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Clinically relevant effects of Mindfulness-Based Stress Reduction in individuals with asthma

Estelle T. Higgins [a], Richard J. Davidson [a,c,d], William W. Busse [b], Danika R. Klaus [b], Gina T. Bednarek [d], Robin I. Goldman [a], Jane Sachs [a], Melissa A. Rosenkranz [a,d,*]

[a] Center for Healthy Minds, University of Wisconsin-Madison, 625 W. Washington Ave, Madison, WI, 53703, USA
[b] Department of Medicine, University of Wisconsin School of Medicine and Public Health-Madison, 600 Highland Ave, Madison, WI, 53792, USA
[c] Department of Psychology, University of Wisconsin-Madison, 1202 W. Johnson St., Madison, WI, 53706, USA
[d] Department of Psychiatry, University of Wisconsin-Madison, 6001 Research Park Blvd, Madison, WI, 53719, USA

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ABSTRACT

Background: Psychological distress and comorbid psychopathology contribute to exacerbation risk in patients with asthma. Thus, interventions designed to reduce stress and improve emotion regulation, such as Mindfulness-Based Stress Reduction (MBSR), may augment standard care. Few studies have addressed this question and a paucity of data exists to determine the ability of MBSR to impact clinical outcomes in asthma.

Methods: This randomized controlled trial investigated effects of MBSR training on asthma control and airway inflammation, in relation to psychological symptoms, in adults with asthma. Participants were randomized to an 8-week MBSR training (n = 35) or wait-list control group (n = 34). Clinically relevant asthma assessments, including Asthma Control Questionnaire and inflammatory biomarkers, were collected at baseline and six approximately-monthly follow-ups. Self-reported mindfulness, distress, depression, and anxiety symptoms were assessed at baseline, post-intervention, and study completion. Chronic stress level was determined at baseline only.

Results: Asthma control improved significantly in individuals randomized to MBSR, relative to wait-list controls ($p = .01$; effect size $d = 0.76$), which was maintained at 4mo post-intervention. 32% of MBSR participants achieved a clinically significant improvement, based on the ACQ6 Minimally Important Difference, relative to 12% of wait-list participants. Moreover, MBSR-related improvement in asthma control was associated with a reduction in distress ($p = .043$) and the intervention was most efficacious for those with the highest baseline depressive symptoms ($p = .023$). Importantly, MBSR also reduced levels of exhaled nitric oxide, a biomarker of airway inflammation, relative to wait-list controls ($p < .05$).

Conclusion: Supporting and extending extant evidence of mind-body relationships in asthma and the benefits of stress reduction for these patients, this is, to the best of our knowledge, the first RCT to demonstrate that training in MBSR improves clinically relevant asthma outcomes. MBSR may thus be a valuable addition to optimal asthma management, particularly for those with comorbid psychopathology.

Clinical trial registration: NCT02157766.

1. Introduction

Mind-body interactions are well-documented in chronic inflammatory diseases, which are highly susceptible to stress-related exacerbations and psychological comorbidities. These linkages present a unique opportunity to evaluate effects of psychological interventions on clinical symptoms and underlying biological mechanisms. Asthma is a chronic inflammatory disease of the airways characterized by airway inflammation, airflow obstruction, and airway hyperresponsiveness, affecting approximately 8% of the population (*Most Recent National Asthma Data | CDC, 2019*). Its burden is substantial, particularly when poorly controlled: individuals reporting poorly controlled asthma demonstrate worse physical and mental health, and more work-related impairments, medical provider visits, and hospitalizations compared to those with well-controlled disease (Williams et al., 2009). Standards of care in asthma consist of controller and rescue medications directed

* Corresponding author. Center for Healthy Minds University of Wisconsin-Madison, 625 W. Washington Ave, Madison, WI, 53703, USA.
E-mail address: melissa.rosenkranz@wisc.edu (M.A. Rosenkranz).

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towards reducing airway inflammation and airflow obstruction (Global Initiative for Asthma [GINA], 2021). Achieving and maintaining asthma control, defined as the degree to which asthma symptoms and disease-related impairments are successfully managed by the individual, is the principal goal of asthma treatment (National Heart, Lung, and Blood Institute / National Asthma Education and Prevention Program [NHLBI/NAEPP], 2020). Recently, asthma care strategies have begun to target treatable traits, or individual characteristics most likely responsible for poor disease control (Agusti et al., 2016; McDonald et al., 2020).

Psychological factors contribute to poor asthma control and exacerbations. For example, mood and anxiety disorder risk in asthma is double that of the general population, and individuals with both asthma and psychopathology show increased asthma severity and functional impairment, poorer asthma control and quality of life, and greater healthcare utilization (Lu et al., 2012; Strine et al., 2008; Richardson et al., 2008). Chronic stress, which increases vulnerability to mood and anxiety disorders, also exacerbates asthma symptoms, likely through increasing airway inflammation (Chen and Miller, 2007; Forsythe et al., 2004). In particular, chronic stress has been shown to promote a shift toward Type 2 inflammatory responses (Chrousos, 2000). The interactions between psychological distress and asthma control and symptoms suggest that behavioral interventions designed to build skills in responding to challenging emotions and experiences, such as mindfulness meditation, should benefit asthma management when combined with standard care.

Mindfulness-Based Stress Reduction (MBSR) is the predominant mindfulness meditation intervention used in medical settings and consists of sustained focused attention on breath, bodily sensations, and mental content (Kabat-Zinn, 1990). Mindfulness-based interventions such as MBSR emphasize the examination of one's relationship to their emotions and sensations: the overall aim is not to reduce symptoms *per se*, but to bring nonjudgmental awareness to all experiences without clinging or avoidance, and thus to buffer the effects of psychological distress on physical symptoms. Though the focus of mindfulness training is not symptom reduction, this is frequently the result in populations with chronic medical illness (e.g., fibromyalgia (Cash et al., 2015), breast cancer survivors (Lengacher et al., 2016), chronic pain (Rosenzweig et al., 2010), and irritable bowel syndrome (Zernicke et al., 2013)). Mindfulness-based interventions have also been shown to reduce psychological distress and enhance quality of life (Wielgosz et al., 2019).

Adaptive psychological outcomes of MBSR are sometimes accompanied by reductions in stress-related biomarkers (Pascoe et al., 2017) and improved immune regulation (for review, see Black and Slavich, 2016). For example, Kabat-Zinn et al. (1998) found that adding mindfulness instruction to treatment as usual resulted in faster clearing of psoriasis lesions. After a 6-week mindfulness intervention, Bower et al. (2015) reported significant reductions in pro-inflammatory gene and transcription factor NF-κB activity in breast cancer survivors. Similarly, Witek Janusek et al. (2019) reported that MBSR was associated with lower IL-6 production and circulating TNF-α levels in women with early-stage breast cancer. In lonely older adults, Creswell et al. (2012) found that NF-κB-related gene expression and CRP levels were down-regulated following MBSR training. Overall, these studies provide evidence that mindfulness interventions can attenuate immune dysregulation in both clinical and non-clinical samples.

Given the evidence that mindfulness interventions can modulate both psychological and immune processes, they have promise for improving outcomes in diseases vulnerable to psychological influence, such as asthma. However, few randomized controlled trials (RCTs) have examined the impact of mindfulness training on clinically-relevant outcomes in asthma and among those that have, most do not assess inflammatory biomarkers of disease activity (for review, see López-Lois et al., 2020; Paudyal et al., 2018). Pbert et al. (2012), for instance, showed MBSR-related improvements in asthma-related quality of life, perceived stress, and medication use, but found no change in lung function and did not evaluate inflammatory biomarkers. Similarly, Manocha et al. (2002) showed transient improvements in mood and lung function after a Sahaja yoga intervention but did not assess inflammation.

Here, we aimed to determine the effects of MBSR training on asthma control and airway inflammation, in relation to distress, in adults with asthma. We hypothesized that MBSR training would decrease the effects of psychological distress on asthma control and inflammation, compared to a wait-list control group.

2. Materials & methods

2.1. Participants

A total of 73 adults with asthma, aged 18–65 years (M = 38.1, 43 female) were enrolled; one participant withdrew prior to data collection, one was discontinued after visit one due to protocol change and was excluded from all analyses (see Supplementary Materials for details), and one was excluded from analyses due to missing data (Fig. 1a). Two MBSR participants were excluded from longitudinal analyses for insufficient MBSR class attendance (<2 classes), resulting in a final sample size of 68 (40 female), not accounting for attrition (Fig. 1a). However, all participants were included in parallel intent-to-treat (ITT) analyses, with missing data imputed. A final sample size of n = 40 per group was our goal, determined by power analyses performed for multiple outcome variables. This sample size was expected to provide high power (>.80) for both local and systemic inflammatory outcomes, based on prior work with comparable sample sizes demonstrating high power to detect effects of MBSR training on local (n = 19; Rosenkranz et al., 2013) and circulating (n = 33; Pace et al., 2009) inflammation.

All participants had a physician's diagnosis of asthma for at least 6 mo, with airway inflammation based on at least 1 of 3 criteria: fraction of exhaled nitric oxide (FeNO) ≥30 ppb, blood eosinophil count ≥150 cells/μL, or percent sputum eosinophils ≥2% of total leukocytes, thus identifying a phenotype of asthma patients with Type 2 inflammation (GINA, 2021). Type 2 inflammation characterizes at least 50% of patients with asthma, with the remaining patients comprising a variety of endotypes that characterize small sub-groups (Fahy, 2015). FeNO of 30 ppb was selected as a midpoint between the threshold indicating presence of Type 2 inflammation (FeNO ≥20 ppb) and high FeNO (≥50 ppb) (Dweik et al., 2011; GINA, 2021). Exclusion criteria included taking >1000mcg Fluticasone or the equivalent, incompatibility with the magnetic resonance imaging (MRI) environment, and previous participation in an MBSR course or significant current practice of meditation or other mind-body techniques (i.e., current meditation practice or daily practice with techniques such as yoga or Tai Chi). Additionally, participants with ongoing medical conditions other than asthma were excluded based on the anticipated impact on participant safety, study outcomes, or ability to complete study procedures. All participants were non-smoking, non-pregnant, with no history of neurological disorder, traumatic brain injury, or bipolar or psychotic disorders. Participants taking limited psychotropic medications, including antidepressants and anxiolytics, were included provided they were on a stable dose for at least 6 months. See Supplementary Table 1 for details regarding participant medication use. Data were collected from 2014 to 2018 within a larger study that included participants without asthma. Participants were recruited from Madison, WI and surrounding areas using flyers and online and newspaper advertisements, in addition to a database of asthmatic individuals who had participated in previous asthma research (for more information, see clinicaltrials.gov NCT02157766). All study sites were located on the University of Wisconsin-Madison campus. The University of Wisconsin-Madison's Health Sciences Institutional Review Board approved the protocol, clinical trial registration was completed prior to recruitment and enrollment, and all participants provided written informed consent and were compensated monetarily,

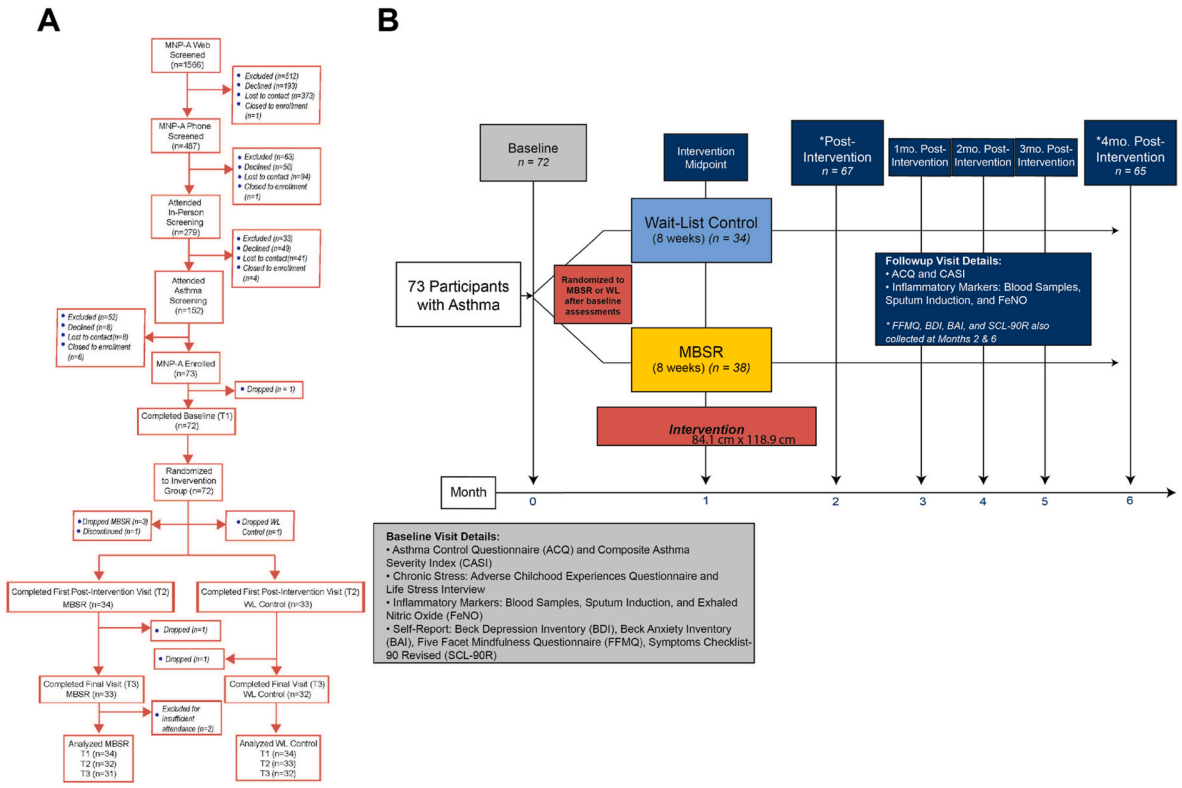

Fig. 1. (A) CONSORT diagram of participants' progress through screening, enrollment, initial visit, randomization, and follow-up visits. MNP-A: Meditation-Naive Participants with Asthma; MBSR: Mindfulness-Based Stress Reduction; WL: Wait-List. (B) Experimental design: baseline psychological measures, inflammatory markers, self-report asthma control and severity, and self-assessed mindfulness were collected prior to randomization to MBSR (n = 38) or wait-list (n = 34) groups. Follow-up visits all included ACQ6, CASI, and inflammatory marker assessment; visits at baseline, post-intervention, and 4mo post-intervention also included FFMQ, SCL-90R, BDI, and BAI assessments.

with bonuses for data collection completion and intervention attendance.

2.2. Study design

Data were collected at seven separate visits at approximately one-month intervals (Fig. 1b). The first visit (month 0) occurred at baseline, prior to randomization to MBSR (initial n = 38) or wait-list (n = 34) groups. The second visit (month 1) occurred at the intervention midpoint. The third visit (month 2) reflects the first post-intervention assessment, and the remaining visits occurred approximately monthly until the final visit (month 6) at approximately 4mo post-intervention. At every visit, self-reported asthma control and severity were assessed and FeNO measurements, sputum inductions, and blood draws were performed. Baseline, month 2, and month 6 visits also included additional self-report assessments and MRI scans (results reported elsewhere). Wait-list controls were offered MBSR, at no cost, after study completion.

2.3. Data acquisition

2.3.1. Asthma control & airway inflammation

2.3.1.1. Asthma control & severity. Clinically, asthma control questionnaires are used to diagnose, assess, and monitor asthma and to tailor treatment (Reddel et al., 2015). Here, asthma control is defined as the degree to which asthma symptoms and disease-related impairments are successfully managed by the individual (NHLBI/NAEPP, 2020) and was assessed using the Asthma Control Questionnaire 6-item version (ACQ6; Juniper et al., 1999a,b). The ACQ6 consists of five Likert-scale questions about symptoms including night awakenings, symptom frequency and severity, and disease-related activity limitations and one question about medication usage. Ratings are made on a 7-point scale indicating the degree of symptom-related impairment during the previous week, then averaged for a total score out of 6. The Composite Asthma Severity Index (CASI; Wildfire et al., 2012) quantifies asthma severity using a combination of impairment, future exacerbation risk, and treatment necessary to attain current levels of control. The questionnaire consists of eight items across multiple symptom and medication dimensions, which are summed for a total CASI score ranging from 0 to 20.

2.3.1.2. Fraction of exhaled nitric oxide (FeNO) & eosinophils (EOS). Fraction of exhaled nitric oxide (FeNO) is a non-invasive biomarker of airway inflammation in asthma which parallels, but has distinctions from EOS; both indicate airway inflammation and predict risks for exacerbations and airflow obstruction (Dweik et al., 2010). FeNO was measured at each visit in breath condensate, according to American Thoracic Society guidelines (NIOX System; Aerocrine, Solna, Sweden; Silkoff et al., 2004). Sputum and blood samples were collected to quantify eosinophilic inflammation. For sputum induction, participants were pre-treated with a beta-agonist to prevent bronchospasm, then inhaled a nebulized 3% buffered saline solution mist and produced sputum at 4-min intervals. Sputum was diluted 1:1 with a 1:10 concentration of dithiothreitol (DTT–SPUTOLYSIN ® Reagent, Calbiochem). Samples were shaken in a 37° water bath and centrifuged, then cytospins were prepared and stained with Giemsa to determine cell distributions. Venous blood samples were collected into EDTA-coated tubes. Slides were prepared for determination of cell differentials (lymphocytes, monocytes/macrophages, neutrophils, eosinophils, and basophils). Our analyses focused on sputum EOS percent and blood EOS total counts.

2.3.2. Self-report

2.3.2.1. Psychological assessments. The Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) each consist of 21 psychometrically validated Likert-scale questions measuring symptoms of depression and anxiety, respectively (Beck, 1961; Beck et al., 1988). Ratings are made on a 4-point scale ranging from 0 to 3 based on severity for each item, with higher scores indicating more severe depressive or anxiety symptoms (Beck et al., 1988). The Symptom Checklist-90 Revised (SCL-90R) consists of 90 Likert-scale questions in nine primary symptom dimensions (Derogatis et al., 1976). Ratings are made on a scale of 0–4, with higher scores indicating increased symptoms and/or severity. We evaluated two global indices: the Global Severity Index (GSI; mean of all items), which reflects both number of symptoms and level of distress, and the Positive Symptom Distress Index (PSDI; mean of items receiving non-zero response), which reflects the intensity of distress experienced (Derogatis et al., 1976).

2.3.2.2. Chronic stress. A composite of the Adverse Childhood Experiences Questionnaire (ACEIQ; World Health Organization [WHO], 2018) and UCLA Life Stress Interview (LSI; Hammen, 1991) scores, completed at baseline, served as a metric of chronic stress. The ACEIQ addresses childhood family dysfunction; abuse and neglect; and peer, community, and collective violence (WHO, 2018). Questions comprised 13 categories and scores were determined with binary scoring according to WHO guidelines, for a summary score ranging from 0 to 13. The LSI for adults (Hammen, 1991) was used to determine recent chronic life stressors. This semi-structured interview assesses individuals' level of function in multiple domains including: intimate relationships, close friendships, social life, family relationships, relationships with children (when applicable), work-life, finances, health of self, and health of family members. In each domain, function over the previous six months was assessed on a scale ranging from 1 (high) to 5 (low) in half-point increments. LSI and ACEIQ scores were each z-transformed, then summed to form the composite "chronic stress" score for each participant.

2.3.2.3. Mindfulness. The Five Facet Mindfulness Questionnaire (FFMQ) is a self-report measure of mindfulness consisting of 39 Likert-scale questions (Baer et al., 2006). Ratings are made on a 5-point scale across five mindfulness facets: Observing, Describing, Acting with Awareness, Non-judging of Inner Experience, and Non-reactivity to Inner Experience (Baer et al., 2006). Analyses here used a total score comprising all items.

2.4. Intervention

Mindfulness training consisted of a standard Mindfulness-Based Stress Reduction (MBSR) intervention, developed by Jon Kabat-Zinn at the University of Massachusetts Medical Center (Kabat-Zinn, 1990). MBSR training involves breath-focused attention, body scan, and mindful awareness in seated positions, walking, and yoga (Kabat-Zinn, 1990). Training was delivered within classes offered to the community, consisting of both study and non-study individuals (class size 15–18 total), by two certified and experienced MBSR instructors, over eight weekly 2.5hr sessions and one 6hr intensive retreat. Eleven cohorts of participants with asthma were enrolled, with 1–7 research participants per cohort. Multiple classes were available to each cohort, resulting in a total of 1–4 research participants with asthma in each class alongside non-study community members who enrolled for a range of individual reasons. The intervention took place at UW Health Integrative Medicine Clinic, WI Psychiatric Institutes and Clinics, UW Arboretum Visitor Center, or The American Center. Daily at-home practice was assigned and recorded by participants weekly. Analyses that include practice aggregate total practice minutes from the beginning of the intervention through study completion.

2.5. Data analysis

Linear regression was used to examine the relationship between psychological and asthma-related variables at baseline, with the "lm" function from the stats package in R (version 4.0.3; R Core Team, 2020). All outcomes reported were primary outcomes. Primary analyses focused on group differences in the change in primary outcomes over time. To assess effects of the intervention, linear mixed modeling was performed using the "lmer" function (Bates et al., 2015) from the lme4 package in R (R Core Team, 2020). P-values were computed using Satterthwaite's method, as implemented in the lmerTest library in R (Kuznetsova et al., 2017; R Core Team, 2020; SAS Institute Inc., 1978). Visit was included as a random effect, and a random intercept was incorporated to adjust for repeated within-subject measures. Models used the maximal random effect structure justified by the data. Secondary analyses included moderation effects to examine the differential impact of psychological variables on change in primary outcomes. These models included main effects of depression, anxiety, global severity index, positive symptom distress index, or baseline chronic stress, along with their interactions with group and visit and a random effect of change in psychological symptoms where applicable. Age and sex were included as nuisance covariates in all models. Analyses began with full models, including psychological variable × group × visit interactions, and omitted non-significant interaction terms through backwards model selection to identify the most parsimonious model. To assess the impact of practice, analogous models featured practice time main effects and interactions within MBSR participants only. Reported results have had influential outliers removed based on Cook's D, with a cutoff threshold of 20% of an F-distribution with p and n-p degrees of freedom, where p is the number of model parameters and n is the number of observations (Kutner et al., 2005). Cook's D values were calculated using the "cooks.distance" function and related to the f-distribution using the "qf" function, from the stats package in R (R Core Team, 2020). Effect size was computed using the "cohens_d" function from the effectsize package in R (Cohen, 1988; Ben-Shachar et al., 2020). Methods used for intent to treat analyses are described in Supplemental Materials.

3. Results

3.1. Baseline characteristics

Sample characteristics and descriptive statistics for all IVs and DVs at baseline are reported in Table 1. There were no statistically significant differences between MBSR and wait-list control groups at baseline in any variable assessed (see Table 1). At baseline, 12 participants reported uncontrolled asthma (ACQ6 $\geq$ 1.5) and 43 participants reported well-controlled asthma (ACQ6 $\leq$ 0.75), with the remainder reporting moderate control (0.75 < ACQ6 <1.5; NHLBI/NAEPP, 2020). Participants in the MBSR group attended 7.6 out of 9 classes (8 weekly classes + all-day intensive) on average (range = 3–9). Means and standard deviations for all outcome variables at each visit are reported in Table 2.

3.2. Intervention validation

Analyses of mixed effects models with FFMQ as the outcome revealed a significant main effect of visit ($t(64) = 3.28$, $p = .002$) and group × visit interaction ($t(64) = -2.356$, $p = .022$), reflecting an increase in mindfulness scores in MBSR participants, but not wait-list controls (Fig. 2). Analyses with each FFMQ sub-scale as the outcome show that these changes were driven by significant group × visit interactions in Non-judging of inner experience ($t(70) = -2.47$, $p = .016$), Non-reactivity to inner experience ($t(62) = -2.35$, $p = .022$), and Observing ($t(63) = -2.34$, $p = .022$).

The mixed effects analysis with PSDI as the outcome showed a significant group × visit interaction ($t(61) = 2.368$, $p = .021$), in which PSDI decreased for participants in MBSR, relative to the control group

Table 1
Baseline descriptive statistics and tests for group differences at baseline for all outcome and independent variables. Chronic stress scores are standardized Life Stress Interview (LSI) scores plus standardized Adverse Childhood Experiences Questionnaire (ACEIQ) scores.

Variable	Group Mean (Range)		p-value
	MBSR (n = 35)	Wait-List Controls (n = 34)	
Age (y)	39.1 (18–65)	37.33 (18–64)	.582
Duration (y since self-reported asthma onset)	18.8 (1–43)	19.8 (3–54)	.722
Childhood Onset (number of participants)	20	20	1
Asthma Control Questionnaire (ACQ6) Score	.8 (0–2.83)	.7 (0–2.67)	.441
Composite Asthma Severity Index (CASI) Score	2.6 (0–8)	2.4 (0–11)	.734
Five-Facet Mindfulness Questionnaire (FFMQ)	103.11 (70–138)	102.94 (73–133)	.967
Chronic Stress	.03 (−2.55-4.5)	.04 (−2.95-4.47)	.973
Beck Depression Inventory (BDI) Score	8.53 (0–26)	8.62 (0–30)	.954
Beck Anxiety Inventory (BAI) Score	6.03 (0–18)	7.09 (0–28)	.397
Global Severity Index (GSI)	0.43 (0.03–1.28)	0.37 (0–1.22)	.425
Positive Symptom Distress Index (PSDI)	1.35 (1–2.4)	1.24 (1–1.93)	.143
Fraction of Exhaled Nitric Oxide (FeNO) (ppb)	40.3 (7–117)	33.7 (6–111)	.279
Blood Eosinophil Count (cells/μL)	213. (17.6–704)	228 (17.6–686.4)	.709
Sputum Percent Eosinophils	2.9 (0–27.3)	1.3 (0–12.3)	.125
FEV_1 (liters)	3.2 (1.94–4.96)	3.3 (1.71–5.3)	.546
FEV_1% Predicted	90.1 (66–111)	93.1 (73–115)	.256

(Fig. 3). The analogous analyses with GSI and BDI as outcomes showed no significant effects, whereas BAI showed only a main effect of visit (t (61) = −2.34, p = .022).

3.3. ACQ6 & CASI

At baseline, ACQ6 was significantly positively associated with GSI (B = 0.658, t (66) = 2.7, p = .009), PSDI (B = 1.1, t (65) = 4.49, p < .001), BDI (B = 0.026, t (66) = 2.268, p = .027) and chronic stress (B = 0.164, t (66) = 3.518, p < .001), but not BAI across all participants (Fig. 4a, 4b, 4c, 4d).

Results of mixed effects models with ACQ6 as the outcome showed a significant group × visit interaction (t (371) = 2.581, p = .01), where ACQ6 improved significantly over time in the MBSR group, but not in the wait-list group (Fig. 5a). 32.26% of MBSR participants (n = 10) achieved the Minimally Important Difference (ACQ6 change ≥0.5) from baseline to final visit, versus 12.5% of WL participants (n = 4; X^2 (1, 63) = 3.56, p = .059). Analysis of mixed effects models with total CASI scores as the outcome revealed no significant effects.

Secondary analyses predicting ACQ6 change over time featured GSI, BDI, BAI, PSDI, FFMQ, or baseline chronic stress as moderators. Results of the mixed effects analysis with time-varying GSI as a moderator showed a significant 3-way interaction between GSI, group, and visit (t (85) = 2.05, p = .043). This effect was driven by a stronger association between the change in GSI and the improvement in ACQ6, for MBSR participants relative to wait-list controls (Fig. 5b). Specifically, the extent to which ACQ6 improved was related to the extent to which GSI improved in MBSR participants, whereas in the wait-list control group, change in GSI was unrelated to the change in ACQ6.

Results of the analysis with baseline BDI as a moderator, predicting ACQ6 change over time, showed a significant 3-way interaction between BDI, group, and visit (t (369) = 2.29, p = .023). Specifically, ACQ6

Table 2A
Means and standard deviations for all outcome variables, at each visit, by group. SCL90-R, BDI, BAI, and FFMQ were collected only at visits 1 (baseline), 3 (post-intervention), and 7 (4mo. post-intervention).

Group Mean (SD)														
Outcome	*Visit One*		*Visit Two*		*Visit Three*		*Visit Four*		*Visit Five*		*Visit Six*		*Visit Seven*	
	MBSR	WL	MBSR	WL	MBSR	WL	MBSR	WL	MBSR	WL	MBSR	WL	MBSR	WL
Asthma Control Questionnaire (ACQ6)	0.82 (0.62)	0.72 (0.68)	0.75 (0.53)	0.75 (0.65)	0.57 (0.44)	0.83 (0.88)	0.46 (0.47)	0.66 (0.71)	0.61 (0.64)	0.75 (0.66)	0.55 (0.42)	0.76 (0.66)	0.48 (0.45)	0.82 (0.89)
Fraction of Exhaled Nitric Oxide (FeNO)	39.76 (25.04)	33.68 (25.75)	34.12 (18.24)	37.23 (28.83)	33.81 (21.36)	34.73 (31.02)	30 (18.96)	37.29 (34.89)	35 (18.97)	36.28 (36.13)	30 (18.25)	34.23 (36.16)	29.29 (16.23)	34.94 (31.24)
Sputum Percent EOS	2.62 (5.3)	1.33 (2.55)	3.12 (4.93)	2.63 (3.36)	2.74 (3.35)	2.61 (6.65)	4.23 (11.17)	1.85 (3.43)	1.97 (3.94)	2.44 (4.43)	1.67 (1.93)	3.25 (6.77)	1.53 (3.5)	3.27 (8.17)
Blood EOS Count	187.91 (109.5)	227.73 (179.75)	221.02 (144.76)	275.93 (191.88)	223.85 (195.55)	260.04 (221.91)	205.54 (136.17)	257.48 (182.98)	205.99 (111.29)	274.22 (206.64)	203.13 (142.99)	286.34 (232.08)	173.16 (86.58)	255.75 (247.69)
Composite Asthma Severity Index (CASI)	2.5 (2.27)	2.41 (2.12)	2.35 (2.63)	2.42 (2.11)	1.91 (2.13)	2.73 (2.39)	1.75 (1.65)	2.75 (1.92)	2.29 (2.37)	2.91 (2.57)	2.17 (1.97)	2.88 (2.66)	2 (2.08)	2.94 (2.58)
Composite Asthma Severity Index (CASI) Medications	1.65 (1.98)	1.53 (1.28)	1.56 (2.03)	1.77 (1.75)	1.34 (1.73)	1.85 (1.73)	1.14 (1.35)	1.68 (1.47)	1.5 (2.24)	1.84 (1.69)	1.4 (1.63)	1.75 (1.52)	1.29 (1.77)	2.03 (1.87)

Table 2B
Means and standard deviations for all outcome variables, at each visit, by group. SCL90-R, BDI, BAI, and FFMQ were collected only at visits 1 (baseline), 3 (post-intervention), and 7 (4mo. post-intervention).

Group Mean (SD)						
Outcome	*Visit One*		*Visit Three*		*Visit Seven*	
	MBSR	WL	MBSR	WL	MBSR	WL
Beck Depression Inventory (BDI)	8.68 (5.91)	8.62 (6.92)	7.31 (7.31)	8.42 (7.16)	7.52 (7.21)	8.22 (7.81)
Beck Anxiety Inventory (BAI)	6.12 (4.46)	7.09 (5.83)	5.25 (3.82)	6.58 (5.85)	4.58 (3.66)	6.45 (5.56)
Positive Symptom Distress Index (PSDI)	1.36 (0.35)	1.24 (0.25)	1.26 (0.23)	1.26 (0.25)	1.26 (0.31)	1.28 (0.28)
Global Severity Index (GSI)	0.44 (0.33)	0.37 (0.27)	0.36 (0.27)	0.37 (0.27)	0.36 (0.31)	0.36 (0.3)
Five Facet Mindfulness Questionnaire (FFMQ)	103.03 (18.41)	102.94 (16.76)	106.22 (19.55)	101.16 (20.41)	108.97 (20.68)	103.16 (20.64)

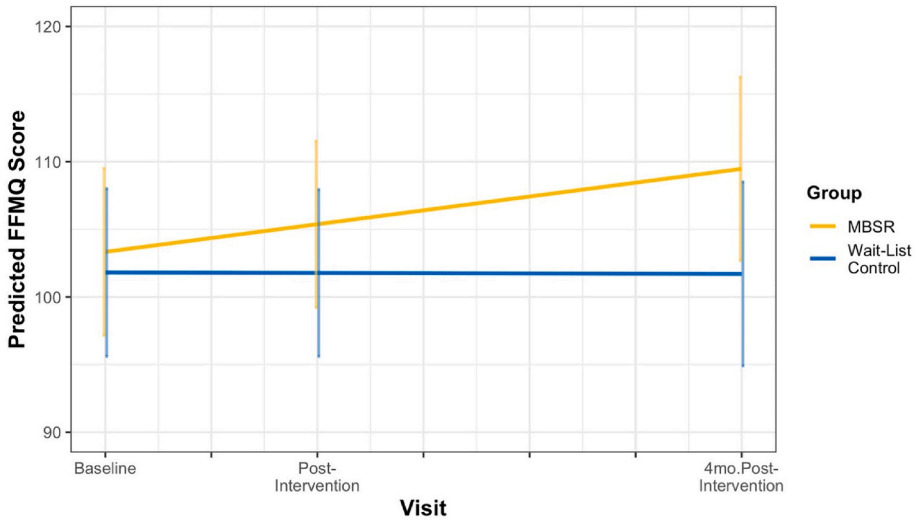

Fig. 2. Predicted Five-Facet Mindfulness Questionnaire scores over time. FFMQ scores improved significantly in those randomized to the MBSR intervention, but not wait-list controls ($p = .022$). 95% confidence bars are based on predicted mean estimate ± 1.96 times the standard error.

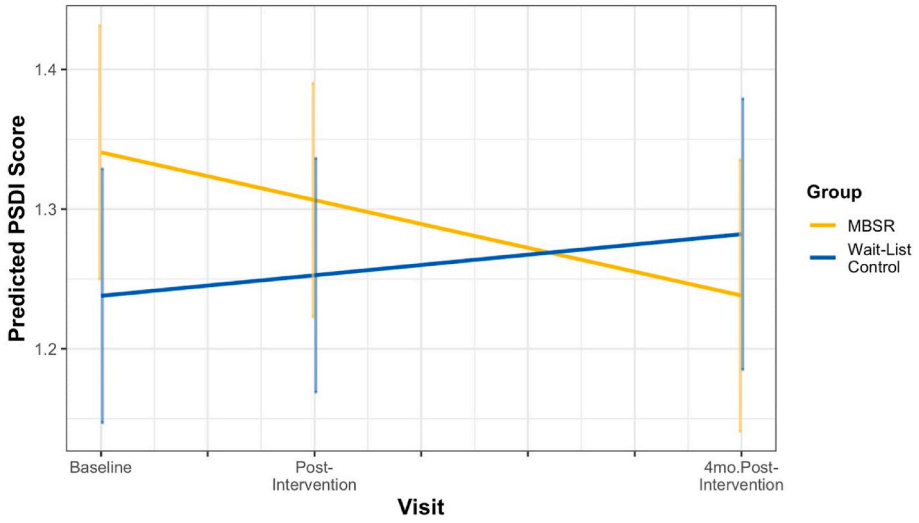

Fig. 3. Predicted Positive Symptom Distress Index (PSDI) scores over time. Distress (PSDI scores) decreased significantly over time in those randomized to the MBSR intervention, relative to wait-list controls ($p = .021$). 95% confidence bars are based on predicted mean estimate ± 1.96 times the standard error.

scores improved to a greater extent over time for MBSR participants with higher baseline depression compared to those with lower baseline depression scores (Fig. 5c). In the wait-list control group, ACQ6 worsened numerically over time for those with higher baseline depression scores, but this change was not significant.

Analyses that included BAI, chronic stress, time-varying BDI, PSDI, or FFMQ as moderators to predict ACQ6 did not show any moderating effects of these psychological variables; only significant group × time interactions were found, that recapitulate the analyses without moderators reported above.

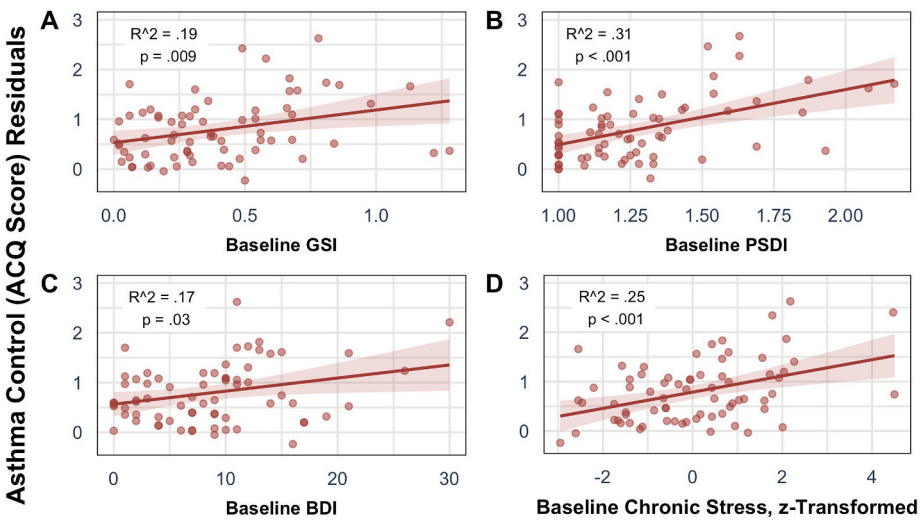

Fig. 4. (A,B,C,D) Relationship between asthma control and psychological symptoms at baseline, adjusted for age and sex. Asthma control (ACQ6 score) is positively associated with A) global severity index (GSI; B = 0.66, p = .009), B) positive symptom distress index (PSDI; B = 1.11, p < .001), C) depression (BDI; B = 0.026, p = .013), and D) chronic stress (B = 0.164, p < .001) at baseline. All models were assessed for influential outliers using cook's d with a cutoff of >20% of the f-distribution, and all final models and plots exclude influential outliers where applicable. Lower ACQ6 scores reflect better asthma control.

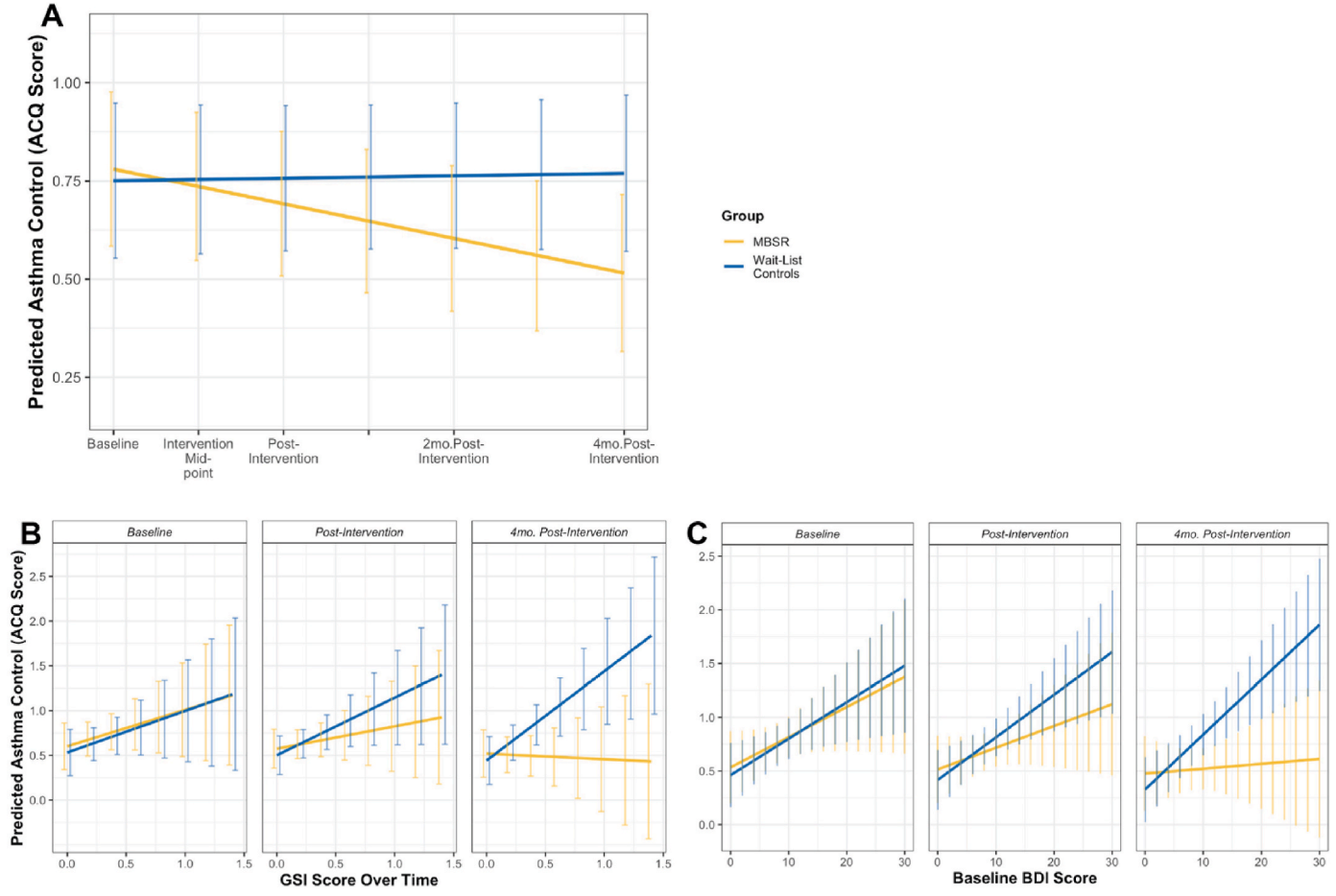

Fig. 5. (A) Predicted asthma control (ACQ6 scores). Asthma control improved significantly in participants assigned to the intervention, but not wait-list controls (group × visit interaction p = .01, main effect of visit p = .001). (B) Predicted association between change in global symptoms (GSI scores) and asthma control (ACQ6 scores) over time. Greater intervention-related improvement in asthma control was associated with greater decreases in global symptoms, relative to wait-list controls (GSI x group × visit interaction p = .043). (C) Predicted association between baseline depressive symptoms (BDI) and asthma control (ACQ6 scores) over time. For participants with higher baseline depressive symptoms, asthma control improved with participation in the intervention, but not for wait-list controls (baseline BDI x group × visit interaction p = .0226). 95% confidence bars are based on predicted mean estimate ± 1.96 times the standard error. Lower ACQ6 scores reflect better asthma control.

3.4. Inflammatory markers

Results of the primary analysis predicting change in FeNO over time showed a significant main effect of visit where FeNO declined over time in both groups (t (65) = −2.348, p = .022). Secondary analyses including time-varying BDI, BAI, GSI, and PSDI as moderators all

showed significant or marginal group × visit interactions, but no moderating relationships, such that FeNO decreased more over time for those in the MBSR group, relative to wait-list controls (BDI t (73) = 2.04, p = .045; BAI t (74) = 2.01, p = .048; GSI t (73) = 1.96, p = .054; PSDI t (77) = 1.78, p = .08) (see Fig. 6). Secondary analyses including baseline BAI, BDI, or chronic stress as moderators to predict change in FeNO all showed significant main effects of visit (BAI t (63) = −2.42, p = .019; BDI t (65) = −2.35, p = .022; chronic stress t (65) = −2.35, p = .022). The model including FFMQ as a moderator showed no significant effects.

Results of the primary analysis predicting change in sputum EOS over time showed no significant effects. Secondary analyses predicting change in sputum EOS over time included BAI, BDI, GSI, PSDI, FFMQ, or baseline chronic stress as moderators. Results of the analysis including baseline BAI as a moderator revealed only a marginal 3-way interaction (t (310) = 1.65, p = .0998), driven by a decrease in sputum EOS in the MBSR group, relative to controls, for those with the highest baseline anxiety. All other analyses that included psychological moderators showed no significant main effects or interactions.

Analyses featuring change in blood EOS count as the outcome showed no significant effects. Similarly, secondary analyses including BAI, BDI, GSI, PSDI, FFMQ, or baseline chronic stress as moderators yielded no significant group differences over time. All model details can be found in Supplementary Tables.

The results of ITT analyses were largely consistent with the results described above. All ITT analyses and their results are described in detail in Supplementary Materials.

3.5. Practice

MBSR participants, including those who attended fewer than 2 training sessions, reported a median of 1717 min of practice (range 0–6884) from baseline to study completion. Total practice includes that completed both in class and at home. Results of mixed effects analyses with total self-reported practice minutes predicting psychological or inflammatory variables and their interactions showed no significant effects of practice.

4. Discussion

In a randomized controlled trial of an 8-week MBSR intervention in adults with asthma, we found that asthma control improved significantly over time in those randomized to MBSR, relative to wait-list controls, and was accompanied by an increase in self-reported mindfulness and a decrease in psychological distress. Improvements in asthma control were bolstered by an MBSR-related decrease in FeNO, relative to the wait-list group. Previous studies have shown improvements in perceived stress, psychological symptoms, and asthma-related quality of life, but this is the first RCT to demonstrate the efficacy of MBSR training in improving disease control and biomarkers of airway inflammation in asthma. Importantly, MBSR was associated with a medium to large improvement in asthma control ($d = 0.76$), whereas the few RCTs that have evaluated between-group effects of complementary interventions over time on asthma control (e.g., breath training, buteyko training) have shown small to medium effect sizes (Thomas et al., 2008; Prem et al., 2013), with the exception of a large effect of progressive muscle relaxation and biofeedback (Georga et al., 2019).[1] Additional RCTs have reported *within-group* changes, with effect sizes that range from small to large, of mindfulness (Ainsworth et al., 2022) or biofeedback (Meuret et al., 2007) on asthma control, but no group differences in change over time. Moreover, in our sample 32.3% of MBSR participants achieved a Minimally Important Difference (MID; change in total score ≥0.5) for the ACQ6, indicating clinically meaningful change in asthma control as determined by the NAEPP Expert Panel Working Group (NHLBI/NAEPP, 2020), compared to only 12.5% of WL participants. The overall mean ACQ6 score change of −0.29 in the MBSR group, though not reaching MID, is on par with placebo-controlled pharmacological treatment-related changes in ACQ6 score, which typically range from −0.1 to −0.36 (Bateman et al., 2015).

National guidelines emphasize the evaluation of asthma control, alongside severity and lung function, to inform asthma diagnosis and treatment (GINA, 2021; Reddel et al., 2015). As such, asthma treatment aims to maximize disease control, reduce impairment, and minimize future exacerbation risk (GINA, 2021). FeNO is used to directly monitor airway inflammation and assess treatment responsivity, with lower FeNO reflecting reduced disease activity and better control (Barnes et al., 2014; Dweik et al., 2011). Asthma control, as assessed by the ACQ6, reflects objective asthma manifestations and is clinically relevant to disease management: higher ACQ6 scores, indicating poorer asthma control, have been associated with elevated inflammatory biomarkers (Demarche et al., 2017), significant asthma burden, and increased healthcare utilization (NHLBI/NAEPP, 2007).

Prior research indicates that poorer asthma control is associated with higher psychological comorbidities (Strine et al., 2008) and perceived stress (Wisnivesky et al., 2010), and that psychological triggers predict increased asthma symptoms, exacerbations, and the need for emergency treatment (Ritz et al., 2015a,b). Our data meaningfully support and extend such findings, indicating clinically relevant interactions between emotions and asthma control. Participants in our study with higher psychological distress, depressive symptoms, or chronic stress reported poorer asthma control at baseline. Importantly, the intervention was most efficacious for those with the highest depressive symptoms at the outset. Depressive symptom scores ranged from 0 to 30 in our sample, and approximately 41% had scores greater than or equal to 10 at baseline, indicating the presence of at least mild depression (Beck et al., 1988). While depression symptoms were not significantly impacted by MBSR training, psychological distress was reduced and training-related improvements in asthma control were associated with a decrease in global distress symptoms over time (as indexed by the global severity index), relative to wait-list controls. Specifically, asthma control improved most in those who experienced a greater decrease in symptoms of distress. This provides direct support for our hypothesis that MBSR buffers the effects of psychological distress on asthma control and provides valuable corroborating evidence that an intervention that targets one's relationship to their emotions modifies disease outcomes to the greatest extent in those with more dysregulated emotion. Indeed, comorbid psychopathology has been identified as a "treatable trait" predicting poorer asthma outcomes (McDonald et al., 2019). Also considering the increased burden individuals with comorbid psychopathology and asthma experience, our data suggest that MBSR can augment standard care and help decrease asthma burden, particularly for those with greater psychological symptoms.

In addition to improvements in asthma control, MBSR was associated with reductions in FeNO. FeNO is a marker of Type 2 airway inflammation, which defines the predominant asthma endotype (Fahy, 2015), and is a valuable tool for preventative care in asthma because it shows elevations in advance of deterioration in disease control (Kharitonov and Barnes, 2000). Furthermore, FeNO is an airway epithelial-derived product reflecting an inflammatory response to the cytokine IL-13, identifying a component of Type 2 inflammation distinct from eosinophil-mediated inflammation (Couillard et al., 2022). This suggests that the IL-13 pathway may be a target in the reduction of FeNO with MBSR training. Although lower FeNO is typically associated with positive asthma outcomes, its attenuation by stress hormones complicates interpretation of relationships between psychological factors and FeNO (Ritz et al., 2011) and assessment of the impact of stress-reduction

[1] Effect sizes were calculated only for studies with sufficient information. Other RCTs examining the impact of complementary interventions—including self-regulation (Baptist et al., 2013) and breathing retraining (Grammatopoulou et al., 2011)—on asthma control did not include sufficient information to calculate an effect size for asthma control.

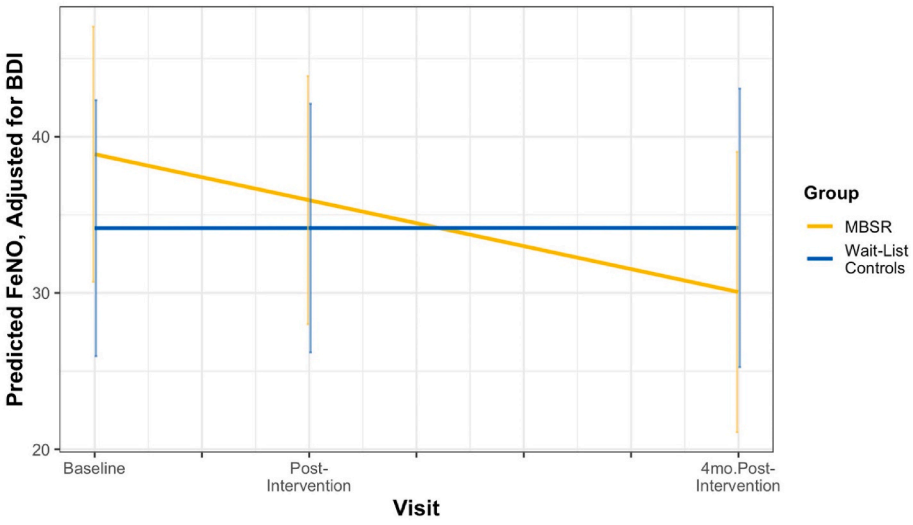

Fig. 6. Predicted Fraction of Exhaled Nitric Oxide (FeNO) levels over time, adjusted for depressive symptoms (BDI). FeNO decreased significantly for participants assigned to the intervention, but not wait-list controls, when accounting for variance in FeNO contributed by depressive symptoms (group × visit interaction $p = .045$, main effect of visit $p = .006$). Analogous interactions were significant when adjusting for anxiety symptoms, and trend-level for psychological distress and global symptoms. Plotted predicted values are adjusted for mean BDI. 95% confidence bars are based on predicted mean estimate ± 1.96 times the standard error. Lower FeNO reflects reduced airway inflammation.

interventions. For instance, despite positive associations between acute stress or anxiety and FeNO (Ritz and Trueba, 2014), depression and prolonged stress have been associated with decreases in FeNO—effects linked to an increase in cortisol (Ritz et al., 2015a,b). Some of these patterns were also apparent in our data, and accounting for the variance in FeNO associated with these psychological symptoms revealed beneficial effects of the intervention on FeNO.

Despite sustained improvements in asthma control and modest improvements in FeNO, MBSR did not have a significant impact on changes in eosinophil populations in our study. It is possible that we simply lacked sufficient power to detect small-to medium-sized effects on this outcome with our moderate sample size. Indeed, there was a trend-level effect showing an MBSR-related reduction in sputum eosinophils for those with the highest baseline anxiety symptoms, suggesting that a larger sample may have provided sufficient power to detect direct changes in eosinophilia. Alternatively, our results may indicate different regulatory mechanisms. Eosinophils and FeNO both reflect inflammation in asthma but are under different regulatory pathways and relationship to asthma control (Couillard et al., 2022). In contrast with FeNO, eosinophils are regulated by IL-5 and associated with severe asthma exacerbations, usually caused by viral respiratory infections and eosinophil recruitment to the airways (Price et al., 2015). Thus, reductions in FeNO may identify IL-13, rather than IL-5-mediated pathways, as the target of regulation by MBSR.

Though not measured in the current study, shifts in autonomic balance may contribute to the observed improvements in asthma control via both Type 2 and non-Type 2-mediated pathways. Catecholamines released as part of sympathetic activation during the stress response can bias the immune system toward Th2 cytokine responses, promote EOS and mast cell degranulation that is central to provoking asthma symptoms (Chen and Miller, 2007; Elenkov et al., 2000), and enhance nitric oxide production (Chi et al., 2003). Catecholamine-induced changes to the propensity for degranulation of EOS and mast cells would not be captured by our measures of EOS abundance but may be reflected in the changes we observed in FeNO. Although a mechanistic role for the autonomic nervous system here is speculative, prior studies have shown reductions in circulating catecholamines (Curiati et al., 2005) or their metabolites (Kopf et al., 2014), as well as reductions in sympathetic activity following mindfulness-based interventions in both clinical and non-clinical samples (Pascoe et al., 2017; Duchemin et al., 2015).

In addition to reductions in Type 2 inflammation, indicated by FeNO, other inflammatory signaling pathways not measured here may contribute to the observed improvement in asthma control. For example, neurogenic inflammation, via release of sensory neuropeptides in the airway, is one important pathway through which psychological stress contributes to airway inflammation in asthma (Rosenkranz, 2007). In a prior study, we showed relative reductions of neurogenic inflammation in skin in healthy volunteers following MBSR training (Rosenkranz et al., 2013), as well as in healthy long-term meditators relative to non-meditating controls (Rosenkranz et al., 2016). Further, meta-analyses of RCTs examining mindfulness-based intervention effects on peripheral immune function show decreases in proinflammatory gene expression and transcription factor NF-κB (Bower and Irwin, 2016; Black and Slavich, 2016), as well as reductions in C-reactive protein and TNF-α (Pascoe et al., 2017). Though these are not the canonical Type 2 immune responses typically associated with the pathophysiology of asthma, they have been shown to contribute to the expression of asthma and poor control (Jiang et al., 2014; Navratil et al., 2009; Ricciardolo et al., 2016). These alternative possibilities provide a rich set of hypotheses that should be tested in future research.

Subsequent studies should also consider whether mindfulness interventions are particularly effective for those with specific characteristics (i.e., personalized medicine). For instance, asthma prevalence is higher in females (Most Recent National Asthma Data | CDC, 2019) and historically, females are more likely to seek out mindfulness training (Upchurch and Johnson, 2019). Indeed, approximately 59% of our sample was female. Although our sample was too small to examine effects of MBSR stratified by sex, future research should evaluate whether the effects of mindfulness differ depending on sex, intervention choice, or personal characteristics, in order to better understand who may benefit most from training in mindfulness.

The interplay between distress and asthma control we report here calls attention to the important contributions of the brain in the expression of inflammatory diseases and highlights the value of interventions that target the mind and brain in the treatment arsenal. Distress impacts peripheral physiology through the descending modulatory influence of emotion-related neural circuits (Eisenberger and Cole, 2012); given the nature of MBSR, the observed improvements in asthma control are likely mediated by the accumulation of small, but persistent shifts in stress appraisal and emotion regulation over time, which downregulate distress and the accompanying peripheral sequelae. There is a growing evidence base that implicates components of stress and emotion-related neural circuitry in both the modulation of peripheral inflammation (for review, see Kraynak et al., 2018) and changes associated with meditation training (for review, see Fox et al., 2016). Our results offer a promising direction for research addressing the neural mechanisms underlying the influence of psychological interventions in asthma.

4.1. Limitations

An important limitation of the current study is the absence of an active control group. Though a wait-list control group was employed to control for variation in outcome measures over time, it is possible that effects reported here were driven by factors that are not specific to training in mindfulness, such as social support or expectancy effects. Indeed, our group has pioneered the development and championed the use of well-matched active control interventions in studies of MBSR (MacCoon et al., 2012). This was a known limitation of our experimental design and was included for reasons of feasibility in the context of the larger study. Nonetheless, this does limit the conclusions that we can draw from our data and future studies are needed to determine the specific effects of mindfulness training on clinical improvement in asthma.

5. Conclusion

Overall, our data suggest that MBSR training was effective in reducing psychological distress, FeNO, and the degree of asthma symptom-related impairments — a clinical improvement that achieved a Minimally Important Difference in approximately one third of MBSR participants, maintained at 4mo post-intervention. Concomitant intervention-related decreases in FeNO corroborate the clinical relevance of this improvement and provide some insight into its biological basis. In addition, we extend prior evidence that psychological factors contribute to asthma, and that an intervention that targets stress and affective responsivity can improve asthma control, particularly for those with more dysregulated emotion. Since the overall goal of asthma treatment and long-term management is to improve asthma control, the patterns we observed here advance MBSR as an effective and accessible behavioral option to augment and potentially reduce the need for pharmacological treatment approaches. Furthermore, as incorporation of the concept of treatable traits into asthma management grows, MBSR may prove to be an effective intervention to reduce the contribution of psychological factors to morbidity, and improve overall disease control.

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Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Declaration of competing interest

Dr. Richard J. Davidson is the founder, president, and serves on the board of directors for the non-profit organization, Healthy Minds Innovations, Inc. No donors, either anonymous or identified, have participated in the design, conduct, or reporting of research results in this manuscript. All other authors have nothing to disclose.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2022.100509.

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