Effects of Mindfulness-Based Stress Reduction on Airway Inflammation in Individuals with Asthma

**Estelle T. Higgins**a, William W. Busseb, Richard J. Davidsonc,d, Greg J. Normana, and \*Melissa A. Rosenkranzc,e

a: Department of Psychology, University of Chicago, Chicago, IL 60637

b: Department of Medicine, University of Wisconsin-Madison, Madison, WI 53792

c: Center for Healthy Minds, University of Wisconsin-Madison, Madison, WI 53703

d: Department of Psychology, University of Wisconsin-Madison, Madison, WI 53706

e: Department of Psychiatry, University of Wisconsin-Madison, Madison, WI 53719

*ethiggins@uchicago.edu*

marosenk@wisc.edu

*Abstract*—Chronic inflammatory diseases such as asthma are highly vulnerable to exacerbations by psychological stress and have high comorbidity with mood and anxiety disorders. Mindfulness-based stress reduction (MBSR), the leading meditation training in healthcare settings, has been shown to decrease stress, reduce psychological symptoms, and improve physical symptoms. Given its psychological and physiological targets, MBSR has promise as an intervention in asthma, a disease marked by interactions between psychological and physiological symptoms. Yet, MBSR’s ability to impact the pathology in specific clinical populations remains largely unexplored. We investigated the effects of an 8-week MBSR training, relative to a wait-list control group, on the association between inflammation, chronic stress, and mood and anxiety symptoms in adults with asthma. Chronic stress and symptoms of depression and anxiety were determined at baseline and clinically-relevant inflammatory markers were collected at baseline and six monthly follow-ups. Results show that asthma control improved significantly over time in individuals randomized to MBSR, relative to controls. Furthermore, chronic stress was increasingly associated with higher sputum eosinophils over time in controls, but those receiving MBSR training were protected from this effect. Supporting and extending existing evidence of bidirectional brain-body communication, our findings suggest that training in MBSR improved asthma control and buffered effects of psychological stress on eosinophilic inflammation. MBSR may thus be a clinically valuable adjunct to asthma treatment.

# Introduction

Brain-body interactions are distinctly evident in diseases of chronic inflammation, which are highly susceptible to stress-related exacerbations and psychiatric comorbidities—offering a critical opportunity to assess the relationships between stress, psychological symptoms, and objective markers of inflammation, and to evaluate the effects of psychological interventions.

Asthma is characterized by chronic airway inflammation and acute episodes of bronchial constriction, and affects approximately 10% of the population.1 During inflammatory responses, upper and lower airways are preferentially targeted by eosinophils (EOS), white blood cells which mediate allergic responses and diseases, and which may cause local damage upon activation.2 Indeed, elevated EOS in asthma are significantly related to poor lung function measures, worsening clinical symptoms and contributing to disease severity.3

Notably, chronic inflammatory diseases like asthma are highly susceptible to psychological influence. Chronic stress is important in exacerbating asthma symptoms; likely through a heightening of airway inflammation.3,4 For instance, repeated or long-term stress is associated with significantly higher inflammatory markers, including elevated EOS values, in both rodent models of asthma and humans with asthma.4,5

In addition to stress, asthma is reciprocally associated with mood and anxiety disorders. The risk for mood or anxiety disorders in asthmatics is double that of the general population and asthmatic individuals with mood and anxiety disorders show increased symptom severity and functional impairment, poorer symptom control and quality of life, and more medical visits and pharmacy fills.6,7,8 Therefore, alongside individual consequences, asthma and psychological comorbidity poses significant economic and public health burden.

Given these associations, this clinical population provides an ideal chance to investigate the effects of an intervention designed to target both physiological and psychological processes through mental training. Mindfulness-Based Stress Reduction (MBSR) is the predominant mindfulness meditation intervention used in clinical settings, consisting of sustained focused attention on the breath, bodily sensations, and mental content.9 During training, practitioners develop an open accepting awareness of what is occurring in the moment, without judgment or reactivity.

Mindfulness-based interventions (MBIs) such as MBSR have been shown to reduce perceived stress and psychological symptoms and to enhance quality of life.10  Furthermore, MBIs are associated with reductions in peripheral biomarkers of immune system activity involved in disease pathogenesis, such as pro-inflammatory processes, and increases in cell-mediated defense parameters.11 MBIs appear to mitigate the effects of stress on inflammation, furthering the hypothesis that psychological states and immune processes influence one another reciprocally. However, there is a paucity of quality evidence examining how mindfulness impacts pathology in specific clinical populations. In particular, MBSR’s ability to impact inflammatory processes and psychological symptoms in asthma remains largely unexplored.12 Given the evidence that MBIs can target both psychological and physiological processes, they have potential to alleviate symptoms in diseases marked by the interaction of psychological and physiological symptoms. Behavioral treatments for such chronic inflammatory conditions may provide a low-cost and accessible addition to improve symptom reduction and disease control, reducing significant personal, public health, and economic burdens.

We aimed to determine the effects of MBSR training on the relationship between airway inflammation, chronic stress, and mood and anxiety symptoms in adults with asthma. We hypothesized that participating in an MBSR intervention would decrease the effects of chronic stress and mood and anxiety symptoms on asthma-related inflammation, compared to a wait-list control group.

# Methods

***Participants*.** This project took place in the context of a larger study including both asthmatic and non-asthmatic participants, approved by the Health Sciences Institutional Review Board at the University of Wisconsin-Madison. A total of 72 asthmatic participants ages 18-65 (mean 38.3y, 42 female) were enrolled; one participant was excluded due to missing data and two MBSR participants were excluded for insufficient class attendance (total n = 69, 42 female).

***Study Design*.** Data were collected at a minimum of three and a maximum of seven visits at approximately one-month intervals. Each visit consisted of pulmonary assessments of airway inflammation, blood draw, MRI scans, and self-report assessments. MRI data are reported elsewhere. The first visit (1) occurred at baseline, prior to randomization. The second visit (2) reflects the first post-intervention assessment, and the final visit (7) occurred approximately six months post-intervention.

***Data Collection*.** The metric of chronic stress used here is a composite of standardized Adverse Childhood Experiences Questionnaire and UCLA Life Stress Interview scores, completed at baseline.13,14 Depression and anxiety were determined at baseline (Visit 1) using the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI).15,16 Mindfulness was assessed over time using the Five Facet Mindfulness Questionnaire (FFMQ) at baseline (Visit 1), Visit 2, and Visit 3.17 Participants completed the Asthma Control Questionnaire (ACQ) and Composite Asthma Severity Index (CASI) at all visits.18,19

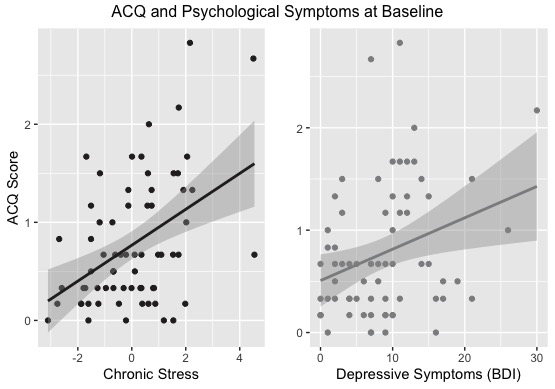
Sputum and blood samples were collected at each visit to quantify the magnitude of inflammation. For collection of sputum, participants inhaled a nebulized 3% saline solution mist and produced sputum at 4-minute intervals. Sputum was diluted, shaken and centrifuged, then prepared and stained with Giemsa to determine cell distributions. To determine blood EOS, counts per 300 cells were used for leukocyte differentials. Fraction of exhaled nitric oxide (FeNO), a non-invasive biomarker of airway inflammation in asthma, was measured at each visit in breath condensate, according to American Thoracic Society guidelines.

***Intervention.*** Participants were randomly assigned to MBSR training (n = 35) or to a wait-list control group (n = 34) after completing baseline assessments. The mindfulness training was a standard eight-week MBSR intervention modeled after that developed by Jon Kabat-Zinn at the University of Massachusetts Medical Center.9 Training was delivered in the context of classes offered to the community, by two certified and experienced MBSR instructors, and daily at-home practice was assigned.

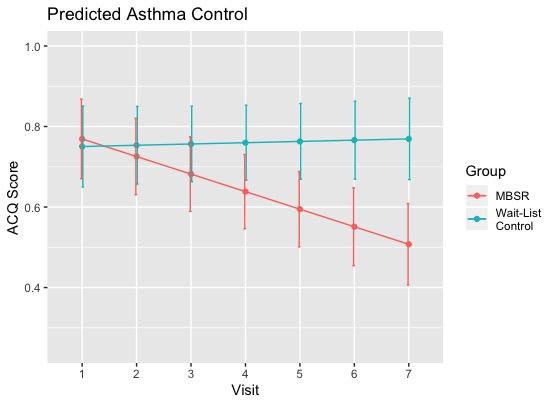
***Statistical Analyses.*** To assess effects of the intervention, analyses of immune measures and asthma control and severity across time were performed using mixed effects models. Models featured main effects of baseline values of chronic stress, depression, and anxiety along with their interactions with group and visit, and covariates of age and sex. Group and visit were added as random effects and a random intercept was included to adjust for repeated within-subject measures. Models included the maximal random effects structure justified by the data. To identify the most parsimonious model, analyses began with full models and omitted non-significant interaction terms.

# Results & discussion

***Mindfulness****.* Analyses of FFMQ revealed a significant main effect of visit (t(64) = 3.279, p = .002) and group x visit interaction (t(64) = -2.356, p = .022), reflecting an increase in mindfulness scores in MBSR participants, but not controls.

***ACQ & CASI.*** At baseline, ACQ was significantly associated with chronic stress (t(64) = 4.162, p < .001) and BDI (t(64) = 2.553, p = .013) for all participants (Fig. 1). Analyses of ACQ over time revealed a significant main effect of visit (t(374) = -3.35, p = .001) and group x visit interaction (t(372) = 2.556, p = .011), where ACQ decreased significantly in the MBSR, but not control, group (Fig. 2). There were no significant effects with CASI.

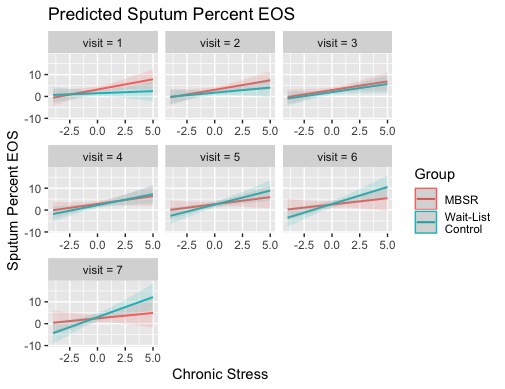
## Fig. 1: Asthma Control is positively associated with chronic stress (p < .001) and depression (p = .013) at baseline.

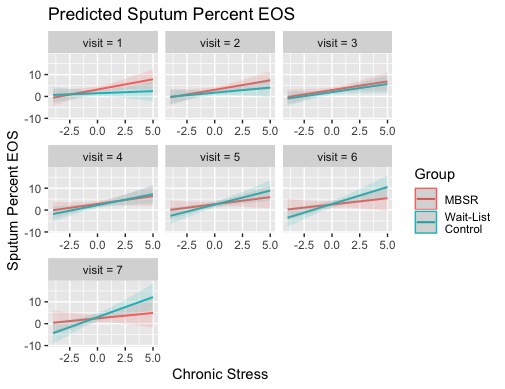


## Fig. 2: Asthma Control improves significantly with training in MBSR, but not in wait-list controls (p = .001).

***Eosinophils****.* Blood EOS count did not differ between MBSR and wait-list groups at baseline (t(54) = -0.899, p = .372). Analyses revealed a significant chronic stress x group interaction (t(60) = 2.53, p = .014), such that the wait-list group showed a strong positive relationship between chronic stress and blood EOS count, but the intervention group showed a weakly negative association; however, these relationships did not significantly change over time. There were no significant effects, or changes over time, of relationships between BDI or BAI and blood EOS.

Percent Sputum EOS did not differ between MBSR and wait-list groups at baseline (t(50) = 1.241, p = .221). Results of analyses showed a significant 3-way interaction between chronic stress, group, and visit (t(104) = 2.198, p = .03) such that the slope of the association between chronic stress and sputum EOS increased significantly over time in wait-list controls. In the MBSR group, this slope decreased numerically over time, but this change in slope was not significant (Fig. 3).





## Fig. 3: Those in the MBSR intervention were protected from the increasingly positive relationship between EOS and chronic stress seen in wait-list controls (chronic stress x group x visit interaction, p = .03).

***FeNO****.*At baseline, FeNO did not differ between MBSR and wait-list groups (t(67) = .941, p = .35). The outcome of analyses revealed a significant main effect of visit when chronic stress (t(63) = -2.32, p = .024), BDI (t(74) = -2.024, p = .047), or BAI (t(63) = -2.028, p = .047) were included, suggesting an overall decline in FeNO over time. No significant group x visit interactions were found.

***Discussion.*** We found that asthma control and mindfulness improved significantly over time in those randomized to MBSR, relative to wait-list controls. Furthermore, the effects of chronic stress on eosinophilic inflammation were greater over time for controls, compared to those who received MBSR training. Nonetheless, we found no significant changes over time in relationships between FeNO and psychological variables. Additionally, we found no significant changes over time in relationships between eosionophilic inflammation and depressive or anxiety symptoms. These results suggest that MBSR improved asthma control and effectively buffered increasing effects over time of chronic psychological stress on eosinophilic inflammation; but did not significantly affect airway inflammation as measured by FeNO, or associations between inflammation and depression or anxiety. Our findings strengthen extant evidence that mindfulness training, which targets stress responsivity, can benefit some psychological and physiological processes. Moreover, they indicate the potential therapeutic value of MBIs for chronic inflammatory conditions, specifically asthma.

Asthma treatment aims to maximize symptom control and minimize future risk.20 Higher ACQ scores, reflecting poorer asthma control, have been associated with elevated FeNO and sputum EOS, higher perceived stress, and psychological comorbidity.7,21,22 Indeed, participants in our study with higher chronic stress and depressive symptoms demonstrated poorer asthma control at baseline, implying important crosstalk between emotion and asthma control. Extending these associations, the significant decrease in ACQ scores over time in the intervention group, but not controls, suggests that MBSR training was effective in reducing the degree of asthma symptom-related impairments. This pattern advances MBSR as a valuable addition to current treatment regimens.

Our results support and extend prior evidence that eosinophilic inflammation is influenced by psychological factors.4,5 Furthermore, these data show that an intervention that targets the psychological factors shown to affect EOS in previous studies, impacts some of these associations over time. Despite minimal correlation between sputum EOS and chronic stress at baseline, sputum EOS increase over time, for those in the wait-list group, particularly those with high chronic stress. This change is weakly negative or absent in the MBSR group. These results indicate that a lack of intervention was associated with amplified relationships between sputum EOS and chronic stress. The absence of a similar amplification in the intervention group suggests that MBSR participation buffers this increase in the effects of chronic stress on EOS-mediated inflammation over time. However, there were no significant interactions with depressive or anxiety symptoms. One interpretation for these observations is that the protective effects of MBSR are not the same across all levels of psychological symptoms and that those with greater chronic stress are more likely to benefit. Overall, these results suggest that MBSR may be a clinically relevant adjunct to asthma treatment, to buffer effects of psychological stress on airway inflammation.

In asthma, rises in exhaled nitric oxide often precede lung function decline and correlate with both airway and circulating EOS.21,23 Notably, FeNO has been shown to be responsive to psychological states.24 FeNO is used clincally to assist in asthma diagnosis and assessment of airway inflammation and medication responsiveness; however, its exact role in asthma characterization and diagnosis remains complex and insufficiently understood.25 In our data, FeNO levels declined over time in all participants, irrespective of the intervention. Fluctuations in external factors, such as environmental and indoor allergens, could contribute to this change. We found no significant group differences in FeNO over time in relation to chronic stress, depression, or anxiety symptoms, which indicates that participating in an MBSR intervention did not significantly affect these relationships. This result is surprising, given previous evidence that FeNO is susceptible to psychological modulation, and work showing MBSR-related decreases in inflammation. FeNO has been positively associated with acute stress, negative affect, and anxiety; however, relationships between FeNO and chronic stress or depression are inconclusive or negative.24 Our findings suggest that FeNO is not related to chronic stress, depression, or anxiety in this sample.

The relationships between psychological factors and asthmatic inflammation reported here implicate the central role of the brain in inflammatory diseases, and highlight the importance of interventions that target the mind and brain in the treatment arsenal. Given the nature of the MBSR intervention, the observed improvements in asthma control and buffering of effects of psychological stress on eosinophilic inflammation must be mediated by changes in brain function, which determine stress responsivity and descending modulatory pathways, to consequently influence peripheral inflammation. The specific neural changes involved will be addressed elsewhere, but these observations provide traction for future research on the neural mechanisms of asthma.

Although this study presents MBSR as a promising complementary treatment for a chronic and pervasive disease, we found no effects of training on the relationships between blood EOS or FeNO and psychological symptoms. This may reflect the relatively small sample size, which limits statistical power and generalizability. Indeed, non-significant trends in our data point to a similar buffering effect of the intervention with blood EOS and FeNO. A larger sample may have provided sufficient power to detect these relationships.

# Conclusion

Ultimately, our results suggest that training in MBSR improved asthma control and buffered the effects of chronic stress on eosinophilic inflammation in the airways, despite not significantly affecting the relationships between psychological symptoms and systemic inflammation or FeNO. These data support the hypothesis that psychological factors contribute to airway inflammation, and that an intervention targeting stress and affective responsivity can buffer those effects. Emphasizing the importance of bidirectional communication between the brain and body within this clinical population, our findings advance MBSR as a promising and accessible behavioral approach which may help alleviate both individual and public health burden. Finally, these findings provide a foundation for future research on neural mechanisms of asthma and MBSR.

references

1. *Most Recent National Asthma Data* | CDC. (2019, May 21).
2. Ramirez, G. A., Yacoub, M.-R., Ripa, M., Mannina, D., Cariddi, A., Saporiti, N., Ciceri, F., Castagna, A., Colombo, G., & Dagna, L. (2018). Eosinophils from Physiology to Disease: A Comprehensive Review. *BioMed Research International*, *2018*.
3. Busse, W. W., & Rosenwasser, L. J. (2003). Mechanisms of asthma. *Journal of Allergy and Clinical Immunology*, *111*(3), S799–S804.
4. Forsythe, P., Ebeling, C., Gordon, J. R., Befus, A. D., & Vliagoftis, H. (2004). Opposing Effects of Short- and Long-term Stress on Airway Inflammation. *American Journal of Respiratory and Critical Care Medicine*, *169*(2), 220–226.
5. Liu, L. Y., Coe, C. L., Swenson, C. A., Kelly, E. A., Kita, H., & Busse, W. W. (2002). School Examinations Enhance Airway Inflammation to Antigen Challenge. *American Journal of Respiratory and Critical Care Medicine*, *165*(8), 1062–1067.
6. Lu, Y., Mak, K.-K., Bever, H. P. S. van, Ng, T. P., Mak, A., & Ho, R. C.-M. (2012). Prevalence of anxiety and depressive symptoms in adolescents with asthma: A meta-analysis and meta-regression. *Pediatric Allergy and Immunology*, *23*(8), 707–715.
7. Strine, T. W., Mokdad, A. H., Balluz, L. S., Berry, J. T., & Gonzalez, O. (2008). Impact of depression and anxiety on quality of life, health behaviors, and asthma control among adults in the United States with asthma, 2006. *The Journal of Asthma: Official Journal of the Association for the Care of Asthma*, *45*(2), 123–133.
8. Richardson, L. P., Russo, J. E., Lozano, P., McCauley, E., & Katon, W. (2008). The effect of comorbid anxiety and depressive disorders on health care utilization and costs among adolescents with asthma. *General Hospital Psychiatry*, *30*(5), 398–406.
9. Kabat-Zinn, J. (1990). *Full catastrophe living: Using the wisdom of your body and mind to face stress, pain and illness*. Delacorte Press.
10. Wielgosz, J., Goldberg, S. B., Kral, T. R. A., Dunne, J. D., & Davidson, R. J. (2019). Mindfulness Meditation and Psychopathology. *Annual Review of Clinical Psychology*, *15*(1), 285–316.
11. Black, D. S., & Slavich, G. M. (2016). Mindfulness meditation and the immune system: A systematic review of randomized controlled trials: Mindfulness meditation and the immune system. *Annals of the New York Academy of Sciences*, *1373*(1), 13–24.
12. Paudyal, P., Jones, C., Grindey, C., Dawood, R., & Smith, H. (2018). Meditation for asthma: Systematic review and meta-analysis. *Journal of Asthma*, *55*(7), 771–778.
13. *WHO | Adverse Childhood Experiences International Questionnaire (ACE-IQ)*. (n.d.). WHO. Retrieved September 4, 2019, from <http://www.who.int/violence_injury_prevention/violence/activities/adverse_childhood_experiences/en/>
14. Hammen, C. (1991). Generation of stress in the course of unipolar depression. *Journal of Abnormal Psychology*, *100*(4), 555–561.
15. Beck, A. T. (1961). An Inventory for Measuring Depression. *Archives of General Psychiatry*, *4*(6), 561.
16. Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology*, *56*(6), 893–897.
17. Baer, R. A., Smith, G. T., Hopkins, J., Krietemeyer, J., & Toney, L. (2006). Using Self-Report Assessment Methods to Explore Facets of Mindfulness. *Assessment*, *13*(1), 27–45.
18. Juniper, E. F., O′byrne, P. M., Guyatt, G. h, Ferrie, P. j, & King, D. r. (1999). Development and validation of a questionnaire to measure asthma control. *European Respiratory Journal*, *14*(4), 902.
19. Wildfire, J. J., Gergen, P. J., Sorkness, C. A., Mitchell, H. E., Calatroni, A., Kattan, M., Szefler, S. J., Teach, S. J., Bloomberg, G. R., Wood, R. A., Liu, A. H., Pongracic, J. A., Chmiel, J. F., Conroy, K., Rivera-Sanchez, Y., Morgan, W. J., & Busse, W. W. (2012). Development and Validation of the Composite Asthma Severity Index – An Outcome Measure for use in Children and Adolescents. *The Journal of Allergy and Clinical Immunology*, *129*(3), 694–701.
20. Global Initiative for Asthma. (2019). *Global Strategy for Asthma Management and Prevention, 2019*.
21. Schleich, F. N., Chevremont, A., Paulus, V., Henket, M., Manise, M., Seidel, L., & Louis, R. (2014). Importance of concomitant local and systemic eosinophilia in uncontrolled asthma. *European Respiratory Journal*, *44*(1), 97–108.
22. Wisnivesky, J. P., Lorenzo, J., Feldman, J. M., Leventhal, H., & Halm, E. A. (2010). The relationship between perceived stress and morbidity among adult inner-city asthmatics. *The Journal of Asthma: Official Journal of the Association for the Care of Asthma*, *47*(1), 100–104.
23. Hoffmeyer, F., Raulf-Heimsoth, M., & Brüning, T. (2009). Exhaled breath condensate and airway inflammation: *Current Opinion in Allergy and Clinical Immunology*, *9*(1), 16–22.
24. Ritz, T., & Trueba, A. F. (2014). Airway nitric oxide and psychological processes in asthma and health: A review. *Annals of Allergy, Asthma & Immunology*, *112*(4), 302–308.
25. Dweik, R. A., Boggs, P. B., Erzurum, S. C., Irvin, C. G., Leigh, M. W., Lundberg, J. O., Olin, A.-C., Plummer, A. L., & Taylor, D. R. (2011). *American Thoracic Society Documents*. *184*, 14.