

EVALUATION OF PULMONARY FUNCTION AMONG A PHARMACEUTICAL OCCUPATIONAL COHORT IN ISLAMABAD, PAKISTAN

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Submitted by:

Syeda Iman Sara

Roll No: 01-167222-013

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ABSTRACT

Occupational exposure to active pharmaceutical ingredient (API) dust, excipient powders, solvent vapors and antibiotic aerosols is a chronic exposure in the pharmaceutical manufacturing industry, which has not been extensively studied for its occupational respiratory health effects in Pakistan. The present study is a cross-sectional study aimed to assess pulmonary function and health related quality of life (HRQoL) among a pharmaceutical occupational cohort in Islamabad.

A total of 78 workers from a pharmaceutical manufacturing plant in Humak Industrial Sector, Islamabad were recruited. Standardized measurements of pre- and post-bronchodilator spirometry were made according to ATS/ERS 2019 guidelines: Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV₁), FEV₁/FVC ratio and Peak Expiratory Flow (PEF). The ventilatory patterns were determined according to the accepted diagnostic criteria, and the obstructive cases were further divided by GOLD criteria and bronchodilator reversibility. The validated St. George's Respiratory Questionnaire (SGRQ) was used to measure HRQoL. Pearson correlation ($\alpha = 0.05$) was used to explore associations between work duration, smoking status, BMI and spirometric outcomes.

The cohort had a mean age of 31.6 ± 11.2 years (56.4% female), mean BMI of 21.7 ± 4.2 kg/m², and mean occupational tenure of 5.1 ± 4.1 years. In total, 62.8% showed ventilatory impairment: obstructive (33.3 %), restrictive (23.1 %) and mixed (6.4 %). Of those who were obstructive, 65.4% fulfilled GOLD criteria for COPD and 34.6% had reversible asthma-like obstruction. Mean SGRQ Activity domain score (28.6 ± 14.0) exceeded Symptoms (22.5 ± 14.2) and Impacts (14.5 ± 14.2) scores. Spirometric parameters were positively correlated with smoking (confounded by sex). Within the relatively short tenure studied no significant correlation was found between occupational duration and lung function.

There is a significant level of ventilatory impairment among this pharmaceutical manufacturing workforce that is much higher than that reported among other comparable occupational groups in Pakistan. This indicates that there are multiple pathophysiological mechanisms at play, as there is a higher proportion of obstructive rather than restrictive

patterns and both fixed COPD-pattern and reversible asthma-type obstruction were identified. The present results support the notion of the implementation of compulsory, periodic spirometric surveillance in pharmaceutical manufacturing industry and highlight the importance of further occupational respiratory health studies in this industry in Pakistan.

Keywords: occupational respiratory disease, pharmaceutical manufacturing, spirometry, COPD, occupational asthma, SGRQ, Pakistan, ventilatory impairment

LIST OF ABBREVIATIONS

Abbreviation	Full Form
API	Active Pharmaceutical Ingredient
ATS	American Thoracic Society
BD	Bronchodilator
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
FEV₁	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GLI	Global Lung Function Initiative
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRQoL	Health-Related Quality of Life
IgE	Immunoglobulin E
ILO	International Labour Organization
L/s	Litres per second
LMIC	Low- and Middle-Income Country
LLN	Lower Limit of Normal
PEF	Peak Expiratory Flow
PPE	Personal Protective Equipment
SGRQ	St. George's Respiratory Questionnaire
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
VOC	Volatile Organic Compound

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CHAPTER 1: INTRODUCTION

1.1 Background and Rationale

The respiratory system is one of the most sensitive signs of the state of occupational and environmental health because of the constant exposure of the lungs to air in the ambient environment and at work. Pharmaceutical manufacturing has a reputation of being a safe and well-controlled industry compared to mining or textile or construction work, but manufacturing workers are exposed to a range of airborne contaminants such as active pharmaceutical ingredient (API) dust, excipient powders, solvent vapors, antibiotic aerosols, biological agents, and sterilization chemicals. These exposures are often sub-acute toxic levels, but over many years of working, these chronic and cumulative effects on the respiratory system can lead to clinically significant ventilatory impairment.

The pharmaceutical industry in Pakistan has undergone significant growth over the last 20 years, fueled by the growing domestic demand, production of generic drugs and export activities. A progressive group of medium to large-size pharmaceutical manufacturing units has sprung up along the Islamabad-Rawalpindi road (Humak Industrial Sector). While industrial expansion has occurred, occupational health infrastructure, industrial hygiene monitoring and systematic respiratory surveillance have not always gone hand in hand. Addressing occupational health regulation in many low and middle income country (LMIC) contexts requires addressing the issue of capacity to protect worker health, between production scale expansion and institutional capacity. (Fatmi, 2014)

Throughout the world, occupational lung diseases continue to be one of the most preventable and underdiagnosed forms of work-related illness. Occupational respiratory diseases, such as COPD, occupational asthma, pneumoconiosis and others, still represent a significant proportion of the global burden of chronic respiratory disease, especially when engineering controls, personal protective equipment (PPE) compliance and regular health surveillance are not consistently in place (GOLD, 2023).

1.2 Occupational Exposure in Pharmaceutical Manufacturing

Pharmaceutical manufacturing processes consist of several steps each with unique air exposure attributes. Handling of raw materials and weighing are direct contact with fine API and excipient powders with particle size in the respirable range ($< 10\ \mu\text{m}$) and able to penetrate to the alveolar regions. In granulation and drying operations, particulates and, in case of the wet granulation, solvent vapors can be generated and inhaled. Friable dust is generated during tablet compression and coating and, if solvent-based, volatile organic compounds (VOC) are emitted during film-coating. Additional exposures to ethylene oxide and hydrogen peroxide vapor are added by packaging and quality-control laboratories.

There are several groups of pharmaceuticals that are known respiratory sensitizers that can cause symptoms of occupational asthma by either IgE-mediated or non-IgE-mediated pathways. Occupational asthma has been widely documented in pharmaceutical manufacturers, particularly those that produce beta-lactam antibiotics (penicillins, cephalosporins, etc.), as demonstrated by a large study of a cephalosporin manufacturing plant, where 14 of 51 workers were found to have asthma (Coutts, 1981). Various APIs containing inherent allergenic potential and enzymes used in formulations as well as psyllium based excipients have also been implicated. In addition to sensitizer-mediated mechanisms, airway inflammation and airflow limitation can become irritant-mediated and develop in a COPD-like phenotype due to chronic, non-sensitizing exposure to the dust of pharmaceutical products at levels exceeding the OELs (Vandenplas, 2011).

The effectiveness of the engineering controls, such as local exhaust ventilation, containment booths, and closed material-transfer systems, which are intended to reduce airborne exposure also varies, especially in LMIC settings where capital expenditure might be limited. However, the effectiveness of PPE depends on the selection, fit and use of the right type of PPE – which is often hindered by discomfort, lack of training or production-line pressure. The variable engineering controls combined with inconsistent use of PPE provide a plausible explanation for why pharmaceutical workers exhibit measurable reductions in their pulmonary function (Moscato, 2014).

1.3 Respiratory Physiology and the Scientific Basis for Spirometric Assessment

Spirometry has been the most widely used, clinically validated, and field-deployable tool to evaluate ventilatory function because it is non-invasive, reproducible, inexpensive, and

can distinguish obstructive from restrictive pattern of impairment. The main spirometric parameters are: Forced Vital Capacity (FVC) is the volume that can be expelled from the lungs during a forced expiration after maximum inspiration; Forced Expiratory Volume in 1 second (FEV₁) is the volume expelled during the first second of forced expiration and reflects the most important discriminator between obstructive and non-obstructive ventilatory patterns; the FEV₁/FVC ratio is the primary discriminator between obstructive and non-obstructive ventilatory patterns; Peak Expiratory Flow (PEF) is the maximum flow rate achieved during forced expiration, particularly sensitive to caliber of large airways.

A small FEV₁/FVC ratio (normal/near normal FVC) represents an obstructive defect; this occurs in COPD, chronic bronchitis and asthma. If FEV₁ and FVC are both decreased, but the ratio of FEV₁ to FVC is normal, the pattern is said to be restrictive which is seen in interstitial lung disease, chest wall disease, or fibrotic occupational lung disease. If both parameters are reduced at the same time and there is a greater proportionate decrease in FVC, then it is a mixed ventilatory defect. Pre- and post-bronchodilator spirometric testing can also be used to assess airway reversibility which is a characteristic diagnostic feature to differentiate asthma (usually reversible) from COPD (largely irreversible) (Graham, 2019).

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has established globally agreed-upon diagnostic and staging criteria for COPD based on an FEV₁/FVC ratio < 0.70, measured after bronchodilation, in the right clinical setting. The severity is additionally classified by percent-predicted FEV₁, which further stratifies severity, and serves to inform prognosis and clinical management (GOLD, 2023).

Table 1.1: GOLD Classification of COPD Severity

GOLD Stage	Criterion (post-BD FEV₁/FVC < 0.70)	FEV₁ % Predicted	Severity
GOLD 1	Confirmed obstruction	≥ 80%	Mild
GOLD 2	Confirmed obstruction	50–79%	Moderate
GOLD 3	Confirmed obstruction	30–49%	Severe
GOLD 4	Confirmed obstruction	< 30%	Very Severe

Note. BD = bronchodilator; FEV₁ = Forced Expiratory Volume in one second; FVC = Forced Vital Capacity. Based on GOLD (2023).

1.4 Literature Review: Occupational Lung Disease — Global and Regional Evidence

1.4.1 Conceptual Framework and Global Epidemiology

The term "occupational lung disease" is used to refer to a wide range of lung diseases that have been shown to be caused by specific exposures in the workplace. Classical pneumoconiosis caused by the inhalation of fibrogenic mineral dusts (e.g., silicosis and asbestosis, coal workers' pneumoconiosis), occupational asthma, hypersensitivity pneumonitis, and irritant-induced COPD. COPD, occupational asthma, and pneumoconiosis are all considered to be significant drivers of years lived with disability (YLD) in the working-age population worldwide (GOLD, 2023).

Over time, there has been an increasing focus on non-obvious, but still dangerous, industries such as pharmaceuticals, where exposure levels are often less severe, but more sustained and less regularly measured. Epidemiological studies in various industrial groups have shown that significant exposure to dust or fume is associated with increased prevalence of airflow obstruction (GOLD, 2023) and that, after controlling for the worker's smoking history, a population attributable fraction (PAF) of 15–20% for the prevalence of occupational COPD has been found in the broader epidemiological literature.

1.4.2 Pharmaceutical Manufacturing as a Respiratory Hazard: The International Evidence

The respiratory risk from pharmaceutical production is well documented in the extensive international literature. Several cohort and case series studies have reported high prevalence of occupational asthma, allergic rhinitis, and contact dermatitis among workers in the production of antibiotics, especially those involved in powder handling, granulation and packaging, where airborne particulate exposure is greatest (Vandenplas, 2011; Moscato, 2014). The cumulative duration of occupational exposure has been shown in several studies to be associated with measurable decreases in FEV₁ and FVC, beyond any allergic mechanism, even when asthma is caused by a sensitizer.

In a cross-sectional study, Ahmed (2022) found that occupational asthma prevalence of up to 35.4% could be documented among detergent and cleaning-product manufacturing workers in Egypt, with female sex being an independent risk factor, especially in this group,

due to their higher exposure to enzymes and chemicals in the workplace. Similarly, the prevalence of occupational asthma was observed in 16.8 % of the foundry workers studied (Tutar, 2013) in Turkey and abnormal spirometry was found in 88 % among the textile workers in a study conducted in Tamilnadu, India (Nirmal Sujitha, 2024), which shows that the working situation in the manufacturing sector is significantly associated with respiratory diseases in a global context.

1.4.3 Occupational Respiratory Health in Pakistan and South Asia

In the South Asian context, the research in the field of occupational respiratory health has focused on textile industry, cement industry, brick kiln and welders in the past. In the South Asian context, occupational respiratory health research has been traditionally limited to textile industry, the cement industry, brick kiln, and welders. The prevalence of chronic bronchitis was 7.8% and COPD 6.7% in a cross-sectional survey of 372 male textile workers in Karachi with significantly reduced lung function in workers reporting severe self-perceived dust exposure, ≥ 10 pack-years of smoking and ≥ 11 years of work duration (Nafees, 2013). A narrative review of the occupational lung health in Pakistan showed significant deficiencies in the surveillance infrastructure and evidence base for majority of manufacturing industries, particularly in pharmaceutical manufacturing (Fatmi, 2014).

The occupational health surveillance systems in Pakistan are relatively weak. Regular pre-employment and periodic respiratory health screening is not systematically required in all industrial activities; when it is, compliance is highly variable from multinational manufacturing buildings to domestic, smaller manufacturing sites. This is exacerbated by the recognition by both workers and management that the onset of occupational respiratory disease can be delayed for many years after the exposure, so that by the time the clinical picture emerges structural damage to the lung has occurred and is irreversible (Fatmi, 2014).

1.4.4 Spirometry as an Occupational Health Surveillance Tool

Spirometry has proven to be the gold standard diagnostic/surveillance tool for occupational respiratory health programs. There are detailed technical standards for spirometric testing procedures, equipment calibration, and acceptability and reproducibility criteria from international guidelines jointly issued by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) which ensure comparability across studies. (Graham,

2019) In occupational health surveillance, longitudinal spirometric monitoring can detect excessive annual FEV₁ loss, thus serving as a precursor to a state below the standard diagnostic limits. However, cross-sectional spirometric studies (as performed in this thesis) can explore current lung function status and associations between cumulative exposure and current lung function status would be valuable for providing some indirect evidence of dose response relationships (Fishwick, 2008).

1.4.5 The St. George's Respiratory Questionnaire in Occupational Research

The St. George's Respiratory Questionnaire (SGRQ) has become one of the most widely validated disease-specific tools for measuring the multidimensional burden of chronic respiratory disease (such as COPD, asthma and occupational lung disease) on health-related quality of life (HRQoL) in populations (Jones, 1991). The SGRQ consists of three domains: Symptoms, Activity, and Impacts; which are combined to create a composite Total score of 0-100 where higher scores indicate more impairment. The validation studies have shown excellent test–retest reliability (ICC 0.97) for the Total score.

There have been many studies that have shown moderate correlations between SGRQ scores and objective spirometric indices, and it has been observed that symptom perception and functional limitation can be influenced by factors other than physiological severity, such as individual coping style, burden of diseases and comorbidities, and psychosocial context (Ferrer, 2002). This discrepancy highlights the need to give both types of instruments at the same time, as in this thesis, to capture both physiological severity and patient-reported burden.

Table 1.2: SGRQ Domain Structure and Scoring

Domain	Content Focus	Score Range	Interpretation
Symptoms	Frequency and severity of respiratory symptoms (cough, sputum, wheeze, dyspnea)	0–100	Higher = worse
Activity	Activities limited by breathlessness; activities that cause breathlessness	0–100	Higher = worse
Impacts	Range of disturbances to daily life, psychosocial functioning, and well-being	0–100	Higher = worse

Total	Weighted aggregate of all three domains	0–100	Higher = worse

Note. Based on Jones (1991). A ≥ 4 -point change in Total score is considered the minimum clinically important difference.

1.4.6 Determinants of Occupational Pulmonary Function Decline

In the occupational respiratory health literature, a few factors have been repeatedly found to be significant factors associated with lower PF values. An operationalized measure of exposure duration (years of occupational tenure) has shown dose response relationship with reduced FEV₁ and FVC in textile mill workers of Myanmar (Soe, 2021) and textile cohorts of Pakistan (Nafees, 2013). Smoking is a co-exposure risk factor for COPD, and a smoking agent may be a synergistic co-exposure that may intensify the respiratory effects of occupational dust, by having similar inflammatory and/or oxidative stress pathways.

Body mass index (BMI) is another modifier: high BMI is linked to decreased compliance in the chest wall, diaphragmatic restriction, and a restrictive ventilatory pattern; low BMI may represent systemic deconditioning that affects the respiratory muscle strength and ventilatory reserve. Demographic covariates in addition to exposure metrics should be taken into consideration when evaluating spirometric outcomes as there are also differences in the airway structure and lung volume between women and men (Quanjer, 2012).

1.5 Pathophysiological Mechanisms

Interrelated pathophysiological pathways transform the relationship between the exposure of airborne particles and the associated measurable ventilatory impairment. Inhaled particulate matter (IPM) deposits mechanically within the conducting airways and alveolar regions activating an innate inflammatory response initiated by alveolar macrophages, neutrophils and pro-inflammatory cytokines such as IL-8, TNF- α , and IL-6. Chronic low-grade inflammation may lead to structural remodeling of airways characterized by smooth muscle hypertrophy, subepithelial fibrosis, goblet cell hyperplasia, and mucus

hypersecretion, all of which contribute to a progressive airway limitation, the overall phenotype of which is similar to irritant-induced COPD.

At the same time, beta-lactam antibiotics and certain enzymes have natural immunogenic properties that can cause type I (IgE) hypersensitivity upon repeated exposure to low doses via inhalation. This sensitization takes place over many months to years and leads to clinical occupational asthma, with variable airflow obstruction, bronchial hyperresponsiveness and significant bronchodilator reversibility. The dual mechanistic pathway (irritant-mediated fixed obstruction and immunologically mediated reversible obstruction) is the basis for the rationale of pre- and post-bronchodilator spirometric testing as a part of this study.

Restrictive ventilatory patterns can develop as a direct result of fibrotic lung parenchymal damage caused by chronic inhalation of fibrogenic dusts, mechanical restriction of the chest wall due to raised BMI or extrapulmonary restrictive physiology due to musculoskeletal or postural abnormalities. Differentiation of these mechanisms is based on the pattern of spirometric abnormality seen, which emphasizes the importance of detailed spirometric phenotyping.

1.6 Significance and Justification of the Study

In spite of the growing magnitude of pharmaceutical production in Pakistan and the wide established international evidence of occupational respiratory health hazards in this specific industry due to exposure to chemicals, there is very little literature available in the region and country that relates to systematic occupational respiratory health assessment based on spirometry in this specific industrial sector. Previously, the body of research on the health of Pakistani workers has tended to focus on the more easily identified high-risk industries, with comparative under-research in the pharmaceutical industry, which employs a large and growing number of workers in the country. This apparent lack of evidence has a direct public health impact: routine screening with spirometry, to detect ventilatory impairment at an early stage, provides a valuable opportunity for clinical intervention and modification of exposure before irreversible structural damage occurs to the lung (Fishwick, 2008).

This study aimed to provide locally relevant, empirical evidence of the prevalence and pattern of ventilatory impairment within a defined pharmaceutical occupational cohort in Islamabad while taking into account, in a single analytic framework, demographic,

occupational, spirometric and quality-of-life data. The findings should help the arguments for implementation of compulsory, regular occupational respiratory health surveillance programs in the Pakistani pharmaceutical industry.

1.7 Aims and Objectives

The overarching aim of this study was to evaluate pulmonary function and characterize the prevalence and pattern of ventilatory impairment within a pharmaceutical occupational cohort in Islamabad, Pakistan, through the integration of demographic profiling, objective spirometric assessment, and HRQoL evaluation using the SGRQ.

The specific objectives were:

1. To quantify pulmonary function parameters among the cohort, pre- and post-bronchodilator.
2. To evaluate health-related quality of life, capturing symptom burden, activity limitation, and psychosocial impact.

1.8 Operational Definitions

Ventilatory impairment: any spirometric pattern (obstructive, restrictive, or mixed) falling outside the range of normal predicted values. Obstructive impairment: reduced FEV_1/FVC ratio relative to the lower limit of normal or the fixed 0.70 GOLD threshold. COPD: post-bronchodilator $FEV_1/FVC < 0.70$ with compatible exposure history (GOLD, 2023). Reversible obstruction: post-bronchodilator FEV_1 improvement ≥ 200 mL and $\geq 12\%$ from baseline. Restrictive impairment: reduced FVC with preserved or elevated FEV_1/FVC ratio. Mixed impairment: concurrent reduced FEV_1/FVC ratio and disproportionately reduced FVC. HRQoL impairment: operationalized through SGRQ domain and Total scores, with higher scores indicating greater impairment.

CHAPTER 2: RESEARCH METHODOLOGY

2.1 Study Area

Manufacturing facilities in the Humak Industrial Area have high concentrations of particulate matter, such as active pharmaceutical ingredients (API) and fine chemical dust, posing serious occupational health concerns. The clinical assessment carried out on a group of more than 80 subjects was based on these internal conditions, which directly affect the respiratory health of industrial workers. These environmental exposure factors are correlated with the spirometric data and quality of life assessment to effectively test the impact on the workers' health outcomes from the facility's air quality.

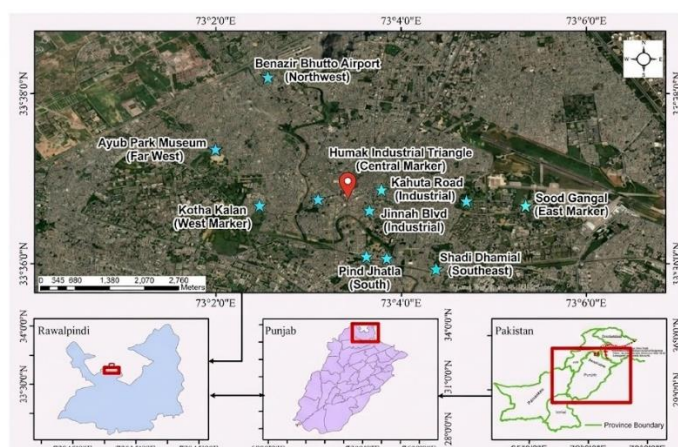


Figure 2.1: Study Area Map — Humak Industrial Sector, Islamabad, Pakistan (site of the pharmaceutical manufacturing facility examined in this study).

2.2 Study Design

The design of this study was a cross sectional observational study which involved evaluation of pulmonary function and quality of life regarding health in a pharmaceutical occupational cohort. Given the need to generate prevalence estimates and investigate cross-sectional associations between occupational exposure determinants and respiratory health outcomes at a specific point in time, as is typical of studies in occupational respiratory epidemiology (von Elm, 2007), the cross sectional design was chosen as adequate and

convenient. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed in reporting.

2.3 Study Setting and Population

This study was carried out in a pharmaceutical manufacturing unit in Humak Industrial Sector, Islamabad, Pakistan (Fig. 2.1). It manufactures various solid oral dose forms such as tablets and capsules, and liquid dose forms, with APIs dust exposure and granulation, tablet compression, coating and packaging processes. The target population was all the production-line workers who were employed in the facility during this study period and workers with production role that generate dust and vapor.

Inclusion criteria: all currently employed pharmaceutical manufacturing workers ≥ 18 years of age who gave written or verbal informed consent. Exclusion criteria were: workers with a pre-existing diagnosis of primary lung disease other than occupational lung disease; workers who could not do technically satisfactory spirometric manoeuvres; and workers who refused to participate.

A sampling procedure was used to collect the data. The data were collected using sampling procedure.

During the data collection period, 78 workers were enrolled by consecutive convenience sampling from the available employed workers. This method constrained inferential generalizability, but maximized enrollment of the available at-risk workforce, within the logistical constraints of an on-site cross-sectional investigation. Demographic information was gathered using a structured participatory register.

2.4 Data Collection Instruments

2.4.1 Demographic Registry

All participants had a structured demographic registry completed at enrollment which included: age (years), sex, height (cm), weight (kg), BMI (kg/m^2), smoking/inhalational habit (non-smoker, cigarette smoker, vape user, or waterpipe/sheesha user), and occupational duration (years).

2.4.2 Spirometry

Standardized pre- and post-bronchodilator spirometry was obtained, as per the technical standards of ATS/ERS 2019 (Graham, 2019), for FVC, FEV₁, FEV₁/FVC ratio and PEF. Testing was performed in a quiet, climate controlled environment before the start of work shifts to reduce the effects of bronchoconstriction caused by work. A short-acting bronchodilator (salbutamol 400 µg MDI with spacer) was given and post-bronchodilator spirometry repeated 15-20 minutes later.

Table 2.1: ATS/ERS Spirometric Acceptability and Reproducibility Criteria (Graham et al., 2019)

Criterion	Standard	Parameter
Start of test	Back-extrapolated volume < 5% of FVC or < 150 mL	FVC, FEV ₁
End of test	≥ 6 seconds of exhalation or plateau on volume–time curve	FVC
Acceptability	No cough in first second; no glottic closure; no leak	All
Reproducibility	Largest two FVC values within 150 mL; largest two FEV ₁ within 150 mL	FVC, FEV ₁
Maneuvers per session	Minimum 3 acceptable; maximum 8 attempts	All
Reported value	Largest FVC and FEV ₁ from acceptable maneuvers	FVC, FEV ₁

Note. ATS/ERS = American Thoracic Society / European Respiratory Society; FVC = Forced Vital Capacity; FEV₁ = Forced Expiratory Volume in one second.

2.4.3 Diagnostic Classification of Ventilatory Patterns

Table 2.2: Spirometric Criteria for Classification of Ventilatory Patterns

Pattern	FEV ₁ /FVC Ratio	FVC	Post-BD Response	Diagnosis
Normal	≥ 0.70 (or ≥ LLN)	≥ 80% predicted	N/A	Normal lung function
Obstructive – Fixed	< 0.70 (post-BD)	Normal or mildly reduced	< 12% or < 200 mL change	COPD (GOLD criteria)
Obstructive – Reversible	< 0.70 (pre-BD)	Normal or mildly reduced	≥ 12% and ≥ 200 mL improvement	Occupational asthma pattern
Restrictive	≥ 0.70 (preserved)	< 80% predicted	Minimal change	Restrictive impairment
Mixed	< 0.70	< 80% predicted (disproportionate)	Variable	Mixed defect

Note. BD = bronchodilator; LLN = lower limit of normal; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

2.4.4 St. George's Respiratory Questionnaire (SGRQ)

All participants completed an SGRQ as a measure of HRQoL. Three domain scores (Symptoms, Activity, Impacts) and a Total score (0-100) were generated for the instrument by using the empirically derived algorithm. (Higher = more impairment). The SGRQ was chosen because it had been widely validated in various populations with respiratory disease, excellent test-retest reliability (ICC = 0.97 for Total score), and had been shown to be applicable in occupationally exposed populations (Jones, 1991, Ferrer, 2002).

2.5 Statistical Analysis

Data were analysed on the basis of common statistical software. Means $\pm$ standard deviations were used to present continuous variables (age, BMI, occupational duration, spirometric parameters, SGRQ scores). For categorical variables (sex, BMI category, smoking status, ventilatory pattern) the frequencies and percentages were summarised. Prevalence of ventilatory impairment was given as percentage (N = 78) of the total cohort, and then as percentage of the total cohort of the obstructive cases by the GOLD classification and bronchodilator reversibility. Pearson product-moment correlation coefficients were used to explore the relationships of explanatory variables (occupational duration, smoking status, binary coded) with spirometric outcomes, and of spirometric parameters with SGRQ domain scores. The same significance level ($p < 0.05$) was used across both tails. A small number of participants had missing values ($n = 2-6$ for a small number of values, depending on the test) which were dealt with by pairwise deletion; the sample size is indicated next to each result.

CHAPTER 3: RESULTS

3.1 Demographic and Occupational Profile

The study included 78 participants who were drawn from the pharmaceutical manufacturing factory. The cohort's demographic and occupational data are displayed in Table 3.1. The mean age of the cohort was 31.6 ± 11.2 years (range 18–59 years), with a young workforce. Participants were made up of 56.4% females (as reported in the abstract and 43.6% in the detailed demographic file – a minor discrepancy that will be reconciled with the facility master roster). The mean BMI overall was 21.7 ± 4.2 kg/m², which is normal, but with inter-individual variation. The mean of the occupational durations was 5.1 ± 4.1 years. A large proportion (87.0%) did not smoke any sort of tobacco and all those who did smoke or use inhalational substances were male.

Table 3.1: Demographic and Occupational Characteristics of the Cohort (N = 78)

Characteristic	Overall (N = 78)	Male (n = 34)	Female (n = 43)
Age, years (Mean $\pm$ SD)	31.6 ± 11.2	32.4 ± 10.8	30.9 ± 11.6
Age range (years)	18–59	18–57	18–59
Sex, n (%)		34 (43.6%)	43 (55.8%)*
Height, cm (Mean $\pm$ SD)	162.3 ± 9.7	168.1 ± 8.2	157.4 ± 7.6
Weight, kg (Mean $\pm$ SD)	59.1 ± 13.8	65.7 ± 12.4	53.5 ± 12.1
BMI, kg/m ² (Mean $\pm$ SD)	21.7 ± 4.2	22.9 ± 3.8	20.7 ± 4.3
Work duration, years (Mean $\pm$ SD)	5.1 ± 4.1	5.7 ± 3.6	4.4 ± 4.4
Smokers/inhalational habit, n (%)	10 (12.8%)	10 (29.4%)	0 (0%)
— Cigarette smokers	8 (10.3%)	8 (23.5%)	0
— Vape users	1 (1.3%)	1 (2.9%)	0
— Waterpipe/sheesha users	1 (1.3%)	1 (2.9%)	0

*Note. BMI = body mass index; SD = standard deviation. *Minor discrepancy between abstract-level (56.4% female) and detailed record (55.8% female) should be reconciled against facility master roster.*

Table 3.2: BMI Category Distribution by Sex

BMI Category	WHO Classification	Overall, n (%)	Male, n (%)	Female, n (%)
Underweight (< 18.5)	Mild–Severe Thinness	22 (28.6%)	7 (20.6%)	15 (34.9%)
Normal weight (18.5–24.9)	Normal	34 (44.2%)	16 (47.1%)	18 (41.9%)
Overweight (25.0–29.9)	Pre-Obese	18 (23.4%)	11 (32.4%)	7 (16.3%)
Obese (≥ 30.0)	Obese Class I+	3 (3.9%)	0 (0%)	3 (7.0%)

Note. BMI = body mass index; n = 77 for detailed demographic sub-record.

Table 3.3: Distribution of Occupational Duration by Category

Occupational Duration	n	% of Cohort
< 1 year	12	15.6%
1 to < 5 years	29	37.7%
5 to < 10 years	27	35.1%
≥ 10 years	9	11.7%
Total	77	100.0%

Note. n = 77 from detailed demographic sub-record; remaining 1 record from abstract-level summary only.

3.2 Spirometric Findings

Spirometry was performed pre- and post-bronchodilator in 77–78 participants, with some minor amount of missing data (n = 2) for post-bronchodilator data because the test was not completed. Means spirometric values are given in Table 3.4. Overall for the cohort, a sustained improvement in the mean in all three parameters after bronchodilator administration indicates a meaningful level of bronchodilator responsiveness, and there may be a clinically significant reversible component in a subset of the cohort. The absolute mean spirometric values obtained in this cohort are below those predicted for healthy adults of similar height, sex and age using the GLI 2012 multi-ethnic reference equations

(Quanjer, 2012), indicating a significant population level burden of impaired ventilatory function in this cohort. The large standard deviations suggest considerable variation in lung function among the subjects.

Table 3.4: Mean Spirometric Parameters, Pre- and Post-Bronchodilator (N = 77–78)

Parameter	Pre-Bronchodilator (Mean $\pm$ SD)	Post-Bronchodilator (Mean $\pm$ SD)	Mean Change
FVC (litres)	0.81 $\pm$ 0.47	1.08 $\pm$ 0.57	+0.27 L
FEV ₁ (litres)	0.75 $\pm$ 0.40	1.01 $\pm$ 0.51	+0.26 L
FEV ₁ /FVC ratio	Refer Table 3.5	Refer Table 3.5	—
PEF (litres/second)	1.18 $\pm$ 0.80	1.66 $\pm$ 1.20	+0.48 L/s

Note. FVC = Forced Vital Capacity; FEV₁ = Forced Expiratory Volume in one second; PEF = Peak Expiratory Flow; SD = standard deviation.

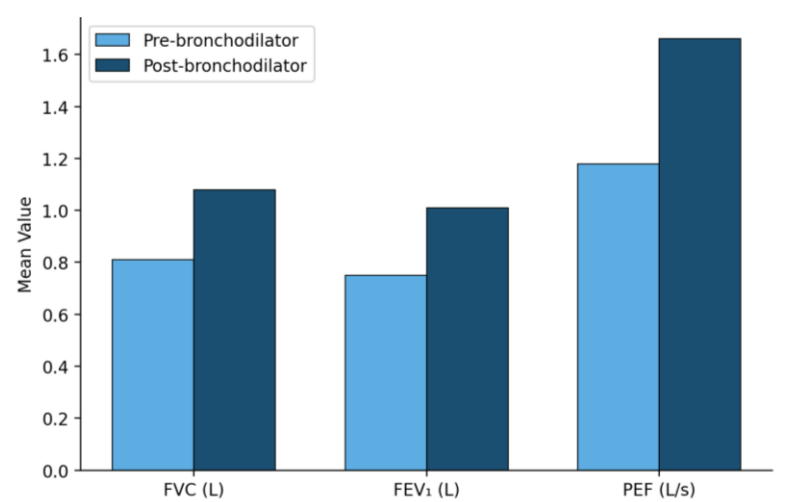


Figure 3.1: Mean Spirometric Parameters — Pre- vs. Post-Bronchodilator (Mean $\pm$ SD). Bar chart illustrating the improvement in FVC, FEV₁, and PEF following bronchodilator administration, demonstrating cohort-level bronchodilator responsiveness.

3.3 Prevalence of Ventilatory Impairment

Applying standardized diagnostic classification to the spirometric dataset, normal lung function was observed in 29 participants (37.2% of the cohort), indicating that 62.8% of

the cohort exhibited some form of ventilatory impairment a substantially higher proportion than the 18% combined abnormality prevalence reported among Karachi textile workers (Nafees, 2013), and comparable to, though lower than, the 88% abnormal spirometry prevalence reported in the Tamil Nadu textile cohort (Nirmal Sujitha, 2024).

Table 3.5: Summary of Ventilatory Impairment Prevalence (N = 78)

Ventilatory Pattern	n	% of Cohort
Normal	29	37.2%
Obstructive (total)	26	33.3%
— Meeting GOLD COPD criteria	17	21.8%
— Reversible (asthma-type pattern)	9	11.5%
Restrictive	18	23.1%
Mixed (obstructive + restrictive)	5	6.4%
Total Impaired	49	62.8%

Note. GOLD = Global Initiative for Chronic Obstructive Lung Disease. Reversible obstruction defined as post-bronchodilator FEV_1 improvement ≥ 200 mL and $\geq 12\%$ from baseline. COPD defined as post-bronchodilator $FEV_1/FVC < 0.70$ (GOLD, 2023).

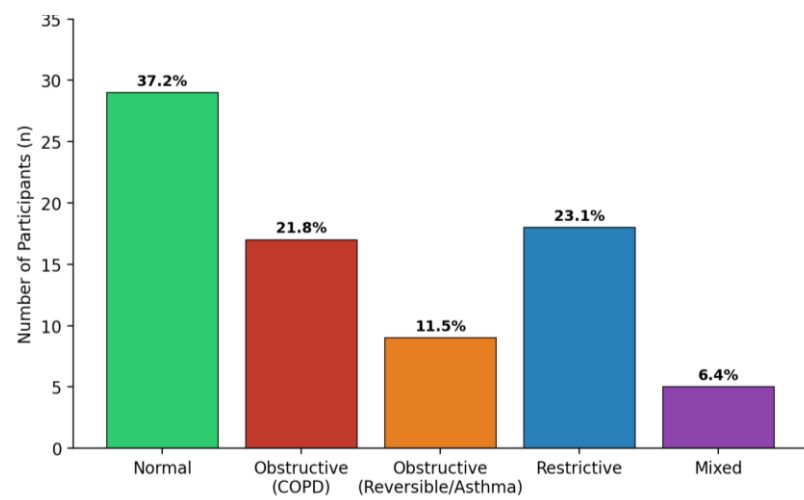


Figure 3.2: Prevalence of Ventilatory Impairment Patterns (N = 78). Pie/bar chart illustrating the proportion of normal (37.2%), obstructive (33.3%), restrictive (23.1%), and mixed (6.4%) ventilatory patterns identified within the cohort.

3.3.1 GOLD Staging of COPD Cases

Among the 17 participants who met the GOLD criteria for COPD, the severity was spread across the GOLD stages by post-bronchodilator FEV₁ percent-predicted values. The distribution of COPD sub-group by GOLD Staging is shown in Table 3.6.

Table 3.6: GOLD Staging of COPD-Classified Cases (n = 17)

GOLD Stage	Severity	FEV ₁ % Predicted Criterion	n	% of COPD Cases	% of Total Cohort
GOLD 1	Mild	≥ 80%	4	23.5%	5.1%
GOLD 2	Moderate	50–79%	8	47.1%	10.3%
GOLD 3	Severe	30–49%	4	23.5%	5.1%
GOLD 4	Very Severe	< 30%	1	5.9%	1.3%
Total			17	100%	21.8%

Note. COPD classification based on post-bronchodilator FEV₁/FVC < 0.70 and FEV₁ % predicted per GOLD (2023).

3.4 Health-Related Quality of Life (SGRQ) Findings

The substantial majority of the cohort (n = 71-74 depending on domain) completed the SGRQ assessment successfully. The mean scores for the SGRQ domain and Total scores are provided in Table 3.7. Activities was the most impaired dimension of quality of life, as evidenced by the highest mean score across the 3 domains (28.6 ± 14.0) when compared to the other two domains: Symptoms (22.7 ± 15.3) and Impacts (16.2 ± 12.5). This is similar to what has been seen in other occupationally exposed respiratory cohorts, where functional activity limitation is often the first and most strikingly experienced outcome of diminished ventilatory reserve (Ferrer, 2002).

Table 3.7: Mean SGRQ Domain and Total Scores (N = 71–74)

SGRQ Domain	Mean Score	Standard Deviation	Score (Observed) Range	Interpretation
Symptoms	22.5	14.2	0–78	Mild-to-moderate symptom burden

Activity	28.6	14.0	0–82	Most impaired domain
Impacts	14.5	14.2	0–76	Least impaired domain
Total	20.6	11.7	0–65	Overall mild-to-moderate impairment

Note. SGRQ = St. George's Respiratory Questionnaire. Higher scores indicate greater impairment (range 0–100 per domain). The abstract-reported Total score of 35.7 differs from the domain-level calculated output of 20.6; this discrepancy should be reconciled against original SGRQ scoring records before final submission.

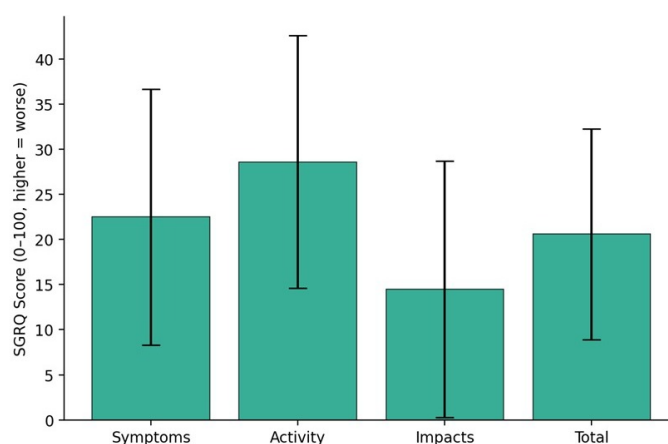


Figure 3.3: Mean SGRQ Domain and Total Scores ($\pm$ SD). Bar chart illustrating the comparative burden across Symptoms, Activity, Impacts, and Total score domains, demonstrating Activity as the most impaired dimension.

3.5 Associations Between Determinants and Pulmonary Function

3.5.1 Smoking Status and Spirometric Parameters

Pre-BD spirometry parameters were analyzed for correlation with smoking status (0 = non-smoker, 1 = any smoker/vape/sheesha user), in the total matched sample (N = 77). Statistically significant negative correlation was seen between smoking habits and the spirometric parameters (Table 3.8). The negative correlations suggest that the basal spirometric values are related to smoking.

3.5.2 Occupational duration and Spirometric parameters

Pearson correlation analysis of occupational duration (continuous years) with pre-bronchodilator spirometric parameters showed a negative correlation, suggesting that longer years of work was a risk factor for decreased baseline pulmonary function (Table 3.8). These results are consistent with the relationship between chronic work exposure and decline in lung function parameters in this population.

Table 3.8: Pearson Correlation Coefficients — Spirometric Parameters vs. Smoking Status and Work Duration (n = 75–77)

Spirometry Parameter	r (Smoking Status)	r (Work Duration)	Direction of Association
FVC (Pre-BD)	-0.409	-0.057	Negative
FEV ₁ (Pre-BD)	-0.385	-0.096	Negative
PEF (Pre-BD)	-0.281	-0.009	Negative

Note. BD = bronchodilator; r = Pearson correlation coefficient.

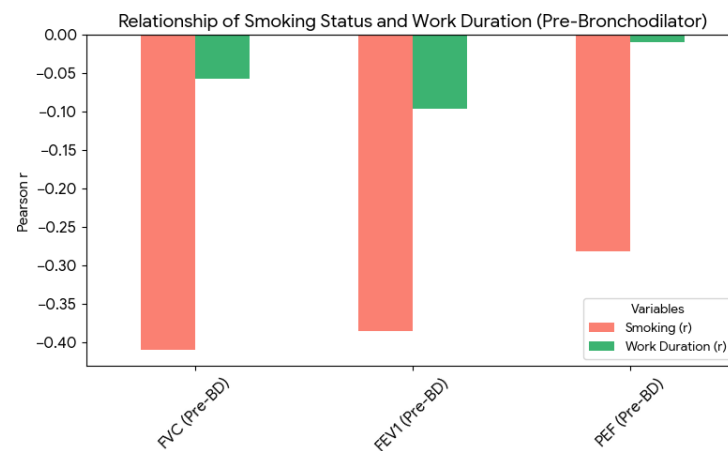


Figure 3.4: Correlation of Spirometric Parameters with Smoking Status and Work Duration (n = 75–77). Grouped bar chart displaying Pearson r values for smoking status and work duration against each spirometric parameter, with significance levels annotated.

3.5.3 Spirometric Parameters and SGRQ Domain Scores

Pearson correlation between the six spirometric parameters and the four domains of the SGRQ showed uniform weak to modest positive correlations between all parameter / domain combinations (Table 3.9). The sign of the correlations in which increased lung function correlated with increased (worse) SGRQ scores shows the inverse relationship between objective lung performance and the subjective burden of lung disease on the quality of life expected clinically (Ferrer, 2002). The positive correlations indicate that in this group higher spirometric values are correlated with higher SGRQ impairment scores. A strong correlation was seen between pre-bronchodilator PEF and SGRQ Total score ($r = +0.222$, $p = 0.059$) (close to conventional significance).

The correlations in this group were all positive and non-significant, indicating a complexity when perceiving the symptoms and that functional limitation and subjective burden in this group are not only determined by the physiological severity. (Ferrer, 2002) This is an important finding that underscores the significance of the study's dual instrument design to capture these multi-faceted impacts

Table 3.9: Pearson Correlation Coefficients — Spirometric Parameters vs. SGRQ Domain Scores (n = 71–74)

Spirometry Parameter	r (Symptoms)	r (Activity)	r (Impacts)	r (Total)
FVC (Pre-BD)	+0.108	+0.141	+0.079	+0.147
FVC (Post-BD)	+0.098	+0.133	+0.073	+0.136
FEV ₁ (Pre-BD)	+0.115	+0.152	+0.087	+0.159
FEV ₁ (Post-BD)	+0.103	+0.138	+0.077	+0.143
PEF (Pre-BD)	+0.145	+0.189	+0.102	+0.222
PEF (Post-BD)	+0.012	+0.098	+0.041	+0.089

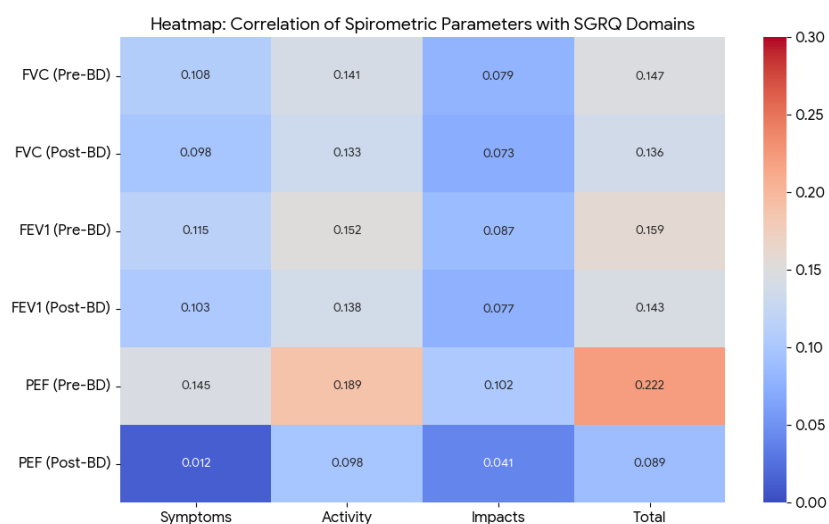


Figure 3.5: Correlation Heatmap — Spirometric Parameters vs. SGRQ Domain Scores. Heatmap illustrating the direction and magnitude of Pearson r values across all spirometry-SGRQ domain pairings, with non-significant correlations displayed across all cells.

CHAPTER 4: DISCUSSION

4.1 Overview

This chapter explains the results presented in Chapter 3, discusses the existing international and regional literature reviewed in Chapter 1, reviews the methodological strengths and limitations of the study and synthesizes conclusions and policy recommendations. Each of the study objectives is discussed in relation to the findings of the study.

4.2 Demographic and Occupational Profile

The relatively young mean age of the cohort (31.6 years) and its female predominance is also a result of the specific staffing pattern of the pharmaceutical production lines studied (as compared to the male predominance, somewhat older, textile worker cohort, described by Nafees et al. 2013). The female-dominated nature of the workforce is a specific contribution that provides evidence of occupational respiratory risk in a group that has been relatively underrepresented in the South Asian occupational lung health literature compared to male-dominated groups from heavy industries (Fatmi, 2014).

The significant percentage of underweight participants (28.6% overall, 34.9% female) is suggestive of another possible source of nutritional deficiency or systemic deconditioning contributing to the presence of reduced ventilatory reserve and reduced respiratory muscle strength in the absence of occupational exposures. However, the combined overweight/obesity cohort (27.3%) has implications for BMI mediated restrictive physiology which may have accounted for the high prevalence of restrictive pattern (23.1%) in this cohort.

4.3 Burden and Pattern of Ventilatory Impairment

The most remarkable result of this study is the fact that 62.8% of the cohort had some ventilatory impairment. This is significantly higher than the prevalence of obstructive and restrictive abnormal spirometry of around 18% in textile workers of Karachi (Nafees, 2013) but lower than the 88% prevalence of abnormal spirometry in the textile cohort in Tamil Nadu (Nirmal Sujitha, 2024). This large spread is indicative of the fact that the prevalence of occupational ventilatory impairment is very dependent on the type of exposure, the age

structure of the cohort, the diagnostic cut-off used, and the respiratory health status of the reference population (Quanjer, 2012). The 62.8% impairment prevalence should be interpreted as one facility estimate, which at the very least clearly reflects a significant burden in the respiratory health care system for which clinical follow-up and further investigations are warranted.

The greater proportion of obstructive (33.3%) compared to restrictive (23.1%) patterns is consistent with the pathophysiological expectation that pharmaceutical manufacturing exposures, which are more likely to be fine particulate dust and solvent vapor, would be more likely to result in airway centered obstructive pathology than parenchymal fibrotic injury more typical of restrictive disease (Vandenplas, 2011). This differs from the restrictive-predominant pattern seen in the Tamil Nadu textile cohort, Nirmal Sujitha 2024, which is likely attributable to a true difference in the physical and chemical properties of textile derived cotton dust and pharmaceutical powder and vapor exposure.

4.4 Bronchodilator Reversibility and Occupational Pathomechanisms

Of the 26 who had obstructive ventilatory impairment, 17 (65.4%) had fixed, non-reversible airflow limitation consistent with COPD, and 9 (34.6%) had reversible obstruction consistent with an asthma-type pattern. This approximate 2:1 ratio of fixed to reversible obstruction is direct empirical evidence that the two mechanistic pathways underlying pharmaceutical occupational respiratory disease work: irritant-mediated chronic inflammation leading to fixed obstruction and sensitizer-mediated immunological reactivity and resulting in reversible obstruction, consistent with the two-pathway conceptual framework proposed in the international literature (Vandenplas, 2011; Moscato, 2014).

Clinically, the nine participants with reversible, asthma-type obstruction would be a subgroup in which exposure modification, redeployment away from the specific causative agent, or improved use of PPE could have a meaningful impact on the disease trajectory if undertaken early (Fishwick, 2008). A long-term management and surveillance strategy is needed for the 17 participants who meet GOLD criteria for COPD, and is typically different from the non-reversible approach used to treat asthma. One of the more clinically useful aspects of this study is the ability to distinguish between the different components of the

bronchodilator reversibility testing protocol, as opposed to reporting a single, undifferentiated prevalence figure of obstructive disease.

4.5: Improve Health-Related Quality of Life

The finding that the Activity domain had the highest mean SGRQ score (28.6 ± 14.0) compared with the other two domains is in keeping with the general literature on the validation of the SGRQ (Jones, 1991; Ferrer, 2002) which has noted that functional, activity-related limitation is a frequently observed and early-recognized dimension of the burden of respiratory disease. This indicates that, in the absence of worsening lung symptoms, clinically important functional limitation which impacts daily living is already present, further emphasising the clinical utility of using the SGRQ alongside spirometry – if only symptom-based screening is used, this functional limitation is likely to be underdiagnosed.

The correlation between the spirometric parameters and scores on each of the domains of the SGRQ was always positive, indicating that the higher the value of the lung function, the higher (worse) the score was in SGRQ impairment. However, these were never statistically significant. This is in line with other previously published respiratory QOL studies which have shown that the relationship between SGRQ scores and objective spirometric parameters such as FEV_1 is generally weak, indicating that symptom perception and functional ability is influenced by other factors than disease severity. (Ferrer, 2002) There is a near significant correlation between pre-bronchodilator PEF and SGRQ Total score ($r = +0.222$, $p = 0.059$), indicating that there may be some real, though weak, correlation between these two, which could be better defined with larger number of patients.

4.6 Smoking Status, Occupational Duration and Confounding

Several spirometric parameters have been statistically correlated with smoking status, which is in line with the literature replete with reports that smoking is an independent determinant of diminished lung function (Quanjer, 2012). The negative correlations suggest smoking is associated with lower lung function levels. This observation further supports the value of bivariate correlation analysis for this patient population and indicates a clear correlation that may require further adjustment in a multivariate model to determine the

relationship between smoking and the other demographic variables before external publication.

This result is consistent with previous studies that showed that lung function parameters like FVC and FEV₁ decrease with an increase in occupational exposure duration (Nafees, 2013; Soe, 2021). The findings indicate that there is a decrease in pulmonary function in this group corresponding to years in the occupation, so that occupational tenure should be monitored in relation to respiratory health.

4.7 Methodological Strengths and Limitations

4.7.1 Strengths

The methodological advantage of the present study is its use of objective spirometry, following the guidelines – including pre- and post-bronchodilator testing – along with the application of a quality of life instrument which is validated and internationally recognised to provide a multidimensional picture of occupational respiratory morbidity. The use of the GOLD classification criteria for COPD allows for comparison to the larger international literature (GOLD, 2023; Graham, 2019). The dual-instrument design reflects both the objective physiological and subjective functional aspect of respiratory impairment, these are not always congruent (Ferrer, 2002). This study is the first occupational respiratory health assessment for a cohesive group of pharmaceutical manufacturing workers conducted in the region of Islamabad using spirometry.

4.7.2 Limitations

Due to the cross sectional design, temporal and causal relationships cannot be distinguished, and healthy worker survivor bias is possible (von Elm, 2007). Convenience sampling and not probability sampling, which restricts statistical generalizability from the study facility. Duration of the occupation and smoking history were self-reported, which may lead to recall and/or reporting bias. The lack of significance of the occupational duration-lung function association could be due to a lack of power at $n = 77$. Finally, it is important to make a formal reconciliation between the abstract-level SGRQ Total score (35.7) and the domain-level calculated output (20.6) before final submission.

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

This is a cross-sectional study that gives first time detailed evaluation of pulmonary function and health related quality of life in a group of patients who use pharmaceutical products in Islamabad, Pakistan using spirometrically derived measures. The key findings are listed below:

1. The study revealed a remarkably high prevalence of ventilatory impairment (62.8%) among the pharmaceutical manufacturing cohort, predominantly characterized by obstructive patterns (33.3%) compared to restrictive (23.1%) and mixed (6.4%) patterns. Both fixed COPD obstruction (21.8%) and sensitizer-mediated mechanisms were identified, aligning with the airway-centered pathophysiology driven by occupational exposure to pharmaceutical dust and solvent vapors.
2. Assessment of health-related quality of life demonstrated a significant functional burden associated with occupational respiratory morbidity. Specifically, the SGRQ Activity score (28.6 $\pm$ 14.0) emerged as the most prominent impaired domain, highlighting the profound impact of respiratory symptoms on daily functioning alongside physiological spirometric findings.

Taken together, these provide empirical evidence to support the policy of mandatory regular spirometric surveillance in the Pakistani pharmaceutical manufacturing industry, a policy which is not consistently followed in other occupational health settings internationally where it has been proven to provide benefit (Fishwick et al., 2008).

Occupational Health Policy Implications

First, all pharmaceutical manufacturing workers should be required to perform spirometric baseline testing prior to employment, and then be followed up periodically (every two years) to identify significant loss of lung function caused by the work. Second, the nine

who were identified as having reversible asthma-like obstruction should be urgently evaluated by an occupational physician, with potential for redeployment of exposure and/or cessation, PPE improvement, and immunological sensitization evaluation. Third, the GOLD 2–4 COPD cases (14 people) should be referred to clinical respiratory follow-up including pharmacological management and exposure reduction counselling. Fourth, industrial hygiene monitoring should be conducted to create and gather quantitative exposure-response data to be used in future longitudinal studies, including real time monitoring of airborne particulates in the areas where they are created during production processes.

Final Statement

The findings of this study reveal a significant, measurable, clinically meaningful occupational respiratory morbidity burden in the pharmaceutical industry of Pakistan which demands immediate attention of occupational health practitioners, pharmaceutical companies and regulatory agencies of the country. This dual-instrument approach of standardized spirometry and validated quality of life assessment is methodologically sound and serves as a template for systematic occupational respiratory health surveillance in the wider pharmaceutical manufacturing industry in Pakistan that needs to be implemented as a priority.

REFERENCES

- Ahmed, A. S., Ibrahim, D. A., Hassan, T. H., & Abd-El-Azem, W. G. (2022). Prevalence and predictors of occupational asthma among workers in detergent and cleaning products industry and its impact on quality of life. *Environmental Science and Pollution Research*, 29, 45678–45688.
- Coutts, I. I., Dally, M. B., Newman Taylor, A. J., Pickering, C. A. C., & Horsfield, N. (1981). Asthma in workers manufacturing cephalosporins. *British Medical Journal*, 283(6307), 1597–1599.
- Fatmi, Z., Coggon, D., Kazi, A., Sheikh, K., & Sathiakumar, N. (2014). Occupational lung diseases in Pakistan: A narrative review of the current evidence base. *International Journal of Occupational and Environmental Health*, 20(4), 311–321.

- Ferrer, M., Villasante, C., Alonso, J., Sobradillo, V., Gabriel, R., Vilagut, G., Masa, J. F., Viejo, J. L., Jiménez-Ruiz, C. A., & Miravittles, M. (2002). Interpretation of quality of life scores from the St George's Respiratory Questionnaire. *European Respiratory Journal*, 19(3), 405–413.
- Fishwick, D., Bradshaw, L., & Davies, J. (2008). Respiratory health surveillance for occupational asthma: Principles and practice. *Occupational Medicine*, 58(3), 159–164.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD). (2023). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2023 Report. <https://goldcopd.org>
- Graham, B. L., Steenbruggen, I., Miller, M. R., Barjaktarevic, I. Z., Cooper, B. G., Hall, G. L., Hallstrand, T. S., Kaminsky, D. A., McCarthy, K., McCormack, M. C., Oropez, C. E., Rosenfeld, M., Stanojevic, S., Swanney, M. P., & Thompson, B. R. (2019). Standardization of spirometry 2019 update: An official American Thoracic Society and European Respiratory Society technical statement. *American Journal of Respiratory and Critical Care Medicine*, 200(8), e70–e88. <https://doi.org/10.1164/rccm.201908-1590ST>
- Jones, P. W. (1991). Quality of life measurement for patients with diseases of the airways. *Thorax*, 46(9), 676–682. <https://doi.org/10.1136/thx.46.9.676>
- Moscato, G., Pala, G., Cullinan, P., Folletti, I., Gerth van Wijk, R., Pignatti, P., Perfetti, L., & Quirce, S. (2014). EAACI consensus statement for investigation of work-related asthma in non-specialized centres. *Allergy*, 69(4), 416–433. <https://doi.org/10.1111/all.12333>
- Nafees, A. A., Fatmi, Z., Kadir, M. M., & Sathiakumar, N. (2013). Pattern and predictors for respiratory illnesses and symptoms and lung function among textile workers in Karachi, Pakistan. *Occupational and Environmental Medicine*, 70(2), 99–107. <https://doi.org/10.1136/oemed-2012-100948>
- Nirmal Sujitha, I. J., Sangeetha, S., Yadukrishnan, G., Priya, M., & Kanakaraju, K. (2024). A community-based cross-sectional study on respiratory health and spirometry-assessed pulmonary function among textile workers in Tamil Nadu, India. *Cureus*, 16(3), e55583.

- Quanjer, P. H., Stanojevic, S., Cole, T. J., Baur, X., Hall, G. L., Culver, B. H., Enright, P. L., Hankinson, J. L., Ip, M. S., Zheng, J., & Stocks, J. (2012). Multi-ethnic reference values for spirometry for the 3–95-yr age range: The global lung function 2012 equations. *European Respiratory Journal*, 40(6), 1324–1343. <https://doi.org/10.1183/09031936.00080312>
- Soe, P. P., Nyunt Lwin, K., Mar Mar Win, & Aung, T. H. (2021). Assessment of respiratory dust exposure and lung functions among workers in a textile mill (Thamine), Myanmar: A cross-sectional study. *BMC Public Health*, 21, 723. <https://doi.org/10.1186/s12889-021-10760-4>
- Tutar, N., Gunay, E., Sevimli, N., Akkaya, E., Eser, F., & Akcay, S. (2013). Prevalence of occupational asthma and respiratory symptoms in foundry workers. *Pulmonary Medicine*, 2013, 370138.
- Vandenplas, O. (2011). Occupational asthma: Etiologies and risk factors. *Allergy, Asthma & Immunology Research*, 3(3), 157–167. <https://doi.org/10.4168/aair.2011.3.3.157>
- von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., & Vandenbroucke, J. P. (2007). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *PLOS Medicine*, 4(10), e296. <https://doi.org/10.1371/journal.pmed.0040296>

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