as poor quality.

Figure 2. Literature flow diagram



All trials were conducted in people with symptomatic asthma. Most were limited to those with stable asthma (e.g., stable dose of asthma medication, no recent use of oral steroids, and/or no recent hospitalization for asthma). Some trials were limited to people with a certain level of beta-agonist use (e.g., twice daily,[33,52] twelve times per week,[39] four times per week,[34,41] or twice weekly[35]), suggesting their asthma was not well controlled. Most trials confirmed reversibility of respiratory symptoms through pulmonary function testing. Trials primarily included adults; only one trial of IMT targeted children (ages 8 to 12),[48] and only four other trials included people younger than 16.[33,36,39,41] Trials used a wide variety of breathing retraining techniques, including interventions that targeted hyperventilation/CO_2 regulation (e.g., Buteyko breathing technique, Papworth method),[33-42] yoga breathing techniques,[43-47] IMT,[48-52] and other controlled breathing approaches using prolonged exhalation or abdominal breathing.[35,53,54] Four of the trials of hyperventilation reduction used alternate breathing techniques for comparison[33,35,36,41] and seven used some kind of usual care, placebo, wait list, or attention control group.[34,35,37-40,42] One trial had more than two study arms, and therefore different treatments. Comparisons from this study will be discussed in different sections of this report.[35]

Thirty-two percent of the trials described allocation as concealed. Asthma symptoms, medication use, and quality of life were almost always based on self-report, and only 41 percent of the trials reported that outcomes assessments were conducted blindly. Lack of blinding may be especially problematic for pulmonary function testing, which is effort-dependent and involves coaching to get an optimal performance. Lack of blinding may also be problematic for self-reported outcomes, where social desirability could introduce bias. Most trials were small, with 68 percent including only 30 or fewer participants per treatment arm. Only a single trial included more than 100 participants per treatment arm.[39] Trials were also inconsistent the degree to which they ensured the sample was limited to asthmatics: 42 percent did not report the use of pulmonary function testing to confirm and asthma diagnosis and 39 percent did not describe limiting excluding participants with other respiratory disorders or people at high risk for other respiratory disorders (e.g., smokers).

Results of Included Studies

We discuss results for the five different types of comparisons separately: hyperventilation reduction breathing techniques compared with control groups (Table 4); yoga breathing compared with control groups (Table 5); IMT compared with control groups (Table 6); other nonhyperventilation reduction breathing techniques compared with control groups (Table 7); and hyperventilation reduction compared with nonhyperventilation reduction breathing techniques (Table 8). Table 9 briefly describes the instruments, including directionality, to aid in the interpretation of standardized scales.

Key Question 1. In adults and children 5 years of age and older with asthma, does the use of breathing exercises and/or retraining techniques improve health outcomes, including: symptoms (e.g., cough, wheezing, dyspnea); health-related quality of life (general and/or asthma-specific); acute asthma exacerbations; reduced use of quick-relief medications or reduced use of long-term control medications, when compared with usual care and/or other breathing techniques alone or in combination with other intervention strategies?

Hyperventilation Reduction Breathing Techniques vs. Control Group

Seven trials (n=1,055) compared breathing retraining targeting hyperventilation reduction with a control group. Six of there were RCTs[35,37-40,42] and one was a randomized crossover trial[34] (Table 4; Appendix C, Evidence Table 1a). The 4-week cross-over trial focused only on one component of the Buteyko breathing technique, specifically mouth-taping,[34] while the remaining provided broader instruction in modification of breathing (Appendix C, Evidence Table 1b). In interventions generally involved controlled, shallow breathing, and encouraging diaphragmatic breathing over chest breathing, with a breath-hold at the end of the exhalation. They advocated breathing through the nose at all times, and in some trials those who had difficulty breathing nasally at night were encouraged to use a porous tape to hold the mouth closed. They trained users to limit what they term "overbreathing" with sighs, yawns, and gasps. They encourage clients to use breathing techniques when they experience asthma symptoms for 5-10 minutes before using bronchodilators. The breathing techniques require repeated practice and technique improves over time with practice. Four of these six trials were fairly extensive interventions, reporting 6 to 12 months of followup.[35,37-39] These trials provided 5 to 13 hours of contact with instructors, encouraged daily practice at home, and two of these included additional lifestyle components beyond breathing retraining, of dietary advice[35] and stress management.[35,38] Only one of these four trials included a control group with matching treatment intensity,[39] the others compared hyperventilation reduction breathing training to usual care,[37,38] or a sham breathing training device.[35]

The two lower-intensity interventions targeted breathing retraining only (i.e., included no co-interventions that were not directly targeting breathing retraining). One trial used a video for both instruction and daily practice, and the other offered approximately two hours of direct instruction. Interventionists in both of these trials encouraged daily practice at home. Both trials reported only 4-week outcomes for all or most outcomes,[40,42] although one also assessed some outcomes at 26-weeks.[42] Both trials attempted to provide attention-control comparators, one with relaxing landscape videos[40] and the other with general asthma education.[42]

Among all of the hyperventilation reduction trials, three used the Buteyko method,[35,39,40] one addressed only a single, narrow aspect of the Buteyko method (mouth-taping),[34] two used the Papworth Method,[38,42] which incorporates many Buteyko methods, and one did not identify its methods as being either Buteyko or Papworth, but the description of the intervention was consistent with Buteyko and Papworth breathing approaches.[37]

All trials were rated as fair quality (Table 10). Two of the trials suffered from fairly high attrition[35,42] and three had greater attrition in the intervention group by at least ten percentage

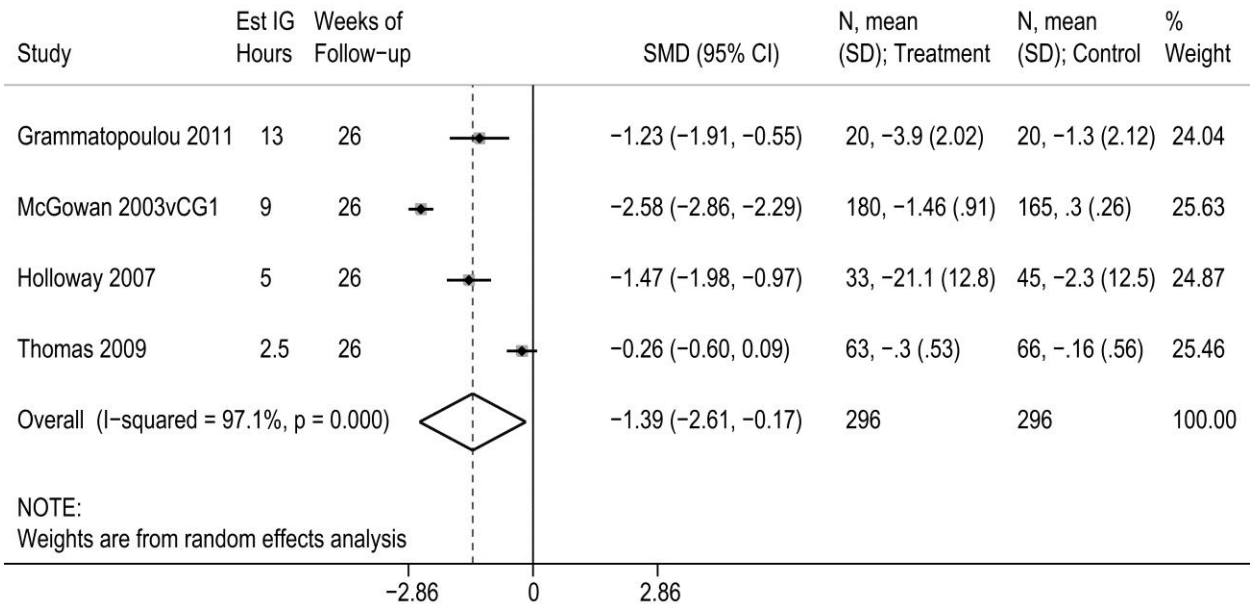
points at one or more followups.[35,38,42] Allocation concealment was reported in only three trials,[37,39,42] and outcomes assessment was only clearly blinded in four of the trials.[34,35,37,39] Only two of the RCTs randomized more than 50 participants per group,[39,42] and, as described above, the three most narrowly-focused trials had only 1-month of followup for all or most outcomes.[34,40,42]

Five of these trials were conducted in the United Kingdom (UK),[34,35,38,39,42] one in was conducted in Greece,[37] and one was conducted in Australia.[40] All trials were conducted in health care settings. The minimum ages of included participants ranged from 14 to 18 years, and most trials included adults up to ages 60 to 72 years. The average baseline reliever used in most trials was one to two puffs per day, generally along with 400 to 600 mcg of ICS use daily (in beclomethasone equivalent), and FEV_1 between 80 percent and 89 percent. The Australian trial had somewhat higher reliever medication use than the other four, with an average of 404 mcg per day at baseline (along with an average 430 mcg of ICS daily).[40]

Asthma Symptoms

All seven trials reported some type of global asthma symptom outcome, which was usually a standardized questionnaire (Table 4; Appendix C, Evidence Table 1c). All four of the most-intensive and comprehensive interventions reported improvements in asthma symptoms at 6- to 12- months of followup.[35,37-39] Only four of the trials provided sufficient information to pool in a meta-analysis of asthma symptom scores, three of the four most intensive trials,[37-39] and one lower-intensity trial comparing 2 to 2.5 hours of Buteyko training with 2 to 2.5 hours of asthma education.[42] The standardized pooled effect size (or standardized mean difference [SMD]) for the four trials with sufficient data to be included in a meta-analysis was -1.39 (95% CI, -2.61 to -0.17), with very high heterogeneity (I^2=97.1, Figure 3).[37-39,42]

Figure 3. Effect of hyperventilation reduction techniques on asthma symptoms at 6 to 12 months



Abbreviations: CI: confidence interval; CG: control group; est: estimated; IG: intervention group; N: sample size; SD: standard deviation; SMD: standardized mean difference

The largest trial showed the largest effect, with SMD of -2.58 (95% CI, -2.86 to -2.29). Symptom ratings on a scale of 0 to 3 dropped from an average of 2.2 at baseline for all groups to 0.7 in the Buteyko group, while the control groups slightly increased to 2.4 to 2.5.[39] This was one of the relatively few trials reporting both allocation concealment and blinding of outcome assessors, although retention was somewhat lower in both control groups (82.5% and 73%) than the Buteyko group (90%).

Two other trials, both with fairly intensive interventions, reported standardized effect sizes greater than 1.2, which would generally be considered large.[37,38] In the trial by Holloway and colleagues, for example, the Papworth intervention group participants showed 18- to 21-point improvements on the 100-point St. George's Respiratory Questionnaire (SGRQ) symptom subscale, compared with two-point improvements in the control group at 6 and 12 month followup.[38] This change is even greater than the change on the SGRQ seen in patients whose treatment was judged to be "very effective" in other research.[73] Outcomes assessment was not blinded in this trial, which may have artificially increased the effect size if intervention participants were more prone to demand characteristics. On the other hand, this trial relied on an asthma registry to recruit patients and did not independently verify the asthma diagnosis with pulmonary function testing. As such, if some of the patients were misdiagnosed and actually had chronic obstructive pulmonary disease or another respiratory condition, then this would likely attenuate the intervention's effect. The asthma registry approach likely increases the applicability to typical clinical settings.

Similarly, the trial conducted in Greece by Grammatopoulou and colleagues[37] showed intervention participants moving from a score consistent with uncontrolled asthma to one in a range similar to those with completely controlled asthma at 26-week followup.[74,75] The average control group score, on the other hand, remained below the average score of someone with well-controlled asthma.

The other fairly intensive trial, which was not included in the meta-analysis, reported mixed results, finding differences in symptom scores from daily diaries, but no group differences in a standardized symptom scale.[35] This was a fairly small trial (n=30 per group) with fairly low followup at 6 months (77% retention in the intervention group vs. 80% in the control group), using a last-observation-carried-forward (LOCF) data substitution method.

The remaining trials, which were all fairly low intensity, did not find improvements in asthma symptoms after 1 to 6 months.[34,40,42] Other than the mouth-taping cross-over trial, these trials showed effect sizes consistent with small beneficial effects, but group differences were not statistically significant.

Medication Use

Medication use was reduced in three[35,39,40] of the five trials reporting this outcome (Table 4; Appendix C, Evidence Table 1d).[34,35,39,40,42] However, this outcome was reported in only two of the four higher-intensity trials.[35,39] In the largest trial, reliever medication use dropped from 18 puffs per week at baseline in all groups to less than one puff per week in the intervention group, compared with no change in either of the control groups at 6-month followup.[39] Although specific data were not shown, this trial also reported greater reductions in the use of controller medication. Although the data were self-reported, and may be subject to demand characteristics

(since Buteyko participants were encouraged to delay bronchodilators), they were gathered by blind outcome assessors.

Reliever medication use was reduced at 6-month followup in the trial by Cooper and colleagues comparing a Buteyko intervention with a sham breathing retraining device.[35] SABA use was reduced by a median of two puffs per day in the intervention group, compared to no change in the control group. Neither ICS use nor prednisone use differed at 6-month followup in this trial. After 6-month followup, 60 of the 69 participants completing the first phase of the trial took part in a steroid-reduction phase. Intervention participants in this phase reduced ICS use by a median of 41 percent, compared with no reduction in the control group. However, this difference was not tested directly; instead, the authors report only the results of the three-way comparison between the Buteyko group and another treatment arm (a device to control the pace of breathing), which was not statistically significant (p=0.70). This is the trial with fairly low and differential retention that used last observation carried forward as a data substitution method. Medication use was not reported in the two other higher-intensity trials that showed large positive effects on asthma symptoms.[37,38]

Medication outcomes were reported in the mouth-taping trial[34] and the other two lower-intensity trials.[40,42] Reductions in bronchodilator use in the trial of video-based instruction[40] were similar to those seen in the trial by Cooper and colleagues.[35] This was a small trial (n=36) with only 4 weeks of followup, but did have very high retention (89% in each group). This trial reported no group differences in ICS use. No group differences in medication use were seen in the mouth-taping trial[34] or the lower-intensity Papworth method intervention.[42]

Quality of Life and Functioning

Six of the trials[34,35,37,38,40,42] reported measures of asthma-related quality of life, functioning, or mental health symptomatology at 1 to 12 months post-baseline, and all but the one study[34] (which focused only on mouth-taping) reported group differences in some measures (Appendix C, Evidence Table 1e).

Asthma-related Quality of Life.

Four trials[34,35,40,42] reported asthma-specific quality of life using standardized measures, including only one of the higher-intensity trials (Table 4; Appendix C, Evidence Table 1e).[35] Two reported statistically significant group differences at one or more time points, up to 6 months post-baseline, the video-based treatment trial and the lower-intensity Papworth trial.[40,42]

Functioning and Mental Health.

Changes in SF-36 scores were reported in two trials, and although many SF-36 subscale outcomes were reported in these two trials, group differences were rarely seen (Appendix C, Evidence Table 1e).[35,37] Two trials, including one by Holloway and colleagues with a large effect on asthma symptoms,[38] reported improvements in mental health outcomes of depression and anxiety at 26 weeks.[38,42] Anxiety and depression scales scores indicated that participants were not, on average, anxious or depressed either before or after treatment. Reductions were small in magnitude (e.g., group differences of 1.6 on a 68-point rating scale). Group differences were maintained in one of these trials to 1 year.[38]

Yoga Breathing vs. Control

Five trials (n=360) compared yoga with a control group (Table 5; Appendix C, Evidence Table 2a).[43-47] All were fairly to highly intensive interventions and all required daily practice at home in addition to supervised sessions (Appendix C, Evidence Table 2b). Two programs conducted in India were very intensive.[43,47] One included 4-hour sessions daily for 2 weeks covering yoga practice, lectures, group discussions, diet (including a study-provided breakfast), and stress management, followed by an additional 4 weeks of home practice.[47] Another trial involved a 70-minute-long daily yoga session for 6 months and all patient were hospitalized initially to facilitate training.[43] The duration of the inpatient stay was not specified. This trial was limited to male vegetarians aged 25 to 50 years.

A third trial in India was focused specifically on yoga breathing exercises among people with at least 6 months of prior yoga experience, compared with the use of meditation.[46] Both treatment arms involved 20 minutes of practice twice daily for 12 weeks, although the number of these sessions that were supervised versus those conducted at home was not described. In this study, the authors reported that participants "had no history of regular medication and they were advised to discontinue if on any medication." It was unclear if this is referring to all medication, or only asthma medication. No age limits were reported and the average age in this trial was 29 years.

The final two trials were conducted in the US.[44,45] One compared an eight-session yoga class with a stretching class.[45] This trial was limited to participants aged 18 and over, with an average age of 51 years. The other trial involved a comprehensive naturopathic treatment program that included yoga as well as dietary restriction, nutritional supplements, and a guided journaling session.[44] Participants in this trial were predominantly female and the average age was 44 years.

All trials were rated fair quality and three had substantial quality issues that limit our confidence in results (Table 11).[43,44,46] Two of these trials were quite intensive and conducted in India.[43,46] These trials included only 17 to 25 people per group, failed to report both allocation concealment and blinding of outcomes assessment, and provided no information on refusals or exclusions prior to randomization. In addition, one did not indicate how they divided the participants into groups and failed to report the use of pulmonary-function testing to confirm reversibility for asthma diagnosis.[43] Also, the usual-care group in this trial received only bronchodilators, antibiotics, and expectorants, but not ICS. The other trial did not report the proportion of participants with followup, and it was unclear if their group assignment was truly random.[46] The third trial was conducted in the US and involved a comprehensive naturopathic intervention, which did not allow us to determine the effect of yoga breathing techniques specifically.[44] Outcomes assessment in this trial was not blind, and it was unclear whether those assigning participants to groups had access to intake assessment data. This trial also did not report the use of pulmonary function testing in the diagnosis of asthma, number or refusals or exclusions prior to randomization, nor did they describe whether they excluded people with other respiratory disorders or recent use of oral steroids from their sample.

The Indian trial of daily 4-hour sessions also failed to report both allocation concealment and blinding of outcomes assessment, but had retention above 90 percent in both groups and good assessment procedures.[47] The US-based yoga class trial had the best methods of the group, but had low and somewhat differential retention (79% in the intervention group vs. 67% in the control group).[45]

Asthma severity was not consistently described in this subgroup of studies, but average severity would likely be considered to be moderate according to National Asthma Education and Prevention Program (NAEPP) as based on either daily reliever use[45] or FEV_1 in the "moderate asthma" range.

Asthma Symptoms

All but one trial[45] showed greater improvement in the yoga groups on at least one measure of asthma symptoms, including all three trials conducted in India (Table 5; Appendix C, Evidence Table 2c).[43,44,46,47] The US-based trial of an eight-session yoga class reported no group differences in asthma symptoms.[45] Although it was difficult to compare effect sizes across different measures, the largest effect size appeared to be found in one of the lower quality trials based in India, comparing yoga breathing exercises with meditation.[46] This trial reported a 64 percent reduction in symptoms in the intervention group at 12 weeks, compared with a six percent reduction in symptoms in the meditation group.

Another trial with a very intensive intervention reported a very large effect size at 2- and 4-week followup, but the effect was attenuated (yet still statistically significant) after 8 weeks.[47] In this trial and the US-based trial of a comprehensive naturopathic intervention,[44] both groups showed improvements in a Juniper symptom subscale well beyond the level of clinical significance (i.e., improvement of 0.5 points).[73] Greater improvements were apparent, however, in those participating in the yoga interventions than those in the control groups.

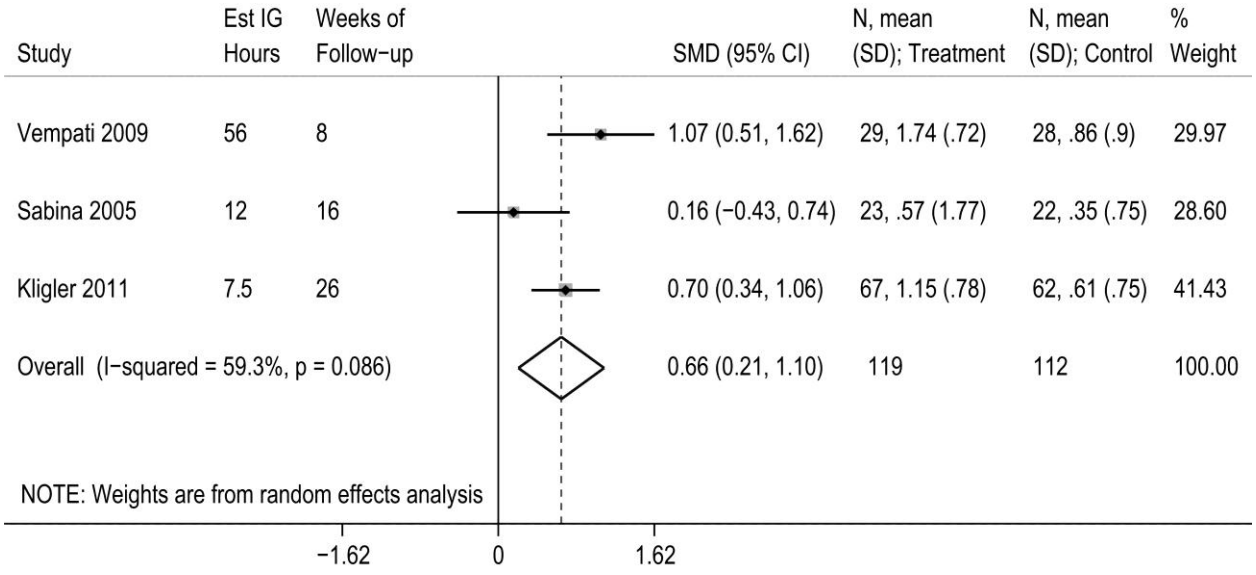
Medication Use

Three trials reported medication use,[43,45,47] including two trials conducted in India (Table 5; Appendix C, Evidence Table 2d).[43,47] One trial found that 53 percent of yoga participants reduced medication required to control their dyspnea, compared with 18 percent in the control group after 26 weeks, but the specific type of medication was not reported.[43] In the trial of daily 4-hour yoga sessions, as with asthma symptoms, both groups showed improvement in medication use: yoga participants reduced rescue medication use by an average of 1.5 puffs per day after 8 weeks compared with a reduction of 0.5 puffs per day among control participants.[47] There were no statistically significant group differences between those taking the yoga class and those on the waiting list after 16 weeks.[45]

Quality of Life and Functioning

Three of the trials reported functioning or quality of life outcomes (Appendix C, Evidence Table 2e).[44,45,47] The pooled standardized effect size for overall asthma-related quality of life in these three trials was 0.66 (95% CI, 0.21 to 1.10, I^2=59.3%, Figure 4), consistent with improved asthma-related quality of life in yoga breathing groups compared to controls.

Figure 4. Effect of yoga breathing techniques on quality of life at 2 to 6 months



Abbreviations: CI: confidence interval; est: estimated; IG: intervention group; N: sample size; SD: standard deviation; SMD: standardized mean difference

The eight-session yoga class did not lead to greater improvement in overall asthma-related quality of life than being on a waiting list after 16 weeks.[45] Participants in both the comprehensive naturopathic intervention[44] and the daily 4-hour sessions[47] showed greater improvement overall asthma-related quality of life (again exceeding the threshold for clinically significant improvement) as well as the "activities" and "emotions" subscales than the usual care groups after 8[47]and 26 weeks.[44] As before, however, the usual-care participants also showed clinically and statistically significant improvement in both of these trials. There were also group differences on the SF-36 subscales of physical and social functioning, role limitations due to physical limits, and both of the summary component scores (physical and mental) in the trial involving a comprehensive naturopathic treatment program.[44]

Inspiratory Muscle Training vs. Control

Five small trials (n=169) examined the effect of IMT on asthma (Table 6; Appendix C, Evidence Tables 3a and 3b) after 8 to 26 weeks.[48-52] Three of these trials, all conducted by the same researcher in Israel, compared the use of a training device that controlled the level of resistance associated with inhalation with a sham device that provided no resistance.[50-52] Level of resistance was gradually increased over the course of training with the active device, but the sham device provided no resistance at any setting. Participants' average age ranged from 34 to 40 years, and no age limitations were listed for any of these trials. One trial was limited to women categorized as being in the mild-persistent to moderate range of asthma. Participants used an average of 3.2 puffs per day of reliever medication and had a baseline FEV_1 of 83 percent.[51] The second trial was limited to those using two or more puffs of SABA daily, with an average use of 2.7 puffs of reliever per day and a baseline FEV_1 of 91 percent.[52] The third trial

was limited to people with severe asthma. Participants in this trial used an average of six puffs of reliever medication per day and had an average baseline FEV_1 of 59 percent, the lowest of all included trials.[50]

The fourth trial was conducted among children in Brazil who had previously received no treatment for asthma and whose asthma was poorly controlled.[48] Baseline FEV_1 was not reported in this trial. The trial compared a 14-session program that included one-on-one instruction as well as IMT with the use of a breathing training device that built up inspiratory muscles through gradually increasing the resistance required for inspiration, plus medication (rescue and preventive) and three monthly medical visits for medication monitoring and general asthma education. This was compared with asthma education and medication alone.

The final trial was conducted in South Africa among inactive nonsmokers with moderate-persistent asthma and an average age of 22 years.[49] This trial instructed participants in diaphragmatic breathing. Participants were told hold a weight on their abdomen while breathing through a 1 centimeter wide tube. Control group participants received no breathing training.

All trials were rated fair quality, and all but one[50] had fairly substantial quality issues (Table 12).[48,49,51,52] The trials conducted in Israel included 15 or fewer participants per treatment group in all cases,[50-52] although followup rates where high in two of the three trials.[50,52] None of these trials reported whether allocation was concealed or whether they excluded participants with other respiratory disorders. None of these trials provided detailed inclusion/exclusion criteria and two them also failed to report information on baseline comparability of the treatment groups.[51,52]

The trials in South Africa[49] and Brazil[48] were also fairly small including 22 to 25 participants per treatment arm with 100 percent followup. Neither trial, however, reported allocation concealment or blinding of outcomes assessment. In addition, the Brazilian trial did not appear to use pulmonary testing to confirm asthma diagnosis, provided little detail on their outcomes assessment methods, and they did not report whether IMT trainers were in contact with the larger asthma treatment team (and perhaps providing advice or support for general asthma management and medication use such as encouraging patients to use controllers consistently) as part of the fourteen IMT-focused sessions.[48] In addition, children receiving only asthma education and medication showed little improvement, which suggests these treatments were suboptimal. The South African trial did report the use of pulmonary testing to confirm asthma diagnosis, but provided no description of refusals and exclusions prior to randomization.[49] They also reported no information on changes in asthma symptoms, medication use, or quality of life, but only reported pulmonary function outcomes.

Asthma Symptoms

Only two of the trials reported asthma symptoms at followup (Table 6; Appendix C, Evidence Table 3c).[48,50] The Brazilian trial reported that all of the children in the control group regularly experienced daytime symptoms after 3 months, compared with none of the children receiving IMT.[48] Similarly, 22 of the 25 control group children experienced frequent asthma attacks, compared with only two of the 25 IMT participants.[48] Large group differences were also found for nighttime symptoms. The fact that the children receiving only medication management and asthma education were still experienced high levels of asthma symptoms suggests that their treatment may not have been as effective as they would have been in the US.

The Israeli trial with the fewest quality concerns reported greater improvement in morning chest tightness, cough, daytime asthma symptoms, and nighttime asthma symptoms

after 6 months in IMT participants as recorded in daily diaries, compared with those using a sham device.[50]

Medication Use

Only four trials reported some kind of group difference in change in bronchodilator use (Table 6; Appendix C, Evidence Table 3d).[48,50-52] As with asthma symptoms, medication effects were large in the Brazilian trial: at 3-month followup 16 percent of the children in the IMT group were using bronchodilators compared with 84 percent of the control group children.[48] They did not report on controller medication use, which is unfortunate since the children in both groups were previously untreated, initiating both rescue and controller medication in this trial, and we cannot tell if the level of recommended controller medication use was comparable between groups.

All three Israeli trials reported statistically significant reduction in beta-agonist use at final followup in those using the active training device, but no such change in those who used the sham device after 13 to 26 weeks.[50-52] Groups were not statistically compared directly with each other in two cases,[51,52] however, and in one of these that provided sufficient data to calculate a standardized effect size, the effect was not statistically different from zero.[52]

Quality of Life

Two trials reported functioning outcomes (Appendix C, Evidence Table 3e).[48,50] The Brazilian trial reported that none of the children undergoing IMT had difficulty with activities of daily living at 3-months followup, but all of the control children did.[48] One of the Israeli trials reported an average decline of 1.7 days of missed work in the prior three months, compared with almost no change in the control group participants.[50]

Other Nonhyperventilation Reduction Breathing Techniques vs. Control

Three heterogeneous trials (n=186) compared a nonhyperventilation reduction breathing technique with a control group (Table 7; Appendix C, Evidence Tables 4a and 4b).[35,53,54] One trial conducted in the UK was limited to people with dysfunctional breathing, according to the Nijmegen questionnaire.[54] This instrument was designed to identify patients with chronic or habitual breathing patterns that induce hyperventilation, and assesses symptoms purported to identify hyperventilation (some of which may also be related to asthma symptoms) such as accelerated or deepened breathing, being unable to breath deeply, palpitations, tightness around the mouth, tingling fingers, and dizzy spells. The intervention consisted of "established physiotherapy methods" including a focus on slow diaphragmatic breathing in one 45-minute group session and two one-on-one 15-minute followup sessions. This was compared with general asthma education plus the opportunity to have a one-on-one asthma review.[54] At baseline, participants used an average of 1.5 canisters of reliever medication per three months and an average daily dose of 600 mcg per day of an ICS.

The second trial, conducted in the US with paid volunteers, examined the use of biofeedback for breathing retraining.[53] The intervention group engaged in biofeedback targeting respiratory resistance, respiratory reactance, and heart rate variability (HRV) as well as training in pursed-lip abdominal breathing with prolonged exhalation. This trial had three different control groups: biofeedback targeting only HRV, placebo biofeedback involving bogus "subliminal suggestions designed to help asthma," and waiting list. The first three groups

involved weekly biofeedback sessions for 10 weeks, plus the request to practice at home 20 minutes twice daily with a home-training unit. The trial did not report baseline medication use or FEV_1 values, but reported that participant's asthma was most commonly rated as being in the moderate persistent range based on medication level according to National Health, Lung and Blood Institute (NHLBI) criteria.[1]

The final trial compared the use of a device to modify breathing to achieve an inspiration-to-expiration cycle of 1:2 with a sham device that did not modify breathing.[35] Participants were expected to practice using the device at home twice a day for six months. The average age of participants for this trial was 44 years, and was limited to participants aged 18 to 70 years.

All three trials were rated as fair quality (Table 13).[35,53,54] The trial limited to those with dysfunctional breathing did not report allocation concealment or blinding of outcomes assessment, and did not report whether they excluded people from the trial who had other respiratory disorders.[54] In addition, the control group had substantially lower retention than the intervention group (75% vs. 94%), and they did not report using any data substitution methods or quantitative assessment of the impact of the higher attrition in the control group. The main concerns of the biofeedback trial included lack of information on allocation concealment, higher retention in the wait list group than all other groups (92% vs. 74% to 79%), and fairly small sample size (22 to 25 per group), although they did report blinded outcomes assessment.[53] The third trial had fairly low and somewhat differential retention (73% in the intervention group vs. 83% in the control group), conducted many statistical comparisons for the relatively small sample, and did not clearly describe whether baseline differences were controlled for, but did report blinded outcomes assessment[35] All three trials reported pulmonary function testing to confirm asthma diagnosis.

In the trial of diaphragmatic breathing people with dysfunctional breathing, asthma symptoms showed greater improvement in the intervention than the control group at 4-week followup, but the difference attenuated slightly and was no longer statistically significant at 26 weeks (Appendix C, Evidence Table 4c).[54] Intervention participants showed a median increase of 0.42 points at four weeks and 0.33 at 26 weeks on the Juniper Asthma Quality of Life Questionnaire symptoms subscale, which are short of the 0.5-point change signifying likely clinically significant improvement.[73]

There were no differences between groups at 26 weeks in the number of canisters used of either bronchodilators or ICS (Appendix C, Evidence Table 4d). However, the number of canisters is a very gross measure of medication use, and baseline median canister use was only zero to two canisters and had a highly skewed distribution. Thus, the quality of the evidence on medication use is very weak. Asthma-related quality of life improved by a median of 0.60 points in the intervention group at 4 weeks, compared with little change in the control group (0.09 points)(Appendix C, Evidence Table 4e). This difference was statistically significant as well as exceeding the criteria for clinical significant change.[73] Improvements were even greater at 26 weeks, but the effect was no longer statistically significant. This is likely due to the fact that attrition of three participants reduced power in this small study of 33 participants.

The comparison between the active biofeedback groups targeting breathing in addition to HRV vs. HRV-only tests the unique contribution of breathing retraining.[53] No differences were found between these groups on either asthma symptoms or controller medication use at 12 weeks. Both of these two groups, however, did show greater reductions in number of asthma exacerbations and controller medication use than the placebo and waitlist groups, suggesting

biofeedback targeting HRV may have contributed to improvement in asthma. This trial did not examine quality or life or functioning.[53]

No differences on asthma symptoms, medication use or quality of life were noted at 6-month followup in the trial comparing the device to train prolonged exhalation with a placebo device.[35]

Hyperventilation Reduction Breathing Techniques vs. Other Breathing Techniques

Four RCTs (n=285) directly compared the use of breathing techniques targeting hyperventilation reduction with another breathing technique that did not target hyperventilation reduction. Three of these trials used the Buteyko approach[33,35,36] and one was modeled after the Papworth technique (Table 8; Appendix C, Evidence Tables 5a and 5b).[41] One of these involved a 10-hour Buteyko intervention and was described above, compared to the use of a device to modify breathing to achieve a typical yoga inspiration-to-expiration cycle of 1:2 with minimal one-on-one instruction and no components addressed other than the breathing technique.[35]

The remaining trials employed comparators targeting controlled or paced breathing, but did not encourage to use of slow, nasal, shallow breathing with breath-holding or other techniques focused on reducing hyperventilation.[33,36,41] All of these trials involved at least five contacts, usually face-to-face. The two trials that provided multiple face-to-face contacts used an approach that was initially intensive, meeting every day for 5 to 7 days for training.[33,36] All three trials attempted to provide the same frequency and hours of treatment in both treatment groups. However, in one trial more than half of the Buteyko participants received additional instruction sessions and the average number of followup phone calls was seven in the Buteyko group, compared to one in the comparison group.[33]

In addition to breathing retraining in the nonhyperventilation reduction groups, one trial also included general asthma education and relaxation techniques,[33] and another included shoulder and upper arm stretches.[41]

All four trials were rated as fair quality (Table 14). One trial had a number of quality-related issues, despite having followup on 95 percent of participants, including only a small number of participants randomized (n=20 or fewer per group), a very wide age range (age 12 to 70), no information on blinding of outcomes assessment, and reliance on self-report of variability in breathing symptoms that improve with beta-agonist use for asthma diagnosis.[33] Additionally, the Buteyko intervention was more intensive than the comparator.

Another trial reported good procedures, but was rated as “fair” quality because of the small number of participants (n=57 total) and retention below 90 percent.[41] The remaining two failed to report either allocation concealment or blinding of outcomes assessment, and had either fairly high attrition overall[35] or higher attrition in the Buteyko breathing technique group than the other intervention group,[36] in addition to other minor issues.

These trials were conducted in Australia,[33,41] the UK,[35] and Canada.[36] Average age ranged from 44 to 47, and all but one had a wide age range from 12 to 18 years up to 65 or older. Asthma severity was quite high in one trial, where participants were using an average of almost 900 mcg of reliever medication per day and 1,250 mcg of ICS (in beclomethasone equivalents).[33] Baseline FEV_1 was 74 percent in this trial. Participants in the remaining trials were using two to three puffs of reliever medication per day along with 650 to 850 mcg of ICS, with an average FEV_1 around 80 percent.[35,36,41]

Asthma Symptoms

Two trials reported no group differences in asthma control, with little improvement in either group at 13 and 26 weeks (Table 8; Appendix C, Evidence Table 5c).[33,36] Two reported no or minimal group differences but did report improvement in both treatment groups for either the asthma control questionnaire and physician global rating at 28 weeks[41] or median change in the symptoms subscale of the Mini-Asthma Quality of Life Questionnaire at 26 weeks.[35] Within-group change in the latter was not tested statistically, but both groups showed a median improvement of more than 0.5, which is considered a clinically significant differences.[76] The best quality trial in this group showed almost no group differences on five additional symptom scales; both groups improved on two of the two additional symptom scales.[41]

Medication Use

Two[33,35] of the three[33,35,41] trials reporting reliever medication use found greater reductions with Buteyko breathing technique than either abdominal breathing[33] or a device to train in the use of prolonged exhalation after 13 to 26 weeks (Table 8; Appendix C, Evidence Table 5d).[35] The trial with the greatest baseline asthma severity (and the most quality concerns, including more intensive intervention contacts in the hyperventilation reduction group than the comparison breathing intervention) showed the greatest improvements in reliever use, reporting median reductions of 904 mcg per day in bronchodilator use at 3-month followup in the hyperventilation-prevention group, compared with a 57 mcg reduction in the control group.[33] The hyperventilation group went from using approximately nine to 10 puffs of beta-agonist per day to approximately one puff every other day. The remaining trial reported reductions in reliever medication by almost two puffs per day in both the hyperventilation-reduction group and the controlled breathing with stretching group.[41]

All four trials reported results for controller medication. Two trials reported little change in ICS use for either group,[33,35] including the trial with the most dramatic results for beta-agonists.[33] Of the remaining trials, one reported that use was reduced by 50 percent in both the Buteyko and the controlled breathing groups,[41] and other trial reported greater reductions in ICS use and a greater likelihood of discontinuing long-acting beta-agonists with hyperventilation reduction techniques than with a more typical physiotherapeutic approach.[36] In this trial, ICS use was reduced by an average of 317 mcg in the hyperventilation-prevention group and only 56 mcg in the physiotherapy group. Two trials reported no differences between groups in prednisone use.[33,35]

Quality of Life

All four trials reported an asthma-specific quality of life outcome, and none found that any group showed greater improvement (Appendix C, Evidence Table 5e). Although the statistical significance of within-group change was not reported, both groups showed increases of more than 0.5 on the Juniper-Asthma Quality of Life Questionnaire in two trials,[35,36] which is the threshold for clinically significant change.[73]

One trial reported functioning outcomes and found that scores on the subscale role limitation due to physical problems improved by a median of 25 points on a 100-point scale at 3 months in the hyperventilation-prevention group, while the median change in the device-assisted yoga-style breathing was zero.[35] Other functioning subscales showed little improvement in either group.

Key Question 1a. Does the efficacy and/or effectiveness of breathing techniques for asthma health outcomes differ between different subgroups (e.g., adults/children; males/females; different races or ethnicities; smokers/nonsmokers; various types and severities of asthma; and/or different coexisting conditions)?

The trials were heterogeneous on too many factors and reporting was too inconsistent to allow us to asses the impact of population characteristics such as demographic characteristics or baseline asthma severity on effect size across studies. However, two trials did report results of subgroup analyses examining differential effects of treatment by different characteristics.[34,42] It was unclear if these analyses were planned *a priori*, but they do target subgroups hypothesized to gain the greatest benefit from the specific interventions of their trials, based on the physiologic models of action for their interventions. Neither trial reported conducting tests for interactions before exploring subgroup analyses. The UK trial that compared a relatively low-intensity Papworth-style intervention with an asthma education comparator of comparable intensity found that results were consistent between those who scored in the "disordered breathing" range on the Nijmegen questionnaire and those who did not.[42] Similarly, the trial of nighttime mouth-taping did not find larger effect among the subgroup of people who were rated as being "mouth breathers" at baseline.[34]

Key Question 1b. Does the efficacy and/or effectiveness of breathing techniques for asthma health outcomes differ according to variations in implementation (e.g., trainer experience) and/or nonbreathing components of the intervention (e.g., anxiety management)?

Interventions that included co-interventions in addition to breathing retraining[35,38,44,47] (e.g., dietary advice, relaxation training) were likely to show a benefit, and interventions that provided comprehensive training and education on breathing retraining were more likely to show a benefit than interventions that isolated one aspect of breathing retraining (e.g., prolonged exhalation,[35,53] mouth taping,[34] strengthening inspiratory muscles[50-52]), which generally showed no benefit. For example, 83 percent of trials reporting extra non-breathing components reported a positive effect on asthma symptoms and 100 percent reported reductions in reliever medication use (of those reporting these outcomes), compared with 36 and 33 percent respectively among trials that restricted their interventions to breathing training. However, as discussed next, intensity of intervention (measured in hours of contact) and comprehensiveness (measured in number of intervention components) are likely confounded.

More comprehensive programs were also more likely to offer more hours of exposure to interventionists, and data were insufficient to truly tease apart the effects of hours of contact from the effects of the content that was presented. However, we were able to compare patterns of results among the 13 trials that had the same number of contact hours in the treatment and comparator groups[35,36,39-42,45,46,50-54] with the 10 trials which intervention participants received more hours of contact than those in the comparator group.[33-35,37,38,43,44,47-49] One trial had two intervention arms with matching intensity and a third with greater intensity.[35] Based on the number of trials reporting positive results (and not magnitude of effects), trials that matched intensity between treatment groups were less likely to show reductions in reliever medication use (83% of trials with more intensive intervention than control groups showed reductions in reliever use, compared with 30% of those with matching intensity in the two groups). However,

comparable differences were not seen for asthma symptoms or quality of life outcomes. This exploratory analysis is limited by incomplete and perhaps selective reporting of these major outcomes.

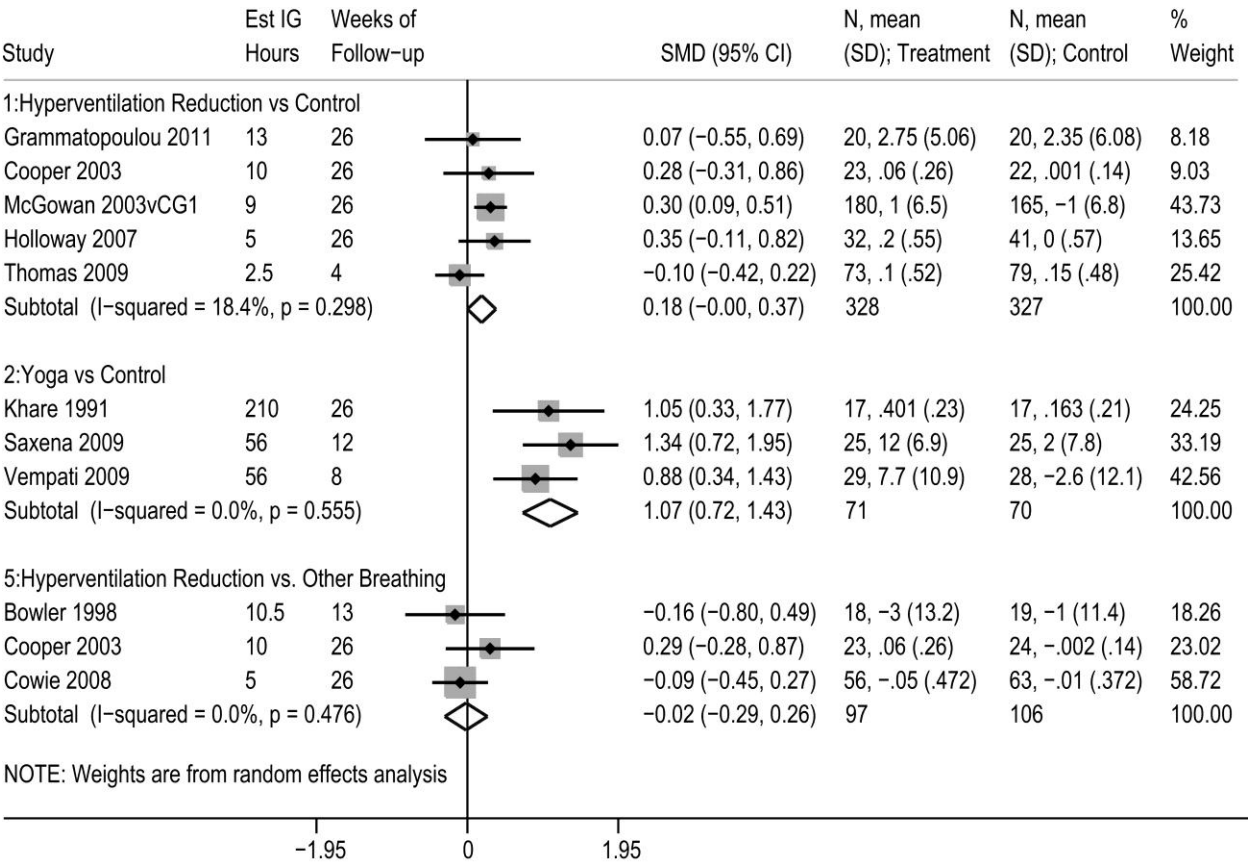
Trials that compared any breathing retraining with either another breathing technique or an intervention likely to induce relaxation or a reduced state of autonomic arousal[33,35,36,40,41,45,46,53] (k=8) were less likely to show group differences on asthma symptoms and quality of life compared with trials containing control groups that did not include either of these components (k=15).[34,35,37-39,42-44,47,49-52,54] Again, one trial with three arms could be counted in either group.[35] Seventy-five percent of trials with a nonbreathing or nonrelaxation comparator showed greater improvement on a measure of asthma symptoms in the intervention than the control group, compared with 12.5 percent of those with breathing or relaxation comparison comparators. Similar results were seen for quality of life in these trials (20% showing benefit when compared with another breathing technique and/or relaxation vs. 57% showing benefit when compared with nonbreathing/ relaxation control). These data are purely exploratory and do not account for magnitude or precision of effect, and they do not consider the impact of incomplete and perhaps selective reporting. As such, these data must be interpreted cautiously.

Key Questions 2. In adults and children 5 years of age and older with asthma, does the use of breathing exercises and/or retraining techniques improve pulmonary function or other similar intermediate outcomes when compared with usual care and/or other breathing techniques alone or in combination with other intervention strategies?

Hyperventilation Reduction Breathing Techniques vs. Control Group

All seven trials reported one or more pulmonary function outcomes, primarily FEV_1, FVC, and PEF at 4 to 52 weeks (Table 4; Appendix C, Evidence Table 1f).[34,35,37-40,42] The standardized pooled effect size of five trials that could be combined showed minimal impact of hyperventilation reduction techniques on FEV_1 (SMD=0.18, 95% CI, 0.00 to 0.37, I^2=18.4%, Figure 5).[35,37-39,42] The two trials that could not be pooled were the video-based interventions with matched-intensity control video for comparison, which found small statistically nonsignificant differences in improvement in peak flow daily diaries,[40] and the mouth-taping trial, which found a nonstatistically significant reduction in FEV_1 during the mouth-taping portion of the trial.[34]

Figure 5. Effect of breathing retraining for asthma on pulmonary function at 1 to 6 months



Abbreviations: CG: control group; CI: confidence interval; est: estimated; IG: intervention group; N: sample size; SD: standard deviation; SMD: standardized mean difference

Group differences were only found in one trial, and were only compared to one of the two control groups.[39] In this trial, percent predicted FEV_1 increased from 80 to 81 percent in the Buteyko group while dropping from 75 to 74 percent in the nurse education control group. However, the lower-intensity control group of asthma education only (which was not included in the meta-analysis) did not show a drop and did not differ from the Buteyko group in change from baseline. Three trials measured end-tidal CO_2,[37,38,42] which is a specific target of interventions to reduce hyperventilation. Only one trial found group differences, reported at 4, 12, and 26 weeks.[37] Breathing rate was reduced in two of these trials, which suggests that participants did modify their breathing as instructed, but that modification did not always alter the CO_2 levels as hypothesized by the Buteyko method proponents.[37,38]

Yoga Breathing vs. Control

Neither of the US-based trials improved pulmonary function outcomes,[44,45] despite the positive effects on other outcomes for the comprehensive naturopathic treatment program (Table 5; Appendix C, Evidence Table 2f).[44] However, intensive yoga training in India resulted in

substantial improvements in pulmonary function with a standardized pooled effect size for these three trials of 1.07 (95% CI, 0.72 to 1.43 I^2=0.0%, Figure 5).[43,46,47] The trial with the largest effect (and the greatest quality concerns) showed improvement in percent predicted FEV_1 of 12 percentage points, compared with only two percentage points in the control group.[46] The best-quality trial of the three Indian trials reported improvements of 7.7 percentage points in the intervention group on percent predicted FEV_1 compared with a 2.6 percentage point reduction in the control group at eight-week followup.[47] Group differences were also found on FVC,[43] FEV_1/vital capacity (VC) ratio,[43,47] and PEF readings[43,46,47] in the trials conducted in India, but not in those conducted in the US.[44,45] Only one of the trials reported that outcomes assessment was blinded.[45] None of the trials described training or quality assurance measures for the spirometry technicians, and only one provided any detail about spirometry procedures beyond naming the machine that was used. The best-quality intensive India-based trial[47] reported taking the best of three FEV_1 readings, in accordance with ATS standards.[11]

Inspiratory Muscle Training vs. Control

Results from IMT trials were mixed and could not be pooled due to substantial differences in population, setting, and treatment approach in the three trials reporting the same outcome. Treatment-naïve Brazilian children with previously uncontrolled asthma improved PEF readings by an average of 80 percent after 3 months of IMT training along with asthma medication management and education, compared to almost no change on average in those receiving medication and asthma education alone (Table 6; Appendix C, Evidence Table 3f).[48] Lack of improvement in the control group suggests that medication management may have been suboptimal in this group. Among adults, two trials showed improvements in both FEV_1 and FVC, one with the use of an IMT device,[50] and the other using weights placed on the abdomen while in a semi-recumbent position.[49] Another trial found no differences in FEV_1.[51]

Other Nonhyperventilation Reduction Breathing Techniques vs. Control

Spirometry results did not change over time in either the trial of prolonged exhalation using a training device[35] or in any of the treatment groups in the biofeedback trial (Appendix C, Evidence Table 4f).[53] The remaining trial in this group did not report pulmonary function testing.[54]

Hyperventilation Reduction Breathing Techniques vs. Other Breathing Techniques

All four trials in this group reported change in FEV_1 at13 to 28 weeks (Appendix C, Evidence Table 5f). None found group differences, and there was little change within groups in any trials. The standardized pooled effect size of the three trials that provided sufficient data for analysis was -0.02 (95% CI, -0.29 to 0.26, I^2=0.0%, Figure 5).[33,35,36] Only one trial reported PEF, and found no group differences.[33] Other measures of pulmonary function similarly showed no group differences including end-tidal CO_2,[33,41] provocative dose of methacholine causing 20 percent reduction in FEV_1,[35] and FVC.[41] One trial did find that those undergoing Buteyko breathing technique had lower minute volume, a specific target of hyperventilation-reduction approaches, than those being trained in abdominal breathing.[33] Thus, participants did modify their breathing in a manner consistent with the Buteyko breathing technique approach, but this

change did not alter the amount of CO_2 in their exhalation, which suggests that CO_2 levels may not be an important trigger for asthma as suggested by Buteyko breathing technique proponents.

Key Question 2a. Does the efficacy and/or effectiveness of breathing techniques for other asthma outcomes differ between different subgroups (e.g., adults/children; males/females; different races or ethnicities; smokers/nonsmokers; various types and severities of asthma; and/or different coexisting conditions)?

The best-quality trial of yoga conducted in India displaying large benefits of treatment reported that participants with exercise-sensitive asthma showed a greater improvement on FEV_1 than those whose asthma was not sensitive to exercise.[47] This analysis did not appear to be planned a priori, nor did the intervention particularly target factors that purported to differentially affect those with exercise-sensitive asthma. No other trials reported subgroup analyses for any pulmonary function outcomes.

Key Question 2b. Does the efficacy and/or effectiveness of breathing techniques for other asthma outcomes differ according to variations in implementation (e.g., trainer experience) and/or nonbreathing components of the intervention (e.g., anxiety management)?

Benefits were more likely to be seen if the control group did not involve breathing training of any kind or relaxation techniques (42% positive vs. 14% positive with breathing/relaxation comparison group). These data are preliminary, however, and only valid for hypothesis generation and did not account for effect size.

Key Question 3. What is the nature and frequency of serious adverse effects of treatment with breathing exercises and/or retraining techniques, including increased frequency of acute asthma exacerbations?

Seven trials reported on adverse events,[34,36,38,40,41,44,45] five of which examined a hyperventilation reduction approach compared with either a control or another breathing retraining approach,[34,36,38,40,41] and two examined yoga interventions.[44,45] Three of the seven studies (including one yoga trial[45]) noted that there were no adverse events or harms that occurred in either the intervention or control group over 16 to 52 weeks of intervention and followup.[36,38,45] One study of a Buteyko breathing technique intervention, compared to a relaxation control group, noted that one hospitalization occurred with one member of the control group.[40] Another study comparing a Buteyko breathing technique intervention delivered by video with a placebo intervention involving nonspecific upper body mobility exercises reported 138 adverse events in the Buteyko breathing technique group and 121 in placebo group, none of which was considered to be related to treatment.[41] The trial of comprehensive naturopathic treatment reported mild headache, fatigue, and/or nausea, which they attributed to the use of the supplements and not yoga.[44] In the study focused on the effect of a nighttime mouth-taping intervention, participants reported problems related to the intervention including it being uncomfortable, causing sore lips, making breathing more difficult, feeling unnatural, decreasing sleep quality, causing a feeling a suffocation, or was embarrassing.[34]

Key Question 3a. Do the safety or adverse effects of treatment with breathing techniques differ between different subgroups (e.g., adults/children; males/females; different races or ethnicities; smokers/nonsmokers; various types and severities of asthma; and/or different coexisting conditions)?

No trials examined harms of treatment within subgroups or compared subgroups on likelihood of harms.

Table 4. Overview of results: hyperventilation reduction breathing techniques versus control, sorted by difference in hours between intervention group and control group, then by overall intensity where intensity is matched between groups

Study	Followup*	Group	N randomized	Description	Intensity (total hours)	Baseline SABA use	Baseline ICS use (mcg/d)	Baseline FEV_1 (L)	Asthma sx	Reliever med use	Controller med use	QoL	FEV_1	PEF	Quality¶	Applicability to US health care setting
Grammatopoulou 2011[37]	26w	IG	20	Diaphragm, nasal breathing; short pause	13	NR	NR	83.7	↓				↔		++	Conducted in Greece, limited to those with mild or moderate asthma
		CG	20	Usual care	NR											
Cooper 2003[35]	26w	IG1	30	BBT†	10	2 puffs/d‡	657	80	↓	↓	↔	↔	↔		++	Conducted in the UK, used certified BBT practitioner
		CG	29	Sham device	NR, 1 session				↔							
		CG	49	Usual care	NR											
McGowan[39,77]	26w	IG	200	BBT	2h + 7 sessions	18 puffs/w	NR	76.7	↓↓ (for both groups)	↓↓ (for both groups)	↓↓ (for both groups)		↑		++	Conducted in Scotland, used certified BBT practitioner
		CG1	200	Nurse education	2h + 7 sessions								↔			
		CG2	200	Brief asthma education	2h											
Holloway 2007[38,55]	52w	IG	39	Papworth§	5	NR	NR	89.6	↓↓				↔	↔	++	Conducted in the UK, used respiratory therapist with training in BBT
Opat 2000[40,60]	4w	IG	18	BBT video	19.8	404 mcg/d	430	NR	↔	↓	↔	↑		↔	++	Conducted in Australia, all-volunteer sample
		CG	18	Landscape video	18.6											
Thomas 2009[42,62-64]	4w	IG	94	Papworth	2-2.5	1.4 dose/d	400‡	89.5	↔**	↔	↔	↑**	↔		++	Conducted in the UK
		CG	89	Asthma education	2-2.5											
Cooper 2009‖[34,58,72]	4w	IG	51	Mouth-taping	NA	10 puffs/w‡	567	86.2	↔	↔		↔		↔	++	Conducted in the UK
		CG		Usual care	NA											

*Time to longest followup
†Also included dietary restrictions, stress management and instruction to avoid oversleeping
‡Median
§Also includes stress management
‖Crossover study design, mouth-taping and control phases
¶All trials were rated "Fair"; further gradation is provided as follows: +++ = Minor quality issues, but not meeting criteria for "Good" quality; ++ = Between +++ and + trials in quality; + = Substantial quality issues, but no clear fatal flaw
**Outcome was assessed at 26 weeks

Abbreviations: BBT: Buteyko breathing technique; CG: control group; d: day(s); FEV_1: forced expiratory volume in 1 second; h: hour(s); ICS: inhaled corticosteroids; IG: intervention group; mcg: microgram(s); med: medication; NA: not applicable; NR: not reported; PEF: peak expiratory flow; QoL: quality of life; SABA: short-acting $beta_2$-agonists; sx: symptoms; UK: United Kingdom; w: week(s)

Table 5. Overview of results: yoga breathing techniques versus control, sorted by difference in hours between intervention group and control group, then by overall intensity where intensity is matched between groups

Study	Followup*	Group	N randomized	Description	Intensity (total hours)	Baseline SABA use	Baseline ICS use (mcg/d)	Baseline FEV_1 (L)	Asthma sx	Reliever med use	Controller med use	QoL	FEV_1	PEF	Quality‖	Applicability to US health care setting
Khare 1991[43]	26w	IG	17	Daily yoga	210	NR	NR†	NR	↓		↓‡		↑	↑↑	+	Conducted in India, limited to male vegetarians age 25 to 50, standard of care did not include ICS
		CG	17	Usual care	NR											
Vempati 2009[47,57,66-70]	8w	IG	30	Yoga practice and lectures§	56	2.1 puffs/d¶	339**	66	↓	↓↓		↑↑	↑↑	↑	++	Conducted in India, mild to moderate asthma only
		CG	30	Usual care	NR, 1 session											
Kligler 2011[44]	26w	IG	77	Yoga breathing††	6-9	NR	NR	NR	↓			↑	↔		+	Self-identified sample, intervention included dietary change, supplements and journaling
		CG	77	Usual care	NR											
Saxena 2009[46]	12w	IG	25	Yoga breathing exercise	56	NR	NR	72	↓↓				↑↑	↑↑	+	Conducted in India, limited to those with 26w experience with yoga and no regular use of medication (or advised to discontinue medication if using)
		CG	25	Meditation	56											
Sabina 2005[45]	16w	IG	29	Yoga class	12	1 puffs/d	NR	NR	↔	↔		↔	↔	↔	++	Mild to moderate asthma only, all self-identified sample, conducted in research setting
		CG	33	Stretching class	12											

*Time to longest followup

†19/34 (56%) "disturbed sleep and dyspnea on daily routine work which was relieved by oral drugs"; 8/34 (24%) "asthma required injection frequently to control dyspnea or admission to hospital"

‡Reduction in dose to “control dyspnea,” type of medication not specified
§Also includes dietary advice, instruction on cleansing techniques, meditation and relaxation
‖All trials were rated “Fair”; further gradation is provided as follows: +++ = Minor quality issues, but not meeting criteria for “Good” quality; ++ = Between +++ and + trials in quality; + = Substantial quality issues, but no clear fatal flaw
¶Includes 11 with missing data, unclear if nonusers or simply missing
**Includes 25 with missing data, unclear if nonusers or simply missing
††Also include dietary advice

Abbreviations: CG: control group; d: day(s); FEV_1: forced expiratory volume in 1 second; h: hour(s); ICS: inhaled corticosteroids; IG: intervention group; mcg: microgram(s); med: medication; NA: not applicable; NR: not reported; PEF: peak expiratory flow; QoL: quality of life; SABA: short-acting $beta_2$-agonists; sx: symptoms; w: week(s)

Table 6. Overview of results: inspiratory muscle training versus control, sorted by difference in hours between intervention group and control group, then by overall intensity where intensity is matched between groups

Study	Followup*	Group	N randomized	Description	Intensity (total hours)	Baseline SABA use	Baseline ICS use (mcg/d)	Baseline FEV_1 (L)	Asthma sx	Reliever med use	Controller med use	QoL	FEV_1	PEF	Quality†	Applicability to US health care setting
Lima 2008[48]	13w	IG	25	IMT, meds and asthma education	14.6	NR	NR	NR	↓↓	↓↓				↑↑	+	Conducted in Brazil, limited to 8- to 12-year-old children with untreated, uncontrolled asthma
		CG	25	Meds, asthma education	3											
Shaw 2011[49]	8w	IG	22	Abdominal strengthen-ing	NR	NR	NR	NR					↑↑		+	Conducted in South Africa, only moderate-persistent asthma
		CG	22	Usual care	NR											
Weiner 1992[50]	26w	IG	15	IMT	60	6 puffs/d	NR	59	↓	↓↓			↑↑		++	Conducted in Israel, moderate to severe asthma only
		CG	15	Sham device	60											
Weiner 2002[51]	20w	IG	11	IMT	60	3.2 puffs/d	NR	83		↔			↔		+	Conducted in Israel, limited to females with mild to moderate asthma
		CG	11	Sham device	60					↓						
Weiner 2000[52]	13w	IG	12	IMT	36	2.7 puffs/d	NR	91		↔					+	Conducted in Israel
		CG	11	Sham device	36					↓						

*Time to longest followup

†All trials were rated "Fair"; further gradation is provided as follows: +++ = Minor quality issues, but not meeting criteria for "Good" quality; ++ = Between +++ and + trials in quality; + = Substantial quality issues, but no clear fatal flaw

Abbreviations: CG: control group; d: day(s); FEV_1: forced expiratory volume in 1 second; h: hour(s); ICS: inhaled corticosteroids; IG: intervention group; IMT: inspiratory mucle training; mcg: microgram(s); med: medication; NA: not applicable; NR: not reported; PEF: peak expiratory flow; QoL: quality of life; SABA: short-acting $beta_2$-agonists; sx: symptoms; w: week(s)

Table 7. Overview of results: nonhyperventilation reduction breathing techniques versus control, sorted whether prolonged exhalation was encouraged, then by difference in intensity between groups

Study	Followup*	Group	N randomized	Description	Intensity (total hours)	Baseline SABA use	Baseline ICS use (mcg/d)	Baseline FEV_1 (L)	Asthma sx	Reliever med use	Controller med use	QoL	FEV_1	PEF	Quality¶	Applicability to US health care setting
Lehrer 2004[53,59]	12w	IG	23	Prolonged exhalation with HRV biofeedback	NR, 10 sessions	NR	NR	NR	↔ §		↔ §		↔ ‖		++	All volunteer sample, strict adherence to NAEPP guidelines with monthly visits, conducted in research setting
		CG1	22	HRV biofeedback	NR, 10 sessions											
		CG2	24	Sham device†	NR, 10 sessions											
		CG3	25	Waitlist	Waited for 30w											
Cooper 2003[35]	26w	IG2	30	Prolonged exhalation device	NR, 1 session, 6m practice	2 puffs/d‡	657	80	↔	↔	↔	↔	↔		++	Conducted in the UK, used device that may not be widely available
		CG	29	Sham device	NR, 1 session											
Thomas 2003[54,61,65]	26w	IG	17	Diaphragm breathing	1.25	1.5 can/ 3m	600	NR	↓ ↔ **	↔	↔	↑ ↔ **			++	Conducted in the UK, limited to those with Nijemegen scores suggestive of dysfunctional breathing
		CG	16	Asthma education session	1											

*Time to longest followup
†Includes practice (but with no instruction) of maintaining a state of relaxed alertness, classical music tapes
‡Median
§No differences between biofeedback groups with and without breathing retraining component; both of these groups did differ from either the sham device and waitlist groups
‖No differences in "spirometry", specific measures NR
¶All trials were rated "Fair"; further gradation is provided as follows: +++ = Minor quality issues, but not meeting criteria for "Good" quality; ++ = Between +++ and + trials in quality; + = Substantial quality issues, but no clear fatal flaw
**Statistically significant only at 4w followup

Abbreviations: CG: control group; d: day(s); FEV_1: forced expiratory volume in 1 second; h: hour(s); HRV: heart rate variability; ICS: inhaled corticosteroids; IG: intervention group; mcg: microgram(s); med: medication; NA: not applicable; NAEPP: National Asthma Education and Prevention Program; NR: not reported; PEF: peak expiratory flow; QoL: quality of life; SABA: short-acting $beta_2$-agonists; sx: symptoms; UK: United Kingdom; w: week(s)

Table 8. Overview of results: hyperventilation reduction breathing techniques versus nonhyperventilation reduction breathing techniques

Study	Followup*	Group	N randomized	Description	Intensity (total hours)	Baseline SABA use	Baseline ICS use (mcg/d)	Baseline FEV_1 (L)	Asthma sx or control	Reliever med use	Controller med use	QoL	FEV_1	PEF	Quality‖	Applicability to US health care setting
Cooper 2003[35]	26w	IG1	30	BBT†	10	2 puffs/d‡	657	80	↔	↓BBT	↔	↔	↔		++	Conducted in the UK, used certified BBT practitioner, used device that may not be widely available
		IG2	30	Yoga breathing device	NR, 1 session, practice 6m											
Bowler 1998[33,56,71]	13w	IG1	19	BBT sessions	7-10.5 or more	892 mcg/d	1250	74	↔	↓BBT	↔	↔	↔	↔	+	Conducted in Australia, all volunteer sample, used certified BBT practitioner, high levels of baseline asthma medication use
		IG2	20	Abdominal breathing, asthma education	7-10.5											
Cowie 2008[36]	26w	IG1	65	BBT sessions	NR, 5 sessions	NR	840	81	↔		↓BBT	↔§	↔		++	Conducted in Canada, university setting, used certified BBT practitioner, used certified physiotherapist
		IG2	64	Physiotherapy sessions	NR, 5 sessions											
Slader 2006[41]	28w	IG1	28	BBT video	90	3 puffs/d	NR	80	↔§	↔§	↔§	↔	↔		+++	Conducted in Australia, limited to those with moderate to severe asthma, low baseline scores on mood domains on QoL
		IG2	29	Video-based controlled breathing, mobility and stretching	90											

Study	Followup*	Group	N randomized	Description	Intensity (total hours)	Baseline SABA use	Baseline ICS use (mcg/d)	Baseline FEV_1 (L)	Asthma sx or control	Reliever med use	Controller med use	QoL	FEV_1	PEF	Quality‖	Applicability to US health care setting
																questionnaire, conducted in research setting

*Time to longest followup
†Also included dietary restrictions, stress management and instruction to avoid oversleeping
‡Median puffs per day, typical dose per puff = 100 mcg
§No difference between groups but both groups showed improvement
‖All trials were rated "Fair"; further gradation is provided as follows: +++ = Minor quality issues, but not meeting criteria for "Good" quality; ++ = Between +++ and + trials in quality; + = Substantial quality issues, but no clear fatal flaw

Abbreviations: BBT: Buteyko breathing technique; CG: control group; d: day(s); FEV_1: forced expiratory volume in 1 second; h: hour(s); ICS: inhaled corticosteroids; IG: intervention group; mcg: microgram(s); med: medication; NA: not applicable; NR: not reported; PEF: peak expiratory flow; QoL: quality of life; SABA: short-acting $beta_2$-agonists; sx: symptoms; UK: United Kingdom; w: week(s)

Table 9. Instruments used for measuring asthma symptoms, control, quality of life, or related outcomes

Outcome Measure	Instrument	Number of Items	Range	Directionality (Higher score = better or worse)	Constructs Measured, Subscales
Symptom, Severity, or Control	Asthma Control Questionnaire (ACQ)[78]	7	0-6	Worse	Symptoms, beta$_2$-agonist use, pulmonary function (FEV_1)
	Asthma Control Diary (ACD)[79]	8	0-6	Worse	Morning score: PEFR, awakenings, symptom severity; Bedtime score: activity limitations, shortness of breath, wheezing, bronchodilator use, PEF
	Physician / Patient Global Assessment for Asthma Control	NR	0-100	Better	
	Asthma Control Test (ACT)[74]	22	1-5	Worse	Symptoms and control, activity, health care use
Asthma-Related Quality of Life	St. George's Respiratory Questionnaire[80]	76	0-100	Worse	Symptoms, activity, impacts
	Asthma Quality of Life Questionnaire (AQLQ-Marks)[81]	20	0-4	Worse	Breathlessness and physical restriction, mood disturbance, social disruption, concern for health
	Mini-Juniper Quality of Life Questionnaire (Mini-Juniper)[82]	15	1-7	Better	Overall quality of life, symptom severity, environment impact on asthma, emotional impact of asthma, activity limitations
	Asthma Quality of Life Questionnaire (AQLQ-Juniper)[83]	32	1-7	Better	Symptoms, emotions, environment, physical activities, practical problems
Dysfunctional Breathing	Nijmegen Questionnaire[84]	16	1-5	Worse	Hyperventilation syndrome (chest pain, feeling tense, blurred vision, dizzy spells, feeling confused, faster or deeper breathing, short of breath, tight feelings in chest, bloated feeling in stomach, tingling fingers, unable to breathe deeply, stiff fingers or arms, tight feelings round mouth, cold hands or feet, palpitations, feeling of anxiety)
General Functioning and Quality of Life	Short-form (SF-36) Health Survey[85]	36	0-100	Better	Vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health
Mental Health	Hospital Anxiety and Depression Scale (HADS)[86]	14	0-3	Worse	Anxiety, depression

Abbreviations: FEV_1: forced expiratory volume in 1 second; PEF: peak expiratory flow: PEFR: peak expiratory flow rate

Table 10. Quality and applicability issues: hyperventilation reduction breathing techniques versus control

Study	Study design	Follow-up	Group	N random-ized	Retention	Allocation concealment	Blinding of outcomes assessment	PFT for asthma confirmation	Excluded those with other resp. d/o	Handling of missing data	Overall quality rating†	Other quality concerns or clarifications	Factors limiting applicability to U.S. health care settings
Cooper 2003[35]	RCT	26w	IG1 (BBT)	30	77%	NR	Yes	Yes	Likely*	LOCF	++	Unclear which baseline differences were controlled for, many comparisons on small number of participants	Conducted in the UK, used certified BBT practitioner
			CG	30	80%								
Grammato-poulou 2011[37]	RCT	26w	IG (HRBT)	20	100%	Yes	Yes	NR	NR	NA	++	Assessment of asthma dx not described; Exclusion for other respiratory d/o NR, but did exclude smokers and those age ≥60	Conducted in Greece, only 14% of those sent invitation were randomized (recruited from attendees of asthma department)
			CG	20	100%								
Holloway 2007[38,55]	RCT	26w	IG (Pap-worth)	39	85%	NR	No	U	Likely*	None	++	More smokers in IG but smoking not controlled for in analysis; PFT for confirmation unclear, recruited from registry	Conducted in the UK, used respiratory therapist with training in BBT
			CG	46	98%								
		52w	IG	39	82%								
			CG	46	87%								
McGowan 2003[39,77]	RCT	26w	IG (BBT)	200	90%	Yes	Yes	Yes	Yes	None	++	Specific use of spirometry	Conducted in UK, used

Study	Study design	Follow-up	Group	N random-ized	Retention	Allocation concealment	Blinding of outcomes assessment	PFT for asthma confirmation	Excluded those with other resp. d/o	Handling of missing data	Overall quality rating†	Other quality concerns or clarifications	Factors limiting applicability to U.S. health care settings
			CG1 (Nurse Ed)	200	82.5%							to determine asthma dx not described; no description of refusals or exclusions prior to randomization	Registered BBT practitioner
			CG2 (Intro ed)	200	73.0%								
Opat 2000[40,60]	RCT	4w	IG (BBT)	18	89%	U	NR	No	NR, but age limited to ≤50	None	++	Allocation concealed from participant, NR if concealed from research staff	Conducted in Australia, all-volunteer sample
			CG	18	89%								
Thomas 2009[42,62-64]	RCT	4w	IG (HRBT)	94	78%	Yes	U	NR	Yes	LOCF	++	Blinding of nonself-report outcomes NR	Conducted in the UK
			CG	89	89%								
		26w	IG	94	67%‡								
			CG	89	74%‡								
Cooper 2009[34,58,72]	Cross-over RCT	4w	IG (mouth-taping)	51‖	98%	NR	Yes	Yes	Likely*	None	++	Handling of other respiratory illness NR, but did exclude those with	Conducted in the UK
			CG										

*Did not specifically report excluding those with other respiratory disorders, but did report excluding those with other disorders without listed the specific disorders excluded.
† All trials were rated "Fair"; further gradation is provided as follows: +++ = Minor quality issues, but not meeting criteria for "Good" quality; ++ = Between +++ and + trials in quality; + = Substantial quality issues, but no clear fatal flaw
‡Followup at 26w only measured for quality of life
‖Crossover study design, mouth-taping and control phases

Abbreviations: BBT: Buteyko breathing technique; CG: control group; d/o: disorder(s); HRBT: hyperventilation reduction breathing technique; IG: intervention group; LOCF: last observation carried forward; NR: not reported; PFT: pulmonary function test; RCT: randomized controlled trial; resp: respiratory; U: unclear; UK: United Kingdom; US: United States; w: week(s)

Table 11. Quality and applicability issues: yoga breathing techniques versus control

Study	Study design	Follow-up	Group	N random-ized	Retention	Allocation concealment	Blinding of outcomes assessment	PFT for asthma confirmation	Excluded those with other resp. d/o	Handling of missing data	Overall quality rating†	Other quality concerns or clarifications	Factors limiting applicability to US health care settings
Khare 1991[43]	RCT	26w	IG (yoga breathing)	17	100%	NR	NR	NR	Yes	NA	+	No description of refusals or exclusions prior to randomization	Conducted in India, limited to male vegetarians age 25 to 50, standard of care did not include ICS
			CG	17	100%								
Kligler 2011[44]	RCT	26w	IG (yoga)	77	87	U	No	NR	NR	Yes, RER	+	Did not limit to those without recent oral steroid use, no description of refusals or exclusions prior to randomization	Self-selected participants, Included dietary and journaling treatment components
			CG	77	80								
Sabina 2005[45]	RCT	16w	IG (yoga breathing)	29	79%	Yes	Yes	Yes	Yes	Yes, Method NR	++		Mild to moderate asthma only, self-selected sample, conducted in research setting
			CG	33	67%								
Saxena 2009[46]	RCT	12w	IG (yoga breathing)	25	NR	NR	NR	Yes	Yes	NR	+	Randomization procedures likely not truly random, no description of refusals or exclusions prior to randomization	Conducted in India, limited to those with 26w experience with yoga, limited to those with no regular use of medication or advised to discontinue medication if using
			CG	25	NR								

Study	Study design	Follow-up	Group	N random-ized	Retention	Allocation concealment	Blinding of outcomes assessment	PFT for asthma confirmation	Excluded those with other resp. d/o	Handling of missing data	Overall quality rating†	Other quality concerns or clarifications	Factors limiting applicability to US health care settings
Vempati 2009[47,57,66-70]	RCT	8w	IG (yoga breathing)	30	97%	NR	NR	Yes	Yes	None	++	Good assessment procedures	Conducted in India, mild to moderate asthma only
			CG	30	93%								

*Did not specifically report excluding those with other respiratory disorders, but did report excluding those with other disorders without listed the specific disorders excluded.
†All trials were rated "Fair"; further gradation is provided as follows: +++ = Minor quality issues, but not meeting criteria for "Good" quality; ++ = Between +++ and + trials in quality; + = Substantial quality issues, but no clear fatal flaw

Abbreviations: CG: control group; d/o: disorder(s); ICS: inhaled corticosteroids; IG: intervention group; LOCF: last observation carried forward; NA: not applicable; NR: not reported; PFT: pulmonary function test; RCT: randomized controlled trial; RER-Random Effects Regression model; UK: United Kingdom; US: United States; w: week(s)

Table 12. Quality and applicability issues: inspiratory muscle training versus control

Study	Study design	Follow-up	Group	N random-ized	Retention	Allocation concealment	Blinding of outcomes assessment	PFT for asthma confirmation	Excluded those with other resp. d/o	Handling of missing data	Overall quality rating†	Other quality concerns or clarifications	Factors limiting applicability to US health care settings
Lima 2008[48]	RCT	13w	IG (IMT)	25	100%	NR	NR	No	NA	NA	+	Assessment of symptoms and medication use not described	Conducted in Brazil, limited to 8- to 12-year-old children with untreated, uncontrolled asthma
			CG	25	100%								
Shaw 2011[49]	RCT	8w	IG (abdom-inal strength-ening)	22	100%	NR	NR	Yes	NR	NA	+	Did not report asthma sx or medication use, no description of refusals or exclusions prior to randomization	Conducted in South Africa, did not describe recruitment source, did not describe baseline asthma sx, or med use, University setting with average age 21
			CG	22	100%								
Weiner 1992[50]	RCT	26w	IG (IMT)	15	100%	NR	Yes	Yes	NR	NA	++	Did not provide detailed inclusion /exclusion rules; noted that "most patients in the control group became gradually aware of the fact that they were using a sham device," no description of refusals or exclusions prior to randomization	Conducted in Israel, limited to those with moderate to severe asthma
			CG	15	100%								

Study	Study design	Follow-up	Group	N random-ized	Retention	Allocation concealment	Blinding of outcomes assessment	PFT for asthma confirmation	Excluded those with other resp. d/o	Handling of missing data	Overall quality rating†	Other quality concerns or clarifications	Factors limiting applicability to US health care settings
Weiner 2000[52]	RCT	26w	IG (IMT)	12	92%	NR	NR	Yes	NR	None	+	Did not provide detailed inclusion /exclusion rules; no information on baseline comparability of groups	Conducted in Israel, limited to those with > 1 puff/d beta-agonist consumption
			CG	11	100%								
Weiner 2002[51]	RCT	20w	IG (IMT)	11	91%	NR	Yes	Yes	NR	None	+	Did not provide detailed inclusion /exclusion rules; no information on baseline comparability of groups, no description of refusals or exclusions prior to randomization	Conducted in Israel, limited to females with mild to moderate asthma
			CG	11	82%								

*Did not specifically report excluding those with other respiratory disorders, but did report excluding those with other disorders without listed the specific disorders excluded.
†All trials were rated "Fair"; further gradation is provided as follows: +++ = Minor quality issues, but not meeting criteria for "Good" quality; ++ = Between +++ and + trials in quality; + = Substantial quality issues, but no clear fatal flaw

Abbreviations: abdom: abdominal; CG: control group; d/o: disorder(s); IG: intervention group; IMT: inspiratory muscle training; NA: not applicable; NR: not reported; PFT: pulmonary function test; RCT: randomized controlled trial; US: United States; w: week(s)

Table 13. Quality and applicability issues: other nonhyperventilation reduction breathing techniques versus control

Study	Study design	Follow-up	Group	N random-ized	Retention	Allocation concealment	Blinding of outcomes assessment	PFT for asthma confirmation	Excluded those w/ other resp. d/o	Handling of missing data	Overall quality rating†	Other quality concerns or clarifications	Factors limiting applicability to US health care settings
Cooper 2003[35]	RCT	26w	IG2 (yoga breathing device)	30	73%	NR	Yes	Yes	Likely*	LOCF	++	Unclear which baseline differences were controlled for	Conducted in the UK, used device that may not be widely available
			CG	30	80%								
Lehrer 2004[53,59]	RCT	12w	IG (abdom. breathing with biofeed-back	23	74%	NR	Yes	Yes	Yes	LOCF	++	No description of refusals or exclusions prior to randomization	All volunteer sample, might have higher standard of care since research protocol stipulated strict adherence to NAEPP guidelines with monthly visits, conducted in research setting
			CG1 (biofeed-back)	22	77%								
			CG2 (placebo)	24	79%								
			CG3 (waitlist)	25	92%								
Thomas 2003[54,61,65]	RCT	26w	IG (diaphragm breathing)	17	94%	NR	NR	Yes	NR	None	++		Conducted in the UK, limited to those with Nijemegen scores suggestive of dysfunctional breathing
			CG	16	75%								

*Did not specifically report excluding those with other respiratory disorders, but did report excluding those with other disorders without listed the specific disorders excluded.

†All trials were rated “Fair”; further gradation is provided as follows: +++ = Minor quality issues, but not meeting criteria for “Good” quality; ++ = Between +++ and + trials in quality; + = Substantial quality issues, but no clear fatal flaw

Abbreviations: abdom: abdominal; CG: control group; d/o: disorder(s); IG: intervention group; LOCF: last observation carried forward; NAEPP: National Asthma Education and Prevention Program; NR: not reported; RCT: randomized controlled trial; PFT: pulmonary function test; UK: United Kingdom; US: United States; w: week(s)

Table 14. Quality and applicability issues: hyperventilation reduction breathing techniques versus nonhyperventilation reduction breathing techniques

Study	Study design	Follow-up	Group	N random-ized	Retention	Allocation concealment	Blinding of outcomes assessment	PFT for asthma confirmation	Excluded those with other resp. d/o	Handling of missing data	Overall quality rating†	Other quality concerns or clarifications	Factors limiting applicability to US health care settings
Bowler 1998[33,56,71]	RCT	13w	IG1 (BBT)	19	95%	Yes	NR	No	Likely*	None	+	IG1 more intensive	Conducted in Australia, all volunteer sample, used certified Buteyko practitioner, high levels of baseline asthma medication use
			IG2 (abdom. breathing)	20	95%								
Cooper 2003[35]	RCT	26w	IG1 (BBT)	30	77%	NR	Yes	Yes	Likely*	LOCF	++	Unclear which baseline differences were controlled for	Conducted in the UK, used certified Buteyko practitioner for BBT intervention, used device that may not be widely available for yoga breathing device comparator
			IG2 (yoga breathing device)	30	73%								
Cowie 2008[36]	RCT	26w	IG1 (BBT)	65	86%	Yes	NR	Yes	Yes	None	++	Did not report beta-agonist, use as outcome, but did report other medications; concern about reporting bias	Conducted in Canada, university setting, used certified Buteyko practitioner for BBT intervention, certified physiotherapist of physiotherapy intervention
			IG2 (physio-therapy)	64	98%								

Study	Study design	Follow-up	Group	N random-ized	Retention	Allocation concealment	Blinding of outcomes assessment	PFT for asthma confirmation	Excluded those with other resp. d/o	Handling of missing data	Overall quality rating†	Other quality concerns or clarifications	Factors limiting applicability to US health care settings
Slader 2006[41]	RCT	28w	IG (BBT)	28	82%	Yes	Yes	Yes	No, but limited to non-smokers with ≤ 10 pack-years	None for 28w	+++		Conducted in Australia, limited to those with moderate to severe asthma, low baseline scores on mood domains on quality of life questionnaire, conducted in research setting.
			IG2 (controlled breathing)	29	86%								

*Did not specifically report excluding those with other respiratory disorders, but did report excluding those with other disorders without listed the specific disorders excluded.
†All trials were rated "Fair"; further gradation is provided as follows: +++ = Minor quality issues, but not meeting criteria for "Good" quality; ++ = Between +++ and + trials in quality; + = Substantial quality issues, but no clear fatal flaw

Abbreviations: abdom: abdominal; BBT: Buteyko breathing technique; d/o: disorder(s); IG: intervention group; LOCF: last observation carried forward; NR: not reported; PFT: pulmonary function test; RCT: randomized controlled trial; UK: United Kingdom; US: United States; w: week(s)

Summary and Discussion

Overview of Main Findings

Available evidence suggests that selected intensive behavioral approaches that include breathing retraining exercises may improve asthma symptoms or reduce reliever medication use in motivated adults with poorly controlled asthma. However, the overall body of evidence primarily consisted of small, methodologically limited trials with widely heterogeneous samples, and was further compromised by the heterogeneity of approaches and incomplete and inconsistent outcome reporting (Table 15). Primary outcomes (symptom reduction and reliever medication use) were also self-reported, making them susceptible to social desirability bias. The largest, most coherent body of evidence for a specific breathing training technique assessed hyperventilation reduction techniques and suggested potentially reduced asthma symptoms and reliever medication use. However, not all trials included the main outcomes of interest and, as such, could not be included in the meta-analysis of these outcomes. Further, some studies did report the outcomes of interest, but did not provided the specific statistics required to be included in the meta-analysis. Pooled results for symptom reduction were highly heterogeneous. Hyperventilation reduction techniques were not found to improve pulmonary function tests as measured by FEV_1 or PEF. Yoga was the only technique with evidence that it may improve pulmonary function and symptoms. However, quality issues in these trials limit confidence in results and applicability to the US health care system was very low. The yoga practiced in these trials was likely more intensive than would available to patients in the US. Additionally, yoga may not have the same cultural significance in the US as it does in India. Since pulmonary function tests require maximal effort from the patient to get accurate results, and since technician behavior may affect the likelihood of maximal effort, high-quality training and monitoring of these tests are critical to protect against bias and type I error. Available research on IMT and other breathing retraining techniques was limited to a heterogeneous group of small trials that are best characterized as pilot studies, which provided insufficient evidence to make conclusions about the effectiveness of these interventions.

Programs that included more hours of contact and that also offered intervention components beyond breathing retraining or advice appeared more likely to be found effective. Trials that matched treatment groups for number of hours of contact were less likely to show benefit than those providing extra hours of contact for the intervention group. This suggests that generic benefits of therapeutic contact, such as empathy, encouragement, and self-monitoring techniques, may be important components of treatment. These observations, however, should be considered hypothesis-generating rather than definitive for numerous reasons, including the lack of accounting for effect size and the high heterogeneity on numerous dimensions in these trials, precluding clear isolation of the effects of any specific elements.

Specific mechanisms of action for breathing training may be less important than enhanced self-efficacy and management of anxiety. Although possibly effective interventions were quite intensive, there was no evidence that breathing techniques are harmful, with the exception of minor annoyances associated with mouth taping. Although asthma medications associated with NAEPP guidelines are generally safe and effective, they can be associated with unpleasant or even harmful side effects,[1] so breathing retraining may be worth trying for some patients who are highly motivated to manage asthma symptoms with minimal use of reliever medication. In the US, results of these trials would likely be most applicable to patients with a

high level of motivation, given the fairly high attrition rates in several trials and, in some cases, selected samples.

Hyperventilation Reduction Breathing Retraining Techniques

Hyperventilation reduction techniques had the best evidence base, with 11 efficacy or comparative effectiveness trials. Almost all trials, however, had very small samples, and all had some methodological limitations. The only relatively large-scale trial of any breathing retraining method (n=600 randomized into three groups) investigated the effects of Buteyko techniques and showed substantially larger reductions in both asthma symptoms and reliever medication use in the treatment group than in either of two control groups. Retention in two control groups in this trial, however, was lower in the two control groups than the Buteyko group (90% retention in the Buteyko group vs. 82% in the intensity-matched group vs. 73% in the low-intensity control group).[39] Four of the six trials that compared comprehensive hyperventilation reduction training with a control or placebo reported reductions in asthma symptoms.[37-39,42] The pooled estimate suggested a large effect on asthma symptoms, though only four trials provided sufficient data to be included in the meta-analysis. In general, pooled estimates based on few trials are likely to overestimate true effects,[87] and four trials will provide an estimate that is within 10 percent of the true estimate of effect in only about 50 percent of cases, according in a recent analysis.[88] Thus, the pooled estimate in this case may overestimate the true effect. Of the four trials in the meta-analysis, one was the large trial described above and the other three were limited by either low retention,[42] no report of pulmonary function testing to confirm asthma,[37,42] no report that allocation concealment,[38] and lack of blinding of outcomes assessment.[38]

Hyperventilation reduction interventions did not show greater reduction in asthma symptoms than those involving other breathing techniques. In some cases, both groups improved and in some cases neither group showed improvement.

All trials that showed improvements in asthma symptoms involved at least 5 hours more of intervention contact for study subjects in the treatment group(s), compared with those in usual care or control groups. Most trials included additional, nonbreathing components.[35,37-39] Buteyko techniques required substantial practice on the part of asthma patients, so it is not surprising that extra support was important for patients to master the techniques and maintain their use. On the other hand, greater general support could also explain between-group differences.

Most trials (five of the eight trials reporting reliever medication use) showed greater reductions in reliever medication use with hyperventilation reduction breathing training, compared with either a control group or another breathing approach.[34,35,39,40,42] In most cases, reductions in bronchodilator use generally amounted to an average of 1.5 to 2.5 puffs per day, apparently almost eliminating the use of bronchodilators in two trials.[35,39] In one trial of patients with high medication use (median baseline use was 8.5 to 9.5 puffs per day), intervention participants reduced reliever use by a median of approximately 9 puffs/day, compared with a change in only one-half of a puff per day among those using a competing breathing approach.[33] This finding would be corroborated if the investigators had also demonstrated improvement in asthma symptoms. This trial, however, did not formally report changes in asthma symptoms, although internet-based material found in our grey literature search qualitatively suggest symptoms improvement.[89-91] We have concerns that these data may not be treated as rigorously in internet-based reports as they would be in a peer-reviewed journal, where methods are carefully assessed and statistical significance is generally presented. However, regardless of daily symptoms, participants were able to dramatically reduce reliever medication use without

increasing the risk of a severe exacerbation.[33] The only other high-intensity trial reporting both symptom improvement and reliever medication use found reductions in both symptoms and reliever medication use,[39] while the two trials of the lower-intensity interventions found no group differences for either asthma symptoms or reliever medication use.[40,42]

Practitioners that trained patients in the techniques of hyperventilation reduction generally coached patients to delay using reliever medication until breathing methods were tried and failed. Thus, reductions in reliever medication use may reflect intervention compliance and may not be the result of improved pathophysiology. Despite uncertainty about causal factors or about coherence of medication and symptom-based outcomes, however, a reduction of 1.5 to 2.5 puffs of reliever medication per day, maintained for up to 6 months, could be viewed as clinically significant by most asthma patients. A reduction of nine puffs per day of reliever medication would be considered a large improvement by any standards, although the clinical significance of this is limited by the fact that they only reported short-term (3-month) outcomes.

Changes in controller medication use and asthma-related quality of life were rarely seen in the hyperventilation reduction trials, and none of these trials consistently reported improvement in pulmonary function.

The British Thoracic Society (BTS) recommends that Buteyko breathing techniques be considered to help patients control asthma symptoms.[21] This recommendation was based on three of the trials included in our review,[33,35,40] along with one additional trial that we excluded because it used a relaxation training comparison group.[92] We included six addition published trials and one unpublished trial, all of fair quality, adding 1,145 additional participants. These include trials using hyperventilation reduction techniques that are not specifically limited to Buteyko methods, while the BTS guideline evidence base included trials of Buteyko breathing training. Many of the trials of hyperventilation reduction techniques were conducted in the UK, and are therefore more directly applicable to the British population that they are to Americans.

Yoga Breathing Techniques

The breathing techniques used in yoga are different from hyperventilation reduction methods. The techniques studied in the trials of yoga breathing involve deep breathing, sometimes with mechanically narrowed air passages and prolonged exhalation. In contrast, hyperventilation reduction breathing techniques advocate quiet, shallow breathing with breathing-holding. Both yoga and hyperventilation reduction methods, however, advocate the use nasal breathing rather than mouth breathing, and both appear to the effect of slowing the passage of air in and out of the lungs. It is unclear if the two approaches have similar physiologic effects, so we elected to analyze these interventions separately.

We identified five trials examining yoga breathing techniques. Three very intensive trials were conducted in India, one of which also included dietary advice, cleansing techniques, and meditation. All three reported improvements in asthma symptoms, reductions in medication use, and improved pulmonary function.[43,46,47] These trials had limited applicability to the US health care system due to cultural differences and populations targeted. All three were small studies, one with only 8-week outcomes[47] and two with substantial methodological flaws.[43,46]

Of the two trials conducted in the US,[44,45] one included substantial components in addition to breathing techniques, which made it impossible to determine the role of yoga breathing methods in the improvements in asthma outcomes.[44] The other trial with good applicability to the US reported on the efficacy of an eight-session yoga class and showed no differences between those randomized to yoga class from a stretching class of the same

intensity.[45] Thus, yoga does not appear to improve asthma as one might be typically introduced to yoga in the US.

One trial designed to isolate the effects of yoga breathing exercises (as opposed to a comprehensive yoga program) showed reductions in asthma symptoms and improvement in pulmonary function, but had substantial methodological limitations and very limited applicability to the US as they it was conducted in people with at least 6 months of experience with yoga who were not using medications.[46] Two additional trials focused only on using a device to enhance prolonged exhalation, which is consistent with yoga breathing.[35,53] Neither of these trials showed that this breathing approach in isolation improves asthma symptoms, reduces medication use, or improves pulmonary function, suggesting that a broader program of yoga is needed to see a benefit for asthma. How comprehensive of a program is needed to produce an effect, however, remains an open question.

A recent review of the use of yoga for asthma found evidence to be inconclusive among the seven trials they included in their review. They reported mixed results in trials that were plagued by methodological limitations. We included only two of the trials from their review.[45,47] The remaining trials were excluded because they did not meet our minimum quality criteria,[93,94] were not published in English,[95] used a form of yoga did not appear to include breathing exercises,[96] or were published prior to 1990.[97] The three additional trials that we included were two of the intensive India-based trials[43,46] and one comprehensive program conducted in the US,[44] all of which did show benefits of treatment.

Inspiratory Muscle Training and Other Nonhyperventilation Reduction Breathing Techniques

This body of evidence does not allow us to draw conclusions about the effectiveness of IMT or nonhyperventilation reduction breathing techniques (three small heterogeneous trials). We identified only five IMT trials,[48-52] three of which were conducted by the same researcher,[50-52] and all but one[50] had substantial methodological limitations. The best evidence comes from a small trial of 30 Israeli adults with moderate to severe asthma, who averaged six puffs of asthma medication per day at baseline.[50] IMT participants showed greater improvements than those using a sham device, but no differences were seen in the two very similar trials in participants with lower baseline reliever medication use.[51,52] Another trial by the same author did show that improvements in inspiratory muscle strength as measure by maximal inspiratory mouth pressure were correlated with reductions in SABA use, among those undergoing IMT. This trial was not included in this review because it did not report group-specific outcomes.[98]

The remaining IMT trials showed large group differences for some outcomes, but were relatively small trials with substantial methodological limitations and low applicability to the US.[48,49] Our conclusions are consistent with a Cochrane review that concluded evidence was insufficient to determine whether IMT provides clinical benefit to asthma patients.[99]

Evidence in Support of Specific Techniques

While training in hyperventilation reduction techniques may help improve asthma symptoms and reduce asthma reliever medication use, improvements could not be definitively attributed to the use of the specific techniques espoused for these interventions. Instruction to delay use of reliever medication may be sufficient to reduce reliever medication use. Rather than directly improving asthma, trials might help participants eliminate overuse of reliever

medications, which is still an important positive outcome. Subjective assessment of asthma symptoms is responsive to placebo interventions (e.g., sham acupuncture or a placebo inhaler),[100] and this may be sufficient to improve asthma symptoms in some cases, in addition to the enthusiastic advocacy by a treatment professional and dramatic testimonials,. Some trials attempted to control of the enthusiastic advocacy of the treatment modality by including comparison groups that involved other, plausible breathing retraining. However, it is difficult to say whether the treatment providers were comparable in their conviction that their techniques would be successful.

Another possibility is that these techniques improved asthma through reduction in anxiety or autonomic arousal. Participants in two trials of hyperventilation reduction techniques measuring anxiety did show small reduction in anxiety scores, though clinical significance was questionable because reductions were small and participants averaged in the normal range of anxiety at both baseline and followup.[38,42] A Cochrane review of psychological interventions for adults with asthma included nine trials examining some form of relaxation training, including the trial of biofeedback included in this review.[53] The overall conclusion of the review was that evidence was insufficient to determine whether psychological therapies improve asthma. A closer look at the subset of trials reporting relaxation training, however, frequently showed reductions in asthma medication use without improvements in asthma symptoms or pulmonary function. Thus, another possibility is that the reductions in reliever medication use seen in the trials in the current review may be related to reductions in level of autonomic arousal or anxiety, which may be achieved through the use of relaxation techniques.

The results of the trial of biofeedback included in the current review further support this hypothesis.[53] In this trial, both groups that included biofeedback to reduce HRV (which can reduce autonomic arousal) showed improvements in controller medication use and asthma symptom severity, and improvements in both groups were greater than both the placebo biofeedback group and wait-list controls. Another trial (not included in the current review because the intervention was not a breathing retraining technique) using a “Senobi” stretch, which was designed to lower the level of autonomic arousal, similarly found a greater reduction in reliever medication use in participants doing the Senobi stretch three times daily (reduction from baseline of 1.7 uses per week), compared with those doing a forward bend three times daily (reduction of 0.4 uses per week).[101]

There are a number of possible explanations for the improvements in asthma outcomes reported in the trials in this review, including the placebo effect, lowered autonomic arousal through relaxation or reduced anxiety, deliberately delayed use of reliever medication, lifestyle changes (diet, stress management, nutritional supplements), bias in outcome measurement, or the specific breathing techniques that were the focus of this review. It can be very difficult to isolate critical treatment elements in complex interventions, and use of some elements in isolation may underestimate their importance if the components are dependent on each other or interact with each other, or if individuals vary in the degree to which specific components are necessary or sufficient to gain improvements. Thus, critical intervention components often cannot be elucidated, particularly in a relatively poor and heterogeneous body of research.

Strength of Evidence

The strength of the evidence for each outcome by intervention group is presented in Table 15. In most cases the strength of evidence was insufficient or low. The evidence that hyperventilation reduction breathing techniques can reduce asthma symptoms and reliever

medication use was judged to be low-to-moderate, as was evidence that yoga breathing techniques can improve pulmonary function.

Applicability

Applicability of the included trials to the US setting and health care system was generally low, with trial-specific limitations listed in Tables 4 through 8. Only three of the trials were conducted in the US.[44,45,53] The yoga and IMT trials were conducted primarily in India, Brazil, and Israel, countries with substantial cultural or economic differences from the US. Some yoga and IMT trials were even further limited in their applicability to the general US population by limiting samples to males[43] or females only,[51] vegetarians within a fairly narrow age range,[43] people with six months of yoga experience and not using medications[46] and children with untreated asthma.[48] Further, in some of these trials, the standard of usual care also appeared to be different from the current US standard of care due to nonuse of controller medications[43,46] or poor success in managing asthma, further limiting our confidence in reported between-group differences.[48]

The hyperventilation reduction trials were primarily conducted in the UK[34,35,38,39,54] and Australia,[33,40,41] plus one each in Canada[36] and Greece.[37] They were generally conducted in health care settings, but these countries have very different health care systems from the US. One trial was limited to participants with dysfunctional breathing,[54] which limits applicability to persons with asthma in general. However, this was a pertinent subgroup to the intervention offered, which provided physiotherapy to reduce dysfunctional breathing. Trials of hyperventilation reduction generally used certified Buteyko practitioners and the availability of certified Buteyko practitioners in the US is unknown.

Limitations

Limitations of Our Approach

A potential limitation to our review is that we limited our review to English language publications. Previous research has suggested that evidence for complementary and alternative treatments may be biased if non-English publications are excluded.[102] We did examine the abstracts of any non-English publication that had an English abstract and that could have possibly met inclusion criteria for our review. We found eight English abstracts for non-English articles (Appendix B). Five of them made no mention of a comparison group, a wide variety of specific outcomes were reported, and most missed important details such as time to followup. Most of these abstracts reported improvements in some asthma-related parameter, however there was no indication that all measured outcomes were included and, for this reason, reporting bias appeared likely. Of the three abstracts that did perform group comparisons, only one was clearly a randomized comparison, all were small trials (n<50 in all cases) and none reported asthma symptoms, medication use, or quality of life, again raising concerns about reporting bias in the abstracts. Some proponents of Buteyko breathing techniques suggested that relevant early studies conducted by Buteyko himself may be only published in Russian, however we did not find any studies described with titles indicating that they were likely controlled trials conducted by Buteyko on websites devoted to explaining his research.

Another potential criticism is our exclusion of trials rating as having “poor” methodological quality. While some reviewers may believe that it is important to present all

trials of any quality, we felt that if study results were did not meet some minimal standard of internal validity then those results could be misleading and should not be presented. We found eight trials that were not included because they did not meet our minimal standards for quality or reporting (Appendix D).[93,94,103-108] These trials assessed the effects of hyperventilation reduction breathing techniques,[106-108] nonhyperventilation reduction breathing techniques,[103-105] and yoga.[93,94] One was a mere mention of a trial of biofeedback involving asthma patients with no actual data.[107] Only three of the trials compared treatment groups statistically[94,104,106] and one of these reported group differences.[106] These poor-quality trials were consistent with the included body of literature in that most trials reported a benefit of some kind on at least one outcome, though a variety of outcomes were reported and preferential reporting of statistically significant outcomes was possible.

We were unable to locate seven articles that may have met inclusion criteria (Appendix D).[109-115] We believe it is likely that most if not all would not have met inclusion criteria for several reasons. None of these trials were included in other reviews of breathing retraining, despite the fact that most of them fell in the search window of at least one other review on this topic. Two were conference abstracts by authors of included trials in this review, so conference abstracts could represent early reports on trials that we did include.[112,113] Another study listed "Anonymous" as the author, so was likely a synopsis of another trial rather than original research.[110] We believe the fact that we found these studies at all is testimony to the thoroughness of our grey literature searching.

We excluded trials that used relaxation training as a comparison group, since the efficacy of relaxation training for asthma is plausible but not established,[116] so interpretation may have been difficult, particularly in the case of no differences between groups. A number of included trials had comparators that could plausibly induce a state of relaxation, such as meditation, stretching, and landscape videos with instruction to use "relaxed breathing." We decided to err on the side of inclusion, which may have biased our review on the side of reduced effect sizes. Others may have chosen to exclude these trials. Also, we included trials that included a relaxation component along with the breathing training intervention, and possibly as a result we could not clarify the role of relaxation or reduced autonomic arousal vs. the role of the breathing training specifically in improving asthma outcomes.

When we had insufficient information to fully evaluate a trial, but had enough information to determine that it would likely meet inclusion criteria, we contacted authors and asked for the specific information we needed in order to complete our inclusion/exclusion determination and quality rating. Thus, we included information received through personal communication with authors, including extensive data received on the large Buteyko trial, which had only been published as a conference abstract at the time of this review.[39] These data did not appear in peer-reviewed publications and are not widely available for verification. However, we felt that it was important to attempt to include all pertinent literature, published and unpublished, to minimize publication bias and to have the most complete picture of the evidence possible. Quality standards were consistently applied to published and unpublished data. We did not contact authors who provided sufficient data to assign a quality rating and determine pertinent results, even if some data were missing, so these trials might have been at a slight disadvantage when assigned quality ratings. When we contacted authors, we asked only about information necessary to complete our quality rating or clarify data that were unclear to us.

Limitations of the Literature

Clinical and methodological heterogeneity was substantial across the entire body of literature, but usually a majority of the trials examining the same treatment approach were similar enough to each other to consider combining statistically. Due to heterogeneity of outcomes reported and lack of important outcomes in many trials, however, we were only able to perform meta-analyses for selected (not all) intervention approaches and for a limited number of outcomes. Even when comparable outcomes were reported, some trials were left out of the meta-analysis due to lack of necessary data (usually measures of variability such as standard deviations or confidence intervals). In the end, we were able to combine trials of only two interventions (hyperventilation reduction and yoga breathing training) for only three outcomes: asthma symptoms (hyperventilation reduction approaches vs. control only), quality of life (yoga vs. control only), and pulmonary function testing (for hyperventilation reduction and yoga trials). All pooled data are based on just three to five trials, so pooled results have a high probability of being more the 10 percent off from the true effect estimate.[88]

Finally, there was minimal comparative effectiveness research. Most trials compared a breathing retraining approach with some kind of control group. This was appropriate, given that effectiveness has not been well established for any treatment approaches. Nevertheless, once effectiveness is better established, it will be useful to be able to compare approaches with each other on effectiveness and acceptability to asthma patients.

Evidence Gaps

Evidence gaps for all treatment approaches were substantial. For hyperventilation reduction techniques, there was only a single large trial, and it had not yet been published in a peer-reviewed journal.[39] A fully published account of another large trial of at least fair-quality is crucial to confirm the effects seen in this review. None of the trials were conducted in the US, which would be important if it is to be considered for wide-spread adoption here. Once replication has established its effectiveness more firmly, then examination of components of care can be undertaken. Little evidence was found that was clearly and directly applicable to non-Caucasian adults.

No large-scale trial of yoga training was found, and little evidence was found that was applicable to the US.

No trials of IMT have been conducted in the US, and all trials we found were small, including no more than 25 participants per treatment arm, and most had serious methodologic limitations. Only one investigator in this area has undertaken a systematic program of research to examine effects in different populations, and this work is still in the early stages.

The literature for other nonhyperventilation reduction breathing techniques is in its infancy, and a strong theoretical basis is needed to support further research in these and the other techniques examined.

Future Research

In general, there was little consistency of asthma-related terms used in these trials, and terms were sometimes used vaguely or differently, making it difficult to characterize interventions.

Bruton and colleagues suggest components that should be described when characterizing breathing retraining, and we strongly support their recommendations to improve our

understanding of the interventions and to provide a framework for exploring differential effects of different components of breathing training.[117] They suggest including information on route (nasal or oral), rate (breaths per minute), depth (shallow, normal, etc.), inspiratory and expiratory flow speed, region (e.g., abdominal), timing, regularity (of volume, timing, rate), breath holds, repetitions, and whether manual assistance was involved. Careful and consistent descriptions of specific techniques used would allow exploration of effectiveness of specific elements.

Further evidence would be beneficial for all intervention types. In addition to detailing breathing retraining techniques as described by Bruton and colleagues, future studies should include outcomes of asthma symptoms, reliever medication use, quality of life, and pulmonary function at minimum.[117] Outcome measurements should be repeated over time with follow-up through at least 6 to 12 months. In addition, controller medication use should always be described. And, best practices regarding randomization, blinding, and followup are crucial to any further research in this area. Trials should include asthma treatment with medications and education that is consistent with the standard of care in the United States.

Given that the current state of the evidence differed across intervention approaches, specific suggested next steps by intervention approach include:

Hyperventilation Reduction Breathing Techniques:

- Replication of results of the large, good-quality trial with intensity-matched comparator and valid, blinded outcome assessment
- Trials focused on hyperventilation reduction techniques in children and older adults
- Trials that include substantial numbers of non-Caucasian participants
- Trials that attempt to isolate the necessity or efficacy of specific components of treatment

Yoga Breathing Techniques

- Well-designed and executed replication of a high-intensity approach in the US, without additional nonyoga components

IMT

- Replication of Weiner's 1992 trial,[50] with larger n, in the US.

Table 15. Strength of evidence

Outcome	Group	Number of studies	Risk of bias	Consistency	Directness	Precision	Strength of evidence	Comments
Key Question 1: asthma symptoms (global symptom severity or control, specific symptoms, exacerbations)	Hyperventilation reduction breathing technique versus control	7	Medium	Consistent	Direct	Imprecise	Moderate	Range of effects in 6 comprehensive interventions none to large, 4 of 6 reported benefit; 1 narrowly-focused trial showed no benefit for mouth-taping
	Yoga breathing technique versus control	5	Medium-High	Consistent	Direct	Imprecise	Low	4 of 5 trials report benefit, three with substantial quality concerns
	IMT versus control	2	Medium-High	Consistent	Direct	Imprecise	Insufficient	2 small trials with different populations and methods, both show benefit, one with high risk of bias
	Non-hyperventilation reduction breathing technique versus control	3	Medium	Consistent	Direct	Imprecise	Low	No benefit in trials using biofeedback or breathing device, mixed results in 1 trial of physiotherapy
	Hyperventilation reduction breathing technique versus nonhyperventilation reduction breathing technique	4	Medium	Consistent	Direct	Imprecise	Low	No trial found a benefit of one approach over another; both groups improved in 2 trials, neither group improved in 2 trials
Key Question 1: medication use (reliever)	Hyperventilation reduction breathing technique versus control	5	Medium	Consistent	Direct	Imprecise	Low	3 trials found reduction in reliever medication and 2 lowest-intensity trials did not.
	Yoga breathing technique versus control	2	Medium	Inconsistent	Direct	Imprecise	Insufficient	2 trials with substantial differences in intensity, location, and population and reported contradictory results
	IMT versus control	4	High	Consistent	Direct	Imprecise	Insufficient	4 trials, 3 by one author, 3 with high risk of bias, all show benefit on some measure at some time point

Outcome	Group	Number of studies	Risk of bias	Consistency	Directness	Precision	Strength of evidence	Comments
	Nonhyperventilation reduction breathing technique versus control	2	Medium	Consistent	Direct	Imprecise	Low	No benefit of treatment for any medication outcome in three trials
	Hyperventilation reduction breathing technique versus nonhyperventilation reduction breathing technique	3	Medium	Consistent	Direct	Imprecise	Low	Greater reduction in use with hyperventilation reduction breathing training in 2 of 3 cases, both groups improved in 1 trial
Key Question 1: medication use (controller)	Hyperventilation reduction breathing technique versus control	4	Medium	Inconsistent	Direct	Imprecise	Low	1 of 3 found large benefit, but raw data NR
	Yoga breathing technique versus control	1	High	N/A	Direct	Imprecise	Insufficient	1 trial with high risk of bias showed benefit of yoga
	IMT versus control	0	N/A	N/A	N/A	N/A	Insufficient	0 trials
	Nonhyperventilation reduction breathing technique versus control	3	Medium	Consistent	Direct	Imprecise	Low	No benefit of treatment for any medication outcome in three trials
	Hyperventilation reduction breathing technique versus nonhyperventilation reduction breathing technique	4	Medium	Inconsistent	Direct	Imprecise	Low	No differences in effectiveness in 3 of 4 cases
Key Question 1: quality of life	Hyperventilation reduction breathing technique versus control	4	Medium	Consistent	Direct	Imprecise	Low	Benefit found in 2 of 4
	Yoga breathing technique versus control	3	Medium	Consistent	Direct	Imprecise	Low	3 trials with mixed results, large effect seen in trial with shortest followup
	IMT versus control	0	N/A	N/A	N/A	N/A	Insufficient	0 trials
	Nonhyperventilation reduction breathing technique versus control	2	Medium	Inconsistent	Direct	Imprecise	Insufficient	2 trials with mixed results

Outcome	Group	Number of studies	Risk of bias	Consistency	Directness	Precision	Strength of evidence	Comments
	Hyperventilation reduction breathing technique versus nonhyperventilation reduction breathing technique	4	Medium	Consistent	Direct	Imprecise	Low	No differences in effectiveness in all cases, both groups improved in 1 trial
Key Question 1: Functioning or mental health	Hyperventilation reduction breathing technique versus control	4	Medium	Consistent	Direct	Imprecise	Low	2 of 2 found small benefit for anxiety and depression, 2 of 2 found mixed results for functioning
	Yoga breathing technique versus control	1	High	N/A	Direct	Imprecise	Insufficient	1 trial with substantial nonyoga components showed benefit
	IMT versus control	2	High	Consistent	Direct	Imprecise	Insufficient	2 trials with high risk of bias showing benefit, one in children, one in adults
	Nonhyperventilation reduction breathing technique versus control	1	Medium	N/A	Direct	Imprecise	Insufficient	1 trial with mixed results, benefit primarily seen on role limitations due to physical problems, not other subscales
	Hyperventilation reduction breathing technique versus nonhyperventilation reduction breathing technique	1	Medium	N/A	Direct	Imprecise	Insufficient	Single study showing greater benefit of Buteyko breathing training than yoga breathing training via device on some functioning subscales
Key Question 2: pulmonary function (FEV_1)	Hyperventilation reduction breathing technique versus control	5	Medium	Consistent	Indirect	Imprecise	Low	Small or no benefit found in all trials
	Yoga breathing technique versus control	5	Medium-High	Consistent	Indirect	Imprecise	Low	3 of 5 show benefit of yoga, all 3 high-intensity interventions, 2 with large effects
	IMT versus control	3	High	Inconsistent	Indirect	Imprecise	Insufficient	2 of 3 trials, two with high risk of bias
	Nonhyperventilation reduction breathing technique versus control	2	Medium	Consistent	Indirect	Imprecise	Insufficient	2 trials with different treatment approaches showing no benefit of treatment

Outcome	Group	Number of studies	Risk of bias	Consistency	Directness	Precision	Strength of evidence	Comments
	Hyperventilation reduction breathing technique versus nonhyperventilation reduction breathing technique	4	Medium	Consistent	Indirect	Imprecise	Low	No benefit for FEV_1 in any trials
Key Question 2: pulmonary function (PEF)	Hyperventilation reduction breathing technique versus control	3	Medium	Consistent	Indirect	Imprecise	Low	No benefit found in any trial
	Yoga breathing technique versus control	4	Medium-High	Consistent	Indirect	Imprecise	Moderate	3 of 4 show benefit of yoga, all 3 high-intensity interventions, 2 with large effects
	IMT versus control	1	High	N/A	Indirect	Imprecise	Insufficient	Single trial with large effect, high risk of bias
	Nonhyperventilation reduction breathing technique versus control	0	N/A	N/A	Indirect	N/A	Insufficient	0 trials
	Hyperventilation reduction breathing technique versus nonhyperventilation reduction breathing technique	1	High	N/A	Indirect	Imprecise	Insufficient	1 trial showing no benefit in either group
Key Question 3: harms	Hyperventilation reduction breathing technique versus control	3	Medium	Consistent	Direct	Imprecise	Low	None found adverse effects related to the intervention, one listed minor annoyances associated with mouth-taping
	Yoga breathing technique versus control	2	Medium	Consistent	Direct	Imprecise	Low	No adverse effects related to yoga
	IMT versus control	0	N/A	N/A	N/A	N/A	Insufficient	0 trials
	Nonhyperventilation reduction breathing technique versus control	0	N/A	N/A	N/A	N/A	Insufficient	0 trials

Outcome	Group	Number of studies	Risk of bias	Consistency	Directness	Precision	Strength of evidence	Comments
	Hyperventilation reduction breathing technique versus nonhyperventilation reduction breathing technique	2	Medium	Consistent	Direct	Imprecise	Low	No adverse effects related to interventions

Abbreviations: FEV_1: forced expiratory volume in 1 second; IMT: inspiratory muscle training; N/A: not applicable; PEF: peak expiratory flow

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Abbreviations and Acronyms

AHRQ	Agency for Healthcare Research and Quality
AMED	Allied and Complementary Medicine
ATS	American Thoracic Society
BTS	British Thoracic Society
CCRCT	Cochrane Central Register of Controlled Trials
CER	comparative effectiveness review
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CO_2	carbon dioxide
EPC	Evidence-based Practice Center
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
HRV	heart rate variability
ICS	inhaled corticosteroid(s)
ICTRP	International Trials Registry Platform
ISRCTN	International Standard Randomized Controlled Trial Number
IMT	inspiratory muscle training
LOCF	last observation carried forward
MANTIS	Manual, Alternative and Natural Therapy Index System
mcg	microgram(s)
NAEPP	National Asthma Education Program and Prevention
NHLBI	National Heart, Lung, and Blood Institute
PEDro	Physiotherapy Evidence Database
PEF	peak expiratory flow
RCT	randomized controlled trial
SABA	short-acting $beta_2$-agonists
SIP	scientific information packet
SMD	standardized mean difference
SRC	Scientific Resource Center
TEP	technical expert panel
UK	United Kingdom
US	United States
VC	vital capacity