CHAPTER 7

DISCUSSION

7.0 DISCUSSION

In this 24-weeks randomized controlled trial on chronically pesticide exposed farmers, BFY practice was significantly more observed to be more effective than the wait-list control condition in the alleviation of spirometry-based indices of airflow limitation, in particular FEV1, FVC, FEV25-75, and PEFR. The observed increment in FEV1 by 1.02L over six months in the BFY group seems relevant against an annual decline by 13.1 mL (95% CI, 19.1 to 7.1) and a reduction by 140 ml observed over an average of 3.4 years of pesticide exposure. However, given the lack of specific reports on clinical interventions with spirometry-based pulmonary outcomes in pesticide-exposed populations, there remains an uncertainty in the clinical significance of the observed effect sizes. Nonetheless, the observed change of ~1 liter in FEV1 is larger than the minimal clinically important difference of 100 ml suggested for pharmacological trials. Our observations accord with the previous reports of improvements in pulmonary function parameters with regular yoga practice, particularly breathing-focused practices. Additionally, there have been mixed findings indicating that the effectiveness of yoga-based breathing interventions is influenced by the fitness levels of the subjects, with only marginal improvements in lung functions observed in the eldelry to moderate-but-clinically-significant improvements in COPD patients. This further explains the comparatively larger effect-sizes observed concerning FEV1 and FEV1 (Pred%) in the present pesticide-exposed cohort as compared to the meta-analyzed effect-sizes on patients with COPD [WMD of 125ml for FEV1(L)20 and 3.95% for FEV (Pred%)]. Pesticide exposure has been sought as a risk factor for obstructive pulmonary diseases marked by an early reduction in FEV1.Hence, a significant improvement in FEV1 along with spirometry markers of small airway obstruction FEV25-75 and PEFR deserve clinical attention. The pranayama technique involves controlled breathing techniques that affect the respiratory rhythm, namely through prolongation and shortening of breaths, and sometimes breath-

holding, all implying voluntary control of respiratory muscles. Our results justify the relevance of early intervention in pesticide-exposed populations for the prevention of manifestations of irreversible lung function decline as in COPD.

Though the study subjects did not have the clinical manifestation of COPD/asthma, they had respiratory symptoms. Previous studies on yoga and spirometry variables have given mixed results; in the elderly significant improvements have been reported missing; however, this could be explained by the fact that the magnitude of the effect of yoga interventions on lung function correlates with the fitness levels of subjects. The respiratory exercises used in this protocol (Bhastrika pranayama) are specifically suited to the respiratory system and exercise both inspiratory and expiratory muscles. Therefore, it seems like the effectiveness of yoga-based breathing interventions depends on the subjects fitness levels, with marginal improvements reported in elderly to moderate but clinically significant improvements in COPD patients. The higher impact of based yoga intervention observed could be associated with the subclinical status of the subjects of <40 years of age group.

Further, the choice of intervention, Kapalbhati (fast expirations), involves abdominal wall muscles used for expiration. At the same time, Suryabedhana (slow breath with retention) affects inspiratory muscles in either the inspiratory (concentric isokinetic contraction), retentive (isometric contraction), or expiratory (eccentric isokinetic contraction) phases. Thus, Bhastrika pranayama may increase expiratory as well as inspiratory muscle performance, improving the capacity of the thoracic compartment to create negative and positive pressures in the respiration process compared with the control group. Previous studies reporting negative results of yoga training on FVC and FEV1.

These observations are in accord with the previous reports of improvements in pulmonary function parameters with regular yoga practice, particularly breathing-focused practices.

Pesticides are known neurotoxins, and there are several lines of evidence reported that support that long-term exposure to these chemicals could lead to neuronal loss in specific brain regions and subsequent cognitive impairment. In the present cohort, almost the entire cohort of pesticide-exposed farmers had mild cognitive impairment (MoCA<10), particularly TMT-B. With this high-risk backdrop of cognitive decline, the observed significant and moderate influence of the given BFY intervention on markers of executive function deserves clinical recognition as a preventive measure against the manifestation of neuropsychological disorders. There was no mediating effect of oxidative stress markers on the cognitive outcomes. This explains the need to include more complex integrated framework models involving physiological, neuronal, and psychological mediators rather than isolated generic pathophysiological mechanisms such as oxidative stress when exploring behavioral outcomes of yoga-based practices (YBP).

Hence, the results indicate the optimum window of substantial recovery before the possible manifestation of respiratory illnesses. There have been many hypothetical mechanisms proposed to explain the respiratory effects of yoga.

Further, the results are in line with prior of both short- and long-term effects indicates that yoga practice is associated with improvement in cognitive functioning generally in both long-term (Hedges' g = 0.33) and short-term studies (Hedges' g = 0.56), with medium effect sizes reported in short-term studies' measures of attention and processing speed (Hedges' g = 0.49) and executive functioning (Hedges' g = 0.39). We compared the reported normative data. We could find significant impairment in cognition with respect to TMT-B in the present pesticide-exposed cohort, and BBY intervention seemed to improve the outcome by 44 seconds.

There are several highlights of this study. This is the first report wherein a comprehensive health approach was adopted towards major adverse health aspects of pesticide exposed population to the best of our knowledge. Secondarily, through the study findings, we also present the current status of awareness related to pesticide usage-related health risks amongst Indian farmers. Most of the farmers (n=102, 72.34%) were not using any precautionary measures such as personal protective equipment during spraying operations. As these occupational sprayers were exposed to a mixture of various pesticides, a cumulative effect of pesticides was reflected in depression inactivity of serum cholinesterase activity levels that align with the range of SCE. In addition, approximately 70% of the farmers reported dyspnoea and productive cough symptoms, respectively. The very important aspect of the study has been the focus on the farming population, including their respiratory, cognitive health, and well-being. Further, the trial also explored the potential mechanism of intervention modality related to alleviating oxidative stress that has not been addressed in previous yoga-based studies of pulmonary diseases.

We hypothesized that oxidative stress airway narrowing mitigation resulted in decreased peak expiratory flow rate. To this end, we found a significant mediating effect of augmenting GSH through yoga intervention on FEV25-75, one of the primary spirometry variables of airway obstruction. GSH is the principal small molecular weight thiol in the lungs, which, together with its redox enzymes, provides an important protective antioxidant system. Depletion of GSH has been widely documented to be associated with pesticide exposure. Pulmonary function is indicated by its abundance in the lungs' epithelial lining fluid and correlations between its depletion and exacerbations of chronic pulmonary disease. A 24% mediating effect of GSH upregulation could be established against FEV25-75. We failed to establish a significant mediating effect of alleviating oxidative stress on BBY intervention for other

spirometry parameters. These findings indicate the need to explore other alternate markers. One of such major mechanisms could be inflammation.

Further, other generic mechanisms relaxation of the chest and expansion of the lungs, raising energy levels, and calming the body could be explained by the wide range of adverse biological effects; it has also been associated with adaptive responses and the resolution of inflammation. Therefore, more than being an imbalance with a predictable threshold after which disease or injury ensues, oxidative stress is a dynamic and continuous process. This might explain why supplementing antioxidants has largely failed to improve diseases such as asthma and chronic obstructive pulmonary disease. However, the therapeutic potential of antioxidants could be greatly improved by taking an approach that considers individual and environmental risk factors instead of treating oxidative airway stress broadly.

Though stress reduction has been cited as one of the most positive health benefits of yoga-based interventions, the unexpected lack of significant influence of the yoga intervention on the stress levels of farmers in the present study could be attributed to the floor effect. The baseline levels of the study cohort were only indicative of moderate, and demonstration of a significant stress-reducing effect of yoga would require a higher baseline stress status amongst the study participants. Psychological stress is a well-recognized health concern amongst farmers. Stressors inherent in farm work and lifestyle, such as uncertain and fluctuating economic prospects, are associated with poor physical and mental health outcomes and result in deleterious effects on cognitive function, depression, and high rates of suicide. Notably, there was a significant improvement in the quality of life in the yoga group as compared to the control group, which is a positive health marker indicative of improved capacity to function. This is an important finding to support the health system of the agricultural population to attain sustainable development goals. Individual quality of life (QOL) is a critical foundation of stable and cohesive societies.

The study highlighted other alternate mechanisms of yoga-based practices other than oxidative stress. Exercise-induced widening of respiratory bronchioles, leading to effective perfusion of alveoli in a large number. As integral to many yoga breathing exercises, slow breathing has been shown to positively influence dyspnea and improve resting pulmonary gas exchange and exercise performance in patients with chronic heart failure, possibly by reducing chemoreflex sensitivity. Apart from these models, we hereby report long-term yoga practice was responsible for a generalized reduction in chemoreflex. A shift in this oxidant/antioxidant balance could increase oxidative stress, which may cause cellular damage. Hence, the enhanced ant-oxidative potential of yoga could be used as an effective protective strategy in reducing the exacerbation of lung impairment and overcoming the damage caused by occupational exposure to pesticides in the farmers. The mediation analysis in the present study indicated reduced lipid peroxidation in the yoga group and an indirect role of the same underlying an improvement in the FEV1FVC ratio of pesticide exposed farmers.

Enhanced respiratory surveillance has been stated as a need of hours for pesticide-exposed farmers. Our findings indicate the implementation scope of cost-effective interventions and respiratory surveillance in pesticide-exposed farmers. Further, the effects of yoga may be broader when explored for other adverse health effects associated with pesticide exposure. Hence, given the clinical relevance of subclinical manifestation of health decline due to chronic pesticide exposure, the experimental findings on respiratory, cognitive, and other psychological functions need an immediate translation in farmer communities.

Moreover, we do not have a minimal clinically significant difference established or indicated in literature to monitor the prognosis of lung decline in pesticide exposed farmers.

To the best of our knowledge, this is the first report wherein the effect of a yoga-based pranayama and relaxation-based intervention has been assessed for spirometry-based pulmonary function parameters under the occupational exposure of pesticides. There have been reported associations between accelerated annual decline in FEV1 and cumulative pesticide exposure. The authors reported a reduction in FEV1 /FVC associated with exposure to ChE-inhibiting pesticides. In particular, concerning FEV1/FVC%, there was an evident mediation effect of MDA levels after the following six months of yoga intervention. Redox imbalance in rat tissues exposed with organophosphate pesticides and therapeutic potential of antioxidant. A meta-analysis has already indicated a clinically significant potential of yoga on lung impairment (FEV 1 in COPD patients. There has been based on the existing disease background, results could not be compared. Further, no reports have been available on any trial that targeted lung impairment in pesticide-exposed farmers. We observed a substantial increase in FEV1 compared to, GSH is the most representative antioxidant protein. The enzymatic antioxidant components are composed of enzymes that defend against oxidative stress. GSH-Px uses GSH as a donor of a hydrogen atom to reduce hydrogen peroxide into water. Thus, an increase in GSH could be considered one of the prominent defense mechanisms. The total GSH contents, activities of GSHP, and GST were significantly increased after yoga classes ($p < 0.05$ for GSH-Px and GST; $p < 0.01$ for total GSH, Fig. 3A, B, and D). Yoga practice might enhance the antioxidant system; thus, it could efficiently work to decrease oxidative stress. This finding supports the notion that yoga intervention could aid in alleviating the airway obstruction of small airways caused by continuous exposure to pesticides may affect small airways, leading to peripheral airway obstruction, In the present study noted in the yoga module of the present study that, we have incorporated 45 min for slow-breathing practices, relaxation technique, and meditation, while for asanas (maintaining postures) 15 min was given. It is widely accepted that increased oxygen

consumption during exercise results in the excess generation of ROS. Whereas yoga-based relaxation techniques and meditation were found to be associated with decreased oxygen consumption. Hence, we presume that low oxygen consumption during yoga practice probably reduced serum MDA level in the yoga practitioners of the present study. Oxidative stress is believed to be a possible mechanism of toxicity that plays a crucial role in the toxicological pathway of numerous classes of pesticides, probably due to their metabolism or mitochondrial disruption. The mediation analysis indicated the GSH levels were a significant mediator for the beneficial effect of yoga on FEV25-75.

Long-term yoga practice can alter the automatic output of the brainstem respiratory center in resting conditions and reduce hypercapnic respiratory drive, possibly as the result of repetitive exposure to hypercapnia during specific respiratory exercises.

India is predominantly a rural country, with 70–80% of the population living in villages engaged in agriculture. India's average consumption of pesticides has been documented to be lower than in many other developed economies. However, the unsafe and non-preventive work practices aggravate their exposure to pesticides; Fareed et al. reported a 36.75% prevalence of respiratory morbidities in the pesticide exposed farmer population from North India.

Previous studies have reported that chronic bronchitis was associated with an accelerated lung function decline and a higher mortality rate. When analyzed by serum cholinesterase levels, 75.7% of farmers were found to have levels >4500 U/ml. Studies in developing countries of farmer’s knowledge and practices have reported low to moderate levels of knowledge about pesticides, non-usage of personal protective equipment (PPE), unsafe

pesticide storage at homes, poor disposal of empty pesticide containers, misuse of pesticides and relatively low knowledge about pesticide safety labels.

Almost the entire cohort of pesticide-exposed farmers had mild cognitive impairment. However, in a recent meta-analysis, significant reductions in FEV1/FVC were reported in ChE exposure farmers, indicative of an obstructive defect in the lung function. The present study shows that pesticide toxicity might lead to oxidative stress and airway narrowing resulting in decreased peak expiratory flow rate.

Studies have reported that the effect of pesticides like Organophosphorous compounds could also be due to the production of oxygen-free radicals.

Pesticides are known neurotoxins. Evidence from in-vitro models and animal studies elucidates that long-term pesticide exposure may cause a neuronal loss in specific brain regions, which leads to subsequent cognitive impairment, decreased memory and attention, and loss of motor function. Therefore, an apparent connection between long-term pesticide exposure and cognitive dysfunction has been proposed. Cognitive performance is a significant predictor of subclinical dementia. As far as neuropsychological functioning in pesticide sprayers is concerned, the pesticide molecules are small and lipophilic, which can enter from blood to brain and then in neurons, glial cells, and brain microvessels. Pesticides target and disrupt blood-brain barrier receptors in the central nervous system.

The findings indicate the regular practice of pranayama and relaxation could prevent the deterioration of lung function in pesticide exposed farmers.