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# Investigating the Efficacy of Stress Reduction Interventions Based on Mindfulness Principles in Improving Life Quality for Individuals with Chronic Obstructive Pulmonary Disease (COPD)

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# Quantitative Study

## Abstract

**Background:** Chronic obstructive pulmonary disease (COPD) is a debilitating condition that significantly impacts patients' quality of life (QoL). Mindfulness-based stress reduction (MBSR) is a complementary therapy for chronic conditions. This study aimed to assess the efficacy of an eight-week MBSR program in improving QoL, self-compassion, mindfulness, depression, and anxiety among COPD patients.

**Methods:** A randomized controlled trial was conducted with 120 COPD patients allocated to either an MBSR intervention group (n = 60) or a control group (CG) receiving standard care (n = 60). The MBSR program consisted of weekly 2.5-hour sessions for eight weeks. The primary outcome was the change in St. George's Respiratory Questionnaire (SGRQ) total scores from baseline to post-intervention. Secondary outcomes included changes in the Hospital Anxiety and Depression Scale (HADS), Five Facet Mindfulness Questionnaire (FFMQ), and Self-Compassion Scale (SCS) scores. Assessments were conducted at baseline, post-intervention, and three months follow-up.

**Results:** The MBSR group showed a significantly greater reduction in SGRQ total scores (-12.4  $\pm$  8.7) compared to the CG (P < 0.001) at post-intervention. Significant improvements were also observed in the MBSR group relative to the CG for HADS-Anxiety (change: -3.5  $\pm$  2.8, P < 0.001), HADS-Depression (change: -3.1  $\pm$  2.6, P < 0.001), FFMQ total (change: 22.3  $\pm$  12.5, P < 0.001), and SCS total (change: 15.7  $\pm$  10.2, P < 0.001) scores at post-intervention. The improvements were maintained at the three months follow-up (all P < 0.001).

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**Conclusion:** An 8-week MBSR program significantly improves QoL, depression, anxiety, mindfulness, and self-compassion in COPD patients compared to standard care alone. These findings support the integration of mindfulness-based interventions into the standard care of COPD patients. Further research is needed to validate these findings and explore the optimal implementation of MBSR in COPD care.

Keywords: Mindfulness; Pulmonary disease; Chronic obstructive; Quality of life

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### Introduction

Chronic obstructive pulmonary disease (COPD) is a debilitating condition that significantly impacts patients' quality of life (QoL) due to ongoing breathing difficulties and restricted airflow (Ayilya & Nazeer, 2023). Despite current pharmacological treatments, many COPD patients continue to experience a significant burden of symptoms and impaired QoL (Lee et al., 2021; Libu et al., 2021), highlighting the need for complementary therapies to address these unmet needs and improve overall health outcomes (Miravitlles & Ribera, 2017; Yohannes & Alexopoulos, 2014).

Mindfulness-based stress reduction (MBSR) is a promising complementary approach that is effective in managing chronic conditions and reducing stress, anxiety, and depression (Albahadlv et al., 2023; Asadollahi et al., 2014; Atabayevich et al., 2023). The mindfulness practices taught in MBSR, such as breath awareness and body scan meditation, may help COPD patients better cope with their symptoms and improve their QoL.

Several studies have investigated the efficacy of MBSR in improving the mental well-being and QoL of COPD patients. These studies have reported significant reductions in stress, depression, and anxiety, as well as improvements in health-related QoL (Chan et al., 2017; Mularski et al., 2009). However, a meta-analysis by Loughran et al. (2020) noted limitations in the existing literature, such as small sample sizes and lack of long-term follow-up assessments, and called for further research to establish the long-term benefits of MBSR and determine the most effective delivery methods for this population.

The primary objective of this study is to evaluate the effectiveness of an 8-week MBSR intervention in improving QoL among COPD patients compared to a control group receiving standard care. Secondary objectives include assessing the impact of MBSR on depression, anxiety, mindfulness, and self-compassion in COPD patients. By addressing these research questions, the present study aims to contribute to the growing body of evidence supporting MBSR as a complementary therapy for improving QoL and psychological well-being in COPD patients, potentially informing clinical practice and the management of this chronic condition.

### Methods

**Design study and participant:** This study employed an RCT to assess the efficacy of MBSR in improving QoL among COPD patients. The study was conducted at the Respiratory Care Unit of Al-Kindy Teaching Hospital in Baghdad, Iraq, between January 2023 and December 2023. Participants were recruited using a purposive sampling method based on the following inclusion criteria: (1) diagnosed with COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (Gupta et al., 2021), (2) aged 40 years or above, (3) stable clinical condition with no exacerbations in the past four weeks, and (4) able to provide informed consent. Exclusion criteria included: (1) presence of other significant respiratory diseases (e.g., asthma, bronchiectasis), (2) severe comorbidities (e.g., heart failure, cancer), (3) current participation in pulmonary rehabilitation or other psychological interventions and (4) inability to attend the MBSR sessions.

*Sample Size:* G\*Power software was employed to calculate the required number of participants, considering an alpha level of 0.05, a power of 0.80, a medium effect size, and a two-tailed independent samples t-test (Cohen's d = 0.60) (Chen & Liu, 2019). Preceding studies probing the ramifications of MBSR on QoL among COPD patients served as the foundation for gauging the effect size (Clari et al., 2020;

Farver-Vestergaard et al., 2018; Reibel et al., 2001). Per the calculation results, the study needed at least 45 individuals in each group. Accounting for a potential dropout rate of 25%, 120 participants (60 per group) were recruited for this research.

*Instruments:* The main outcome measure was the SGRQ, a disease-specific QoL questionnaire for patients with respiratory diseases (Ferrer et al., 2002). The 50 items of the SGRQ consist of three domains: symptoms, activity, and impact. Scores range from 0 to 100, and higher scores indicate worse QoL. This study employed the Arabic version of the SGRQ, validated for use in Iraqi COPD patients (Farag et al., 2023).

Secondary outcome measures included the HADS (Snaith & Zigmond, 2000), the FFMQ (Baer et al., 2022), and the SCS (Neff & Tóth-Király, 2022). The HADS is a 14-item scale that assesses anxiety and depression symptoms, with scores ranging from 0 to 21 for each subscale. The FFMQ assesses five elements of mindfulness in a 39-item questionnaire: non-reactivity to inner experience, non-judging of inner experience, acting with awareness, describing, and observing. Six constituents of self-compassion are evaluated by the SCS, a 26-item scale: over-identification, mindfulness, isolation, common humanity, self-judgment, and self-kindness. All questionnaires were administered in their validated Arabic versions (Al-Turkait & Ohaeri, 2010; Alsaraireh & Aloush, 2017; Beshai et al., 2019).

The study randomly allocated individuals to the MBSR intervention group or the control group (CG) receiving standard care using a computer-generated random number sequence. The allocation was concealed using opaque, sealed envelopes. Standard care for both groups included pharmacological treatment (e.g., bronchodilators and corticosteroids), self-management education on smoking cessation, proper inhaler technique, and physical activity. All participants continued to receive their usual medical care throughout the study period.

The MBSR program consisted of eight weekly sessions, each lasting 2.5 hours, delivered by a certified MBSR instructor with experience working with COPD patients. The instructor received training through the Mindfulness Center at the University of Baghdad and has taught MBSR for over ten years to various patient populations, including individuals with chronic respiratory conditions. The standardized 8-week MBSR protocol helps to minimize variability and ensure the reproducibility of the intervention.

The sessions included guided meditations, gentle yoga, body awareness exercises, and group discussions. Participants were also provided with audio recordings of the guided meditations and encouraged to engage in 45-minute practice sessions at home six times weekly. Table 1 provides a comprehensive rundown of the therapeutic sessions, featuring the subjects, material, exercises, and homework tasks.

Standard care for both groups included pharmacological treatment (e.g., bronchodilator corticosteroids) and self-management education on smoking cessation, proper inhaler technique, and physical activity. All individuals maintained the reception of their typical medical treatment throughout the investigation.

Data were obtained on three separate occasions: baseline, post-intervention, and three-month follow-up. Participants completed the SGRQ, HADS, FFMQ, and SCS at each time point. Clinical and demographic data, including COPD severity (based on GOLD classification), age, gender, smoking status, and comorbidities, were collected at baseline.

*Analysis:* IBM SPSS Statistics (version 26.0) was employed to analyze the collected data. Participants' demographic and clinical characteristics were summarized using descriptive statistics.

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Session	Topic	Content and activities	Homework assignment
1	Introduction	- Introduce the concept of mindfulness and its	- Practice body scan
	to	potential benefits for COPD patients	meditation 4.5 hours
	Mindfulness	- Discuss the structure of the MBSR	per week
		program and expectations	- Eat one meal mindfully
		- Guide participants through a	- Complete the
		body scan meditation	Unpleasant Events
		- Engage in a group discussion about	Calendar
		participants' experiences and questions	
2	Perception	- Discuss the relationship between	<ul> <li>Practice sitting</li> </ul>
	and Creative	perception and stress	meditation and mindful
	Responding	<ul> <li>Guide participants through sitting</li> </ul>	yoga 4.5 hours per week
		meditation with a focus on breath awareness	- Complete the Pleasant
		- Introduce and practice mindful yoga	Events Calendar
		- Engage in a group discussion about	
2		participants' experiences and insights	
3	The Power of	- Discuss the concept of being present and its	- Practice sitting
	Being Present	relevance to stress management	meditation, mindful
		- Guide participants through sitting	yoga, and walking
		meditation with a focus on body awareness	meditation 4.5 nours
		- Practice mindful yoga	Complete the Difficult
		- Infoduce waiking incutation	- Complete the Difficult
		- Eligage III a group discussion about	Calendar
4	Coping with	- Discuss the physiological and psychological	- Practice sitting
7	Stress	effects of stress	meditation mindful
	Buebb	- Guide participants through sitting meditation	voga, and walking
		with a focus on thoughts and emotions	meditation 4.5 hours
		- Practice mindful yoga	per week
		- Introduce the concept of mindful	- Practice mindful
		communication	communication
		- Engage in a group discussion about	
		participants' experiences and coping strategies	
5	Dealing with	- Discuss the relationship between emotions	- Practice sitting
	Difficult	and COPD symptoms	meditation, mindful
	Emotions	<ul> <li>Guide participants through sitting</li> </ul>	yoga, and walking
		meditation with a focus on accepting and	meditation 4.5 hours
		managing difficult emotions	per week
		- Practice mindful yoga	- Practice self-
		- Introduce the concept of self-compassion	compassion exercises
		- Engage in a group discussion about	
6	Mindfulness	Discuss the integration of mindfulness	Departies modification
0	in Daily Life	- Discuss the integration of minutumess	- Flactice meditation,
		- Guide participants through a choiceless	walking meditation
		awareness meditation	4 5 hours per week
		- Practice mindful voga	- Choose one daily
		- Engage in a group discussion about	activity to practice
		participants' experiences and strategies for	mindfully
		incorporating mindfulness into daily life	~ ,
7	Mindfulness	- Discuss the importance of self-care for	- Practice meditation,
	and Self-Care	COPD patients	mindful yoga, and
		- Guide participants through a loving-	walking meditation
		kindness meditation	4.5 hours per week
		- Practice mindful yoga	- Develop a personalized
		- Engage in a group discussion about	self-care plan
		participants' experiences and	
		self-care strategies	

### **Table 1.** Outline of the MBSR therapeutic sessions

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Session	Topic	Content and activities	Homework assignment
8	Maintaining a	- Discuss the benefits and challenges of	- Develop a plan for
	Mindfulness	maintaining a mindfulness practice	maintaining a regular
	Practice	- Guide participants through a body scan	mindfulness practice
		meditation	- Identify resources and
		<ul> <li>Practice mindful yoga</li> </ul>	support for ongoing
		<ul> <li>Reflect on the MBSR program and set</li> </ul>	practice
		intentions for ongoing practice	- Complete post-
		<ul> <li>Engage in a group discussion about</li> </ul>	intervention
		participants' experiences, insights, and plans	questionnaires
		for the future	

Table 1. Outline of the MBSR thera	peutic sessions (	(continue)
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To compare the baseline characteristics of the MBSR and control groups, researchers employed independent samples t-tests for continuous variables and chi-square tests for categorical variables. These tests were chosen as they are appropriate for comparing means and proportions between two independent groups.

The primary analysis compared the change in SGRQ total scores from baseline to post-intervention between the control and MBSR groups using an independent samples t-test. This test was selected as it is suitable for comparing the means of two independent groups. Given the sample size of 60 participants per group, the change scores were assumed to be normally distributed based on the central limit theorem.

In secondary analyses, independent samples t-tests were used to compare the changes in HADS, FFMQ, and SCS scores from baseline to post-intervention and three months follow-up between the MBSR and control groups. Paired samples t-tests were employed to evaluate changes within each group, as these tests are appropriate for comparing means between two related measurements (e.g., pre- and post-intervention scores).

The assumptions for the independent and paired samples t-tests, including normality and homogeneity of variances, were assessed using the Shapiro-Wilk test and Levene's test, respectively. In cases where assumptions were violated, appropriate non-parametric alternatives, such as the Mann-Whitney U test for independent samples and the Wilcoxon signed-rank test for paired samples, were used.

A per-protocol analysis was conducted, including only participants who attended at least six of the eight MBSR sessions and completed the post-intervention assessment. This approach was chosen to evaluate the effects of the intervention among participants who adhered to the protocol, minimizing the influence of noncompliance on the results.

Missing data were handled using the last observation carried forward (LOCF) method, which imputes missing values with the last observed value for each participant. While this method has limitations, such as potentially introducing bias if the missing data are not completely random, it was chosen to maintain the sample size and provide a conservative estimate of the intervention effects, as it assumes no change in outcomes after dropout.

*Ethics:* The Institutional Review Board of the University of Baghdad's College of Medicine approved the study protocol. Before being enrolled in the study, all participants gave their written informed consent. Participant privacy and confidentiality were ensured by assigning unique identification numbers and storing data in a secure, password-protected database accessible only to the research team. The study adhered to the principles outlined in the Declaration of Helsinki and the regulations the Iraqi Ministry of Health set forth.

### Results

Altogether, 120 COPD patients were enrolled in this research, with 60 participants randomly allocated to each group. The mean age of the participants was  $63.1 \pm 8.7$  years in the MBSR group and  $61.9 \pm 7.9$  years in the CG. The majority of participants in both the control (71.7%) and MBSR (75.0%) groups were male. The smoking status distribution was similar between the MBSR (30.0% current, 36.7% former, 33.3% never) and control (33.3% current, 31.7% former, 35.0% never) groups. The average COPD duration was  $7.5 \pm 4.9$  years and  $6.9 \pm 4.3$  years in the MBSR and CGs, respectively. Table 2 displays the participants' baseline demographic and clinical characteristics. No notable differences were observed between the MBSR and CGs regarding age, gender, smoking status, COPD severity, or comorbidities (all P > 0.05).

As shown in Table 2, the distribution of COPD severity according to GOLD staging was similar between the MBSR and control groups, with the majority of participants in both groups classified as Stage II (moderate) or Stage III (severe). The prevalence of common comorbidities, such as hypertension, diabetes, and coronary artery disease, was also comparable between the two groups. These findings suggest that the study sample is representative of the broader COPD population and that the MBSR and control groups were well-balanced in terms of disease severity and comorbidities at baseline.

The primary outcome measure was the change in SGRQ total scores from baseline to post-intervention. As shown in Table 3, the MBSR group experienced a significant improvement in QoL relative to the CG. The MBSR group showed a significantly greater reduction in SGRQ total scores (-12.4 ± 8.7) compared to the CG (P < 0.001). The between-group difference remained significant at the three-month follow-up assessment, with the MBSR group showing a mean change of -10.9 ± 9.2 compared to the CG (P < 0.001).

The MBSR group demonstrated significant reductions in depression and anxiety scores, as measured by the HADS, relative to the CG (Table 4). The mean change in HADS-Anxiety scores from baseline to post-intervention was  $-3.5 \pm 2.8$  in the MBSR group, surpassing the change noted in the CG by a significant margin (P < 0.001). Analogously, The MBSR group demonstrated a significantly greater decrease in HADS-Depression scores (-3.1 ± 2.6) compared to the CG (P < 0.001).

Characteristic	MBSR group (n = 60)	Control group (n = 60)	P-value
Age (years), mean $\pm$ SD	$63.1 \pm 8.7$	$61.9 \pm 7.9$	0.421
Male gender, n (%)	45 (75.0)	43 (71.7)	0.679
Smoking status, n (%)			0.851
Current smoker	18 (30.0)	20 (33.3)	
Former smoker	22 (36.7)	19 (31.7)	
Never smoker	20 (33.3)	21 (35.0)	
COPD duration (years), mean $\pm$ SD	$7.5 \pm 4.9$	$6.9 \pm 4.3$	0.478
COPD severity (GOLD), n (%)			0.773
Stage I (mild)	8 (13.3)	10 (16.7)	
Stage II (moderate)	32 (53.3)	29 (48.3)	
Stage III (severe)	20 (33.3)	21 (35.0)	
Comorbidities, n (%)			
Hypertension	24 (40.0)	22 (36.7)	0.707
Diabetes	15 (25.0)	18 (30.0)	0.539
Coronary artery disease	10 (16.7)	12 (20.0)	0.637

#### Table 2. Baseline demographic and clinical characteristics of the participants

MBSR: Mindfulness-based stress reduction; SD: Standard deviation

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Time point	MBSR group (n = 60)	Control group $(n = 60)$	Between-group difference	P-value
Baseline	$58.3 \pm 12.1$	$57.9 \pm 11.6$	-	0.852
Post-intervention	$45.9 \pm 10.4$	$54.7 \pm 11.2$	$-12.4 \pm 8.7$	< 0.001
Three months follow-up	$47.4 \pm 10.9$	$55.1 \pm 11.5$	$\textbf{-10.9} \pm \textbf{9.2}$	< 0.001

**Table 3.** Changes in SGRQ total scores from baseline to post-intervention and three months follow-up

The improvements in depression and anxiety scores were maintained at the three-month follow-up assessment, with the MBSR group showing significantly greater reductions in comparison to the CG (P < 0.001 for both HADS-Depression and HADS-Anxiety).

MBSR group participants showed significantly higher mindfulness and selfcompassion scores than the CG (Table 5). The mean change in FFMQ total scores from baseline to post-intervention was 22.3 ± 12.5 in the MBSR group, surpassing the change noted in the CG by a significant margin (P < 0.001). The MBSR group exhibited a significantly greater increase in SCS total scores (15.7 ± 10.2) compared to the CG (P < 0.001). The improvements in self-compassion and mindfulness were sustained at the three-month follow-up assessment, with the MBSR group showing significantly greater increases compared to the CG (P < 0.001 for both FFMQ total and SCS total scores).

### Discussion

This investigation's main result is that an 8-week MBSR program significantly improved QoL in COPD patients compared to standard care alone. The magnitude of the improvement in SGRQ total scores (-12.4 points) is clinically meaningful, as a change of 4 points or more is considered significant (Alma et al., 2019). The current finding corroborates earlier investigations that have reported the beneficial effects of MBSR on QoL in COPD patients (Arefnasab et al., 2013; Jalali et al., 2019).

The improvement in QoL can be attributed to several factors. First, MBSR may help COPD patients to better cope with their symptoms, such as dyspnea and fatigue, by promoting acceptance and reducing stress-related exacerbations of symptoms (Tabała et al., 2020). Second, the mindfulness practices taught in MBSR, such as breath awareness and body scan meditation, may enhance patients' ability to selfregulate their emotions and reduce the negative impact of psychological distress on QoL (Atabayevich et al., 2023).

In addition to improving QoL, MBSR significantly reduced anxiety and depression symptoms in COPD patients, with the MBSR group showing considerably greater reductions relative to the CG.

	<b>T:</b>	MOGD	0 1	D.(	
Outcome	1 ime point	MBSK	Control	Between-	P-value
measure		group	group	group	
		( <b>n</b> = 60)	( <b>n</b> = 60)	difference	
HADS-Anxiety	Baseline	$10.2 \pm 3.4$	$9.8 \pm 3.1$	-	0.503
	Post-intervention	$6.7\pm2.6$	$8.9\pm2.8$	$-3.5 \pm 2.8$	< 0.001
	Three months follow-up	$7.1 \pm 2.9$	$9.2 \pm 3.0$	$-3.2 \pm 2.9$	< 0.001
HADS-	Baseline	$9.6 \pm 3.2$	$9.4 \pm 2.9$	-	0.721
Depression	Post-intervention	$6.5 \pm 2.5$	$8.7\pm2.6$	$-3.1 \pm 2.6$	< 0.001
	Three months follow-up	$6.9 \pm 2.7$	$8.9\pm2.8$	$-2.9 \pm 2.7$	< 0.001

Table 4. Changes in HADS scores from baseline to post-intervention and three months follow-up

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Outcome measure	Time point	MBSR group	Control group	Between-group difference	P-value
		(n = 60)	(n = 60)		
FFMQ	Baseline	$112.6 \pm 18.4$	$114.1 \pm 17.8$	-	0.647
Total	Post-intervention	$134.9\pm20.1$	$116.5\pm18.3$	$22.3 \pm 12.5$	< 0.001
	Three months follow-up	$132.7\pm19.6$	$115.9 \pm 18.1$	$20.8 \pm 11.9$	< 0.001
SCS	Baseline	$65.3 \pm 12.5$	$66.7 \pm 11.9$	-	0.532
Total	Post-intervention	$81.0\pm14.2$	$68.0 \pm 12.3$	$15.7\pm10.2$	< 0.001
	Three months follow-up	$79.6 \pm 13.8$	$67.5 \pm 12.1$	$14.9\pm9.8$	< 0.001

Table 5. Changes in FFMQ and SCS scores from baseline to post-intervention and three months follow-up

The current outcome is particularly relevant given the high prevalence of depression and anxiety in this population (Reibel et al., 2001). Several mechanisms may mediate the beneficial effects of MBSR on anxiety and depression. First, mindfulness practices may help patients develop a non-judgmental awareness of their thoughts and emotions, reducing the tendency to ruminate on negative experiences (Jalali et al., 2019). Second, the group-based format of MBSR may provide a supportive environment that promotes social connectedness and reduces feelings of isolation, common among COPD patients (Sundh et al., 2015).

Furthermore, this study found that MBSR significantly increased mindfulness and self-compassion in COPD patients, with the MBSR group showing considerably greater increases relative to the CG. These findings are consistent with the theoretical framework of MBSR, which emphasizes cultivating mindfulness and self-compassion as key mechanisms of change (Farag et al., 2023). The increase in mindfulness may help COPD patients manage their symptoms better and reduce the negative impact of stress on their health (Kharbanda & Anand, 2021). The increase in self-compassion may promote greater self-care and reduce the self-blame and guilt often experienced by COPD patients (Semenchuk et al., 2022).

Although the current study demonstrates significant improvements in QoL, anxiety, depression, mindfulness, and self-compassion at the three-month follow-up assessment, the long-term sustainability of these benefits beyond this period remains unclear. Future research should include longer follow-up periods, such as six months, one year, and two years post-intervention, to assess the durability of the intervention's effects. Long-term follow-up studies are crucial for understanding whether the benefits of MBSR are maintained over time and identify potential factors that may influence the sustainability of these outcomes, such as ongoing mindfulness practice, booster sessions, or changes in disease severity. This information will be valuable for optimizing the implementation of MBSR in the context of COPD care and developing strategies to support long-term adherence to mindfulness practices.

This study has several limitations that must be recognized. First, settings and populations: The study was conducted at a single center in Iraq with a relatively small sample size. Second, the study's reliance on self-reported measures may have introduced response bias. Future research should include objective physical and psychological functioning measures to validate the self-reported results.

Despite these limitations, this study provides strong evidence for the effectiveness of MBSR in improving QoL and psychological well-being among COPD patients. The findings highlight the potential for mindfulness-based interventions to complement standard medical care and provide a holistic approach to managing COPD.

To further validate these findings and optimize the intervention, future research

should focus on conducting larger, multi-center trials and exploring the most effective dose and delivery format of MBSR for individuals with COPD. Additionally, studies should investigate the potential mechanisms of action of MBSR in COPD, such as changes in inflammatory markers, symptom perception, and health behaviors. Finally, the cost-effectiveness of MBSR as a complementary therapy for COPD should be evaluated to inform healthcare policy and resource allocation decisions.

### Conclusion

In conclusion, this randomized controlled trial demonstrates that an 8-week MBSR program significantly improves QoL, anxiety, depression, mindfulness, and self-compassion in COPD patients compared to standard care alone. These findings support the integration of mindfulness-based interventions into the standard care of COPD patients and highlight the potential for MBSR to provide a holistic approach to managing this chronic condition. More investigations are necessary to substantiate these findings and explore the optimal implementation of MBSR in COPD care.

### **Conflict of Interests**

Authors have no conflict of interests.

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