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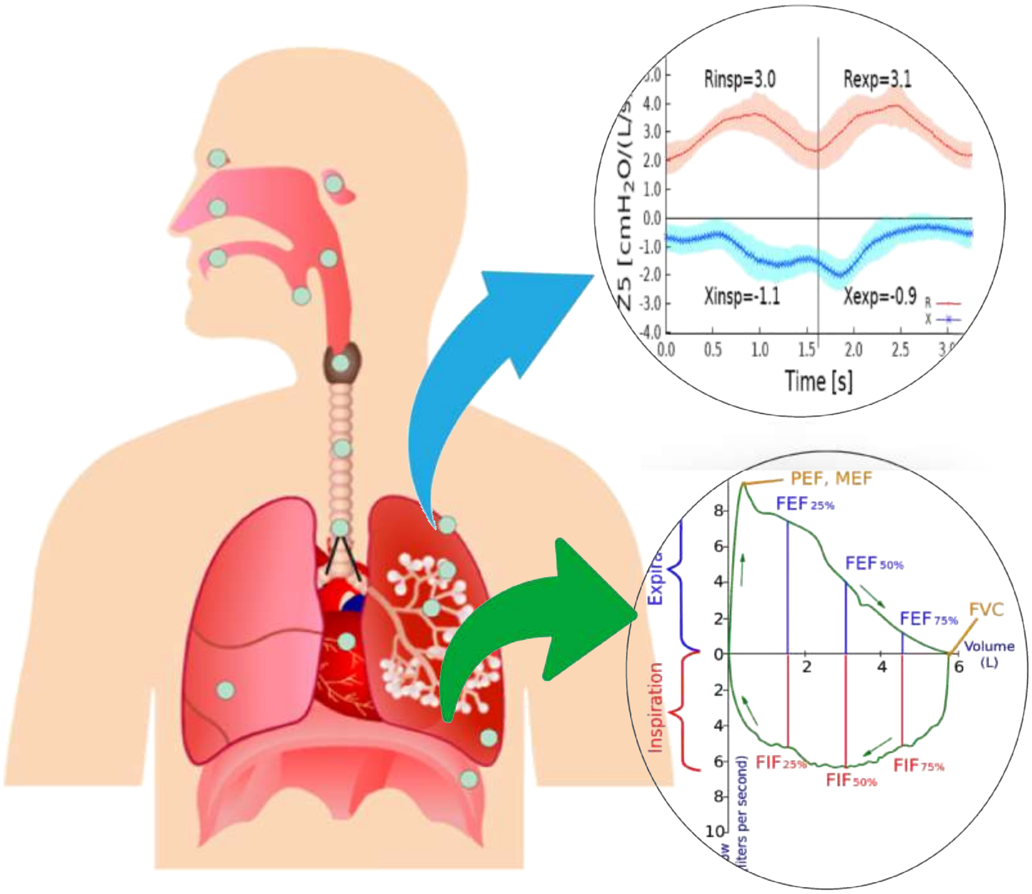

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CHARACTERIZATION OF PREVAILING CHRONIC RESPIRATORY MORBIDITIES AMONG SEVERELY GAS EXPOSED POPULATION OF BHOPAL

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INTRODUCTION

Bhopal Gas Disaster, one of the worst chemical disasters in mankind occurred on 3rd December 1984. During this disaster, several toxic gases were leaked from the pesticide plant of Union Carbide India Limited situated at Bhopal (capital of state Madhya Pradesh, India). The exposed subjects immediately developed a burning sensation in eyes and throats, suffocation, nausea, and severe respiratory distress. Many exposed subjects died immediately and following subsequent weeks, mostly due to respiratory complications. The survivors of this disaster continued to suffer from different morbidity over the last three decades.[1-3]

Following the disaster, area Bhopal city was categorized into gas affected and non-affected areas based on immediate symptoms of inhabitants. The gas affected areas were further subdivided into mild, moderate, and severely affected areas based on the mortality rate between 3rd and 6th December 1984. In January 1985, the Indian Council of Medical Research (ICMR) assembled cohorts from both gas affected and non-affected areas of Bhopal city and initiated a long-term population-based epidemiological study to assess the long-term health effects of toxic gas exposure. A detailed description of these cohorts has been published earlier.[1-3] The health status of the individuals registered under these cohorts are collected by regular surveys. The morbidity is recorded as per self-reported symptoms by the individual him/herself or the family member present at the time of surveys. Since, inception, the respiratory morbidities remained as one of the commonest health problems of the exposed cohorts.[1-3] The lung function of the individuals registered under these cohorts was not systematically examined. We hypothesized that the persistent abnormality in lung function, especially small airways function may be responsible for their respiratory morbidity.

OBJECTIVES

The aim of our study was

(i) to characterize the respiratory symptoms,

(ii) to evaluate the lung function by forced oscillation technique (FOT) and spirometry, and

(iii) to assess the relationships of respiratory morbidity with lung function abnormality.

METHODS

3.1 Study population

This prospective cross-sectional study was carried out from February 2018 to February 2020. The study protocol was approved by the Institutional Ethics Committee of the National Institute for Research in Environmental Health (NIREH/BPL/1EC-prj.19/2017-18/1458). The number of subjects examined during each survey was widely variable.[3] The proposed study was approved to include the subjects belong to the severely exposed cohort only. We decided to enroll all subjects who were available during the survey that carried out before initiation of this study i.e. 54th round of the survey (July – December 2017). The health status of 4170 severely exposed individuals was collected during that survey. Therefore, we set the target of 4000 individuals for this study. The exclusion criteria were those declined to participate and not available on two attempts. The previous study of Bhopal gas disaster cohorts showed the individuals who were <20 years at the time of the disaster had lesser respiratory morbidity as compared to those who were ≥ 20 years old.[3] Therefore, we classified the study population into two age groups: age ≤ 55 years (i.e., age was ≤20 years at the time of the disaster) and age >55 years (i.e., age > 20 years at the time of the disaster) to verify that finding.

3.2 Characterization of chronic respiratory symptoms

We developed a study questionnaire based on INSEARCH (Indian Study on Epidemiology of Asthma, respiratory symptoms and Chronic Bronchitis) questionnaire to characterize respiratory symptoms and smoking habits.[4] Besides, the death of family members within one year following the disaster, whether admitted to a hospital for any complaint within one week after the disaster, the distance of residence from the plant at the time of exposure, and current co-morbidity (e.g. diabetes, hypertension, coronary artery disease, chronic kidney diseases, etc.) were also enquired. The questionnaire was administered by a trained technician and re-evaluated by the principal investigator during lung function tests. The diagnosis of asthma was established by affirmative responses to at least one of the two questions on wheezing and tightness of the chest, plus one of the three questions on the history of the previous diagnosis of asthma, an attack of asthma, use of medication for asthma in the past 12 months. Similarly, the diagnosis of chronic bronchitis was based on the presence of cough with expectoration for ⩾3 months with an affirmative response to one of the two questions i.e. usually cough first in the morning and usually bring out phlegm from the chest first time in the morning. The complaint of breathlessness was defined as an affirmative response to at least one of four questions on breathlessness in different situations i.e., a feeling of morning breathlessness, breathlessness on exertion, breathlessness without exertion, and breathlessness at night. The complaint of cough was defined as an affirmative response to either having cough in the morning or at night. The lung function tests were carried out in those who consented for the same.

3.2.1. Forced Oscillatory Technique (FOT)

Within-breath and whole-breath respiratory system resistance (Rrs) and reactance (Xrs) were measured by Resmon Pro Full device (Restech Srl, Milan, Italy) at 5, 11, and 19 Hz sinusoidal signals. The equipment was calibrated daily before the procedure with reference impedance supplied by the manufacturer. The age in completed years, gender, standing height to nearest centimeter without shoes, and weight rounded off to the nearest kilogram were recorded. The FOT was carried out in an upright sitting position, putting nose clip, supporting the checks, and as per the European Respiratory Society's recommendation.[5] The patients were asked to take quite tidal breaths through an antibacterial filter. Each individual performed at least three FOT, and each test was continued till 15 accepted breaths were recorded. The mean of parameter obtained during three acceptable tests was retained for the analysis. The FOT parameters included in the present analysis were whole breath respiratory system resistance at 5 Hz (R5), whole-breath respiratory system reactance at 5 Hz (X5), and frequency-dependence of resistance calculated as the difference of whole-breath resistance at 5 and 19 Hz (R_{5-19}). R5 and R_{5-19} were considered elevated if the measured values were higher than the upper limit of normal (ULN) of predicted Indian adults' values.[6] The X5 was considered elevated if the observed values were lower than the lower limit of normal (LLN) of predicted values for Indian adults. An abnormal FOT was defined as the presence of elevated R5 or R_{5-19} or X5 or all the three parameters were elevated.

3.2.2 **Spirometry**:

After the FOT, the spirometry was carried out as per ATS-ERS recommendation using PowerCube Diffusion+ (GANSHORN Medizin Electronic, Germany).[7] The spirometry was performed in a sitting position and wearing a nose-clip. The individuals were asked to take a few tidal breaths and then inhale rapidly and maximally, followed by immediate exhalation without any hesitation and maximum force. The forceful exhalation was continued till no more air was expelled out. Each participant performed at least three acceptable maximal forced expiratory maneuvers. The highest value of forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were recorded. The North Indian regression equations were used to estimate predicted values of spirometry parameters, and the lower limit of normal (LLN) was set at the 5^{th} percentile.[8] If both $FEV_1/FVC \geq 0.70$ and FVC ≥ LLN, then spirometry was categorized as normal spirometry. If $FEV_1/FVC < 0.70$, then it was categorized as an obstructive pattern. If $FEV_1/FVC \geq 0.70$ and FVC < LLN, then it was categorized as restrictive spirometry. The severities of obstruction and restriction based on FEV_1% of predicted were as follows; mild (≥70); moderate (≥60 to <70); moderately severe (≥50 to <60); severe (≥35 to <50); and very severe (<35). If the mid expiratory flow rate (MMEF) was less than LLN, it was categorized as low MMEF.

3.3 ANALYSIS

Counts and percentages summarized the categorical variables. The proportions were presented with 95% confidence intervals (CI) and were compared by Pearson's chi-square test. The parametric variables were presented as mean± standard deviation, and the student's t-test was used to compare between two groups. Univariate and multivariate logistic regression analysis was also performed to assess respiratory symptoms' association, age groups with an abnormality in FOT, and spirometry parameters. The odds ratios (OR) with 95% CI were used to assess the associations. The significance was accepted at the 0.05 level. The statistical analysis was carried out by IBM® SPSS® Version 25.

Figure 1: Information collection on questionnaire

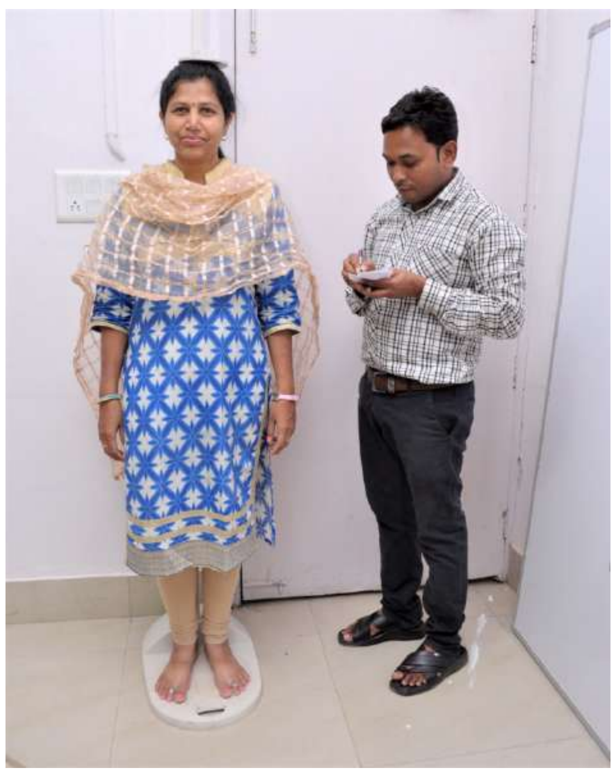

Figure 2: Anthropometric measurement of study participants

Figure 3: Spirometry of study participants

Figure 4: Clinical examination of study participants

Figure 5: Impulse oscillometry of study participants

4. RESULTS

4.1 Demographic characteristics

During the study period, 1695 severely exposed individuals (41.1%) out of the target 4000 were contacted. Of them, 916 individuals (55.7%) participated in this study, and 558 (60.9%) completed the study, i.e. participated in lung function testing (Figure 1). The mean age of the study population was 55.2±12.3 years. Nearly half (48.3%) of the study population were males. The majority of the study subjects (98.9%) were residing within 1 Km of the Union Carbide Plant at the time of exposure. The individuals reported the death of at least one family member (residing with them) within one year after the disaster was 20.7%. A total 220 subjects (24%) claimed that they were admitted to the hospital within one week after the disaster for their symptoms. The demographic characteristics, co-morbidity, and respiratory symptoms of those completed the study (n=558) and those who didn't (n=358) are compared in Table 1. The demographic characteristics of both groups were comparable. Smoking tobacco for more than one year was reported by 168 (18.4%) individuals and 77.4% were active smokers. Except for five females, all smokers were male, and mostly (88.7%) smoked bidi (small hand-rolled cigarettes made of tobacco and wrapped in tend leaves). The number of smokers was significantly less in the age group ≤ 55 years as compared to the age group >55 years (13.9% vs. 22.7%, P<0.01). The predominant comorbidity was systemic hypertension (37.0%; 95% CI: 33.9-40.2), followed by diabetes (14.4%; 95% CI: 12.3 - 16.8). The history of coronary artery diseases was reported by 5.8% (95% CI: 4.5-7.5) subjects. Those who completed the study had less coronary artery disease as compared to those who didn't (4.1% vs. 8.4%; p=0.00). The individuals who completed the study had significantly less breathlessness (71.7% vs. 88.5%; p<0.01), less cough (15.1% vs. 30.7; p<0.01), and less chronic bronchitis (9.9% vs. 24.3%; p<0.01) as compared to those not completed the study.

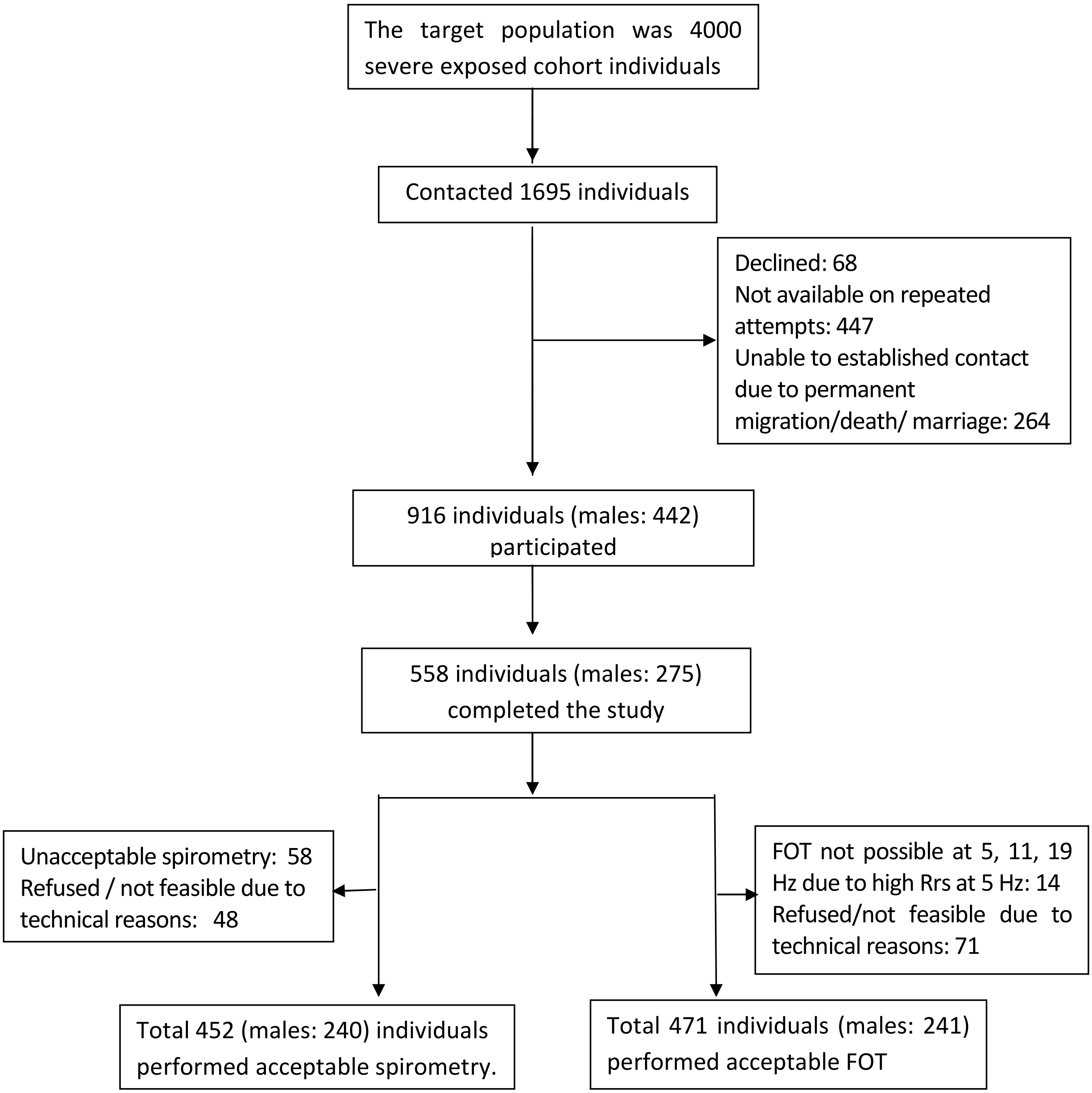

Figure 1: Flow chart of subject recruitment

4.2 Respiratory morbidity

The majority (79.6%; 95% CI: 76.9 – 82.1) had at least one respiratory symptom. The predominant symptom was breathlessness on exertion (76.6%; 95% CI: 73.7-79.2), followed by cough (21.2%; 95% CI: 18.7-23.9). The prevalence of chronic bronchitis and bronchial asthma was observed as 15.5% (95% CI: 13.3-17.9) and 6.6% (95% CI: 5.1-8.3), respectively (Table 1). The age group distribution between males and females in those who completed the study was statistically not different (Table 2). The females had more breathlessness (64.7% vs. 78.4%; p<0.01), less cough (11.7% vs. 18.5%; p=0.03) and had less chronic bronchitis (6.4% vs.13.5%.; p<0.01) as compared to males. The younger individuals (age ≤ 55 years) had less breathlessness (75.9% vs. 80.6%; p=0.05), cough (18.1% vs. 24.2%, p+0.015), and bronchial asthma (4.0% vs. 9.1%, p=<0.01) as compared to older individuals (age >55 years). However, the prevalence of chronic bronchitis was comparable in both age groups (14.3% vs. 16.6%; p=0.19).

TABLE 1. Demographic characteristics and respiratory symptoms of the study population

Variables	Completed the study (n=558)	Not completed the study (n=358)	p-value	Total (=916)
Age (yr), mean ±SD	55.8±11.6	54.3±13.2	0.08	55.2±12.3
Male, n (%)	275 (49.3)	167 (46.6)	0.46	442 (48.3)
Smoked for >1 yr, n (%)	107 (19.2)	61 (17.0)	0.23	168 (18.4) (95% CI: 15.9-20.9)
Comorbidities				
Diabetes mellitus, n (%)	75 (13.4)	57 (15.9)	0.43	132 (14.4) (95% CI: 12.3-16.8)
Hypertension, n (%)	205 (36.7)	134 (37.4)	0.83	339 (37.0) (95% CI: 33.9-40.2)
Coronary artery disease n (%)	23(4.1)	30 (8.4)*	0.00	53 (5.8) (95% CI: 4.5-7.5)
BMI (kg/m^2)	24.6±5.2	-		-
Breathlessness, n (%)	400 (71.7)	317 (88.5)*	0.00	717 (78.3) (95% CI: 75.5-80.8)
Cough, n (%)	84 (15.1)	110 (30.7)*	0.00	194 (21.2) (95% CI: 18.7-23.9)
Chronic bronchitis, n (%)	55 (9.9)	87 (24.3)*	0.00	142 (15.5) (95% CI: 13.3-17.9)
Bronchial asthma, n (%)	38 (6.8)	22 (6.1)	0.79	60 (6.6) (95% CI:5.1- 8.3)

BMI: body mass index; *p-value<0.01; CI: confidence interval

Table 2. The distribution of age group and respiratory symptoms of those completed the study (n=558), stratified by gender

	Male (n=275) n (%)	**Female (n=283) n (%)**
Age group (≤55 yrs)	126 (45.8)	129 (45.6)
Breathlessness	178 (64.7)	222 (78.4)*
Cough	51 (18.5)	33 (11.7)*
Chronic bronchitis	37 (13.5)	18 (6.4)*
Bronchial asthma	18 (6.5)	20 (7.1)

* p<0.05

4.3 Forced oscillation technique

The FOT results were acceptable in 471 (84.4%) out of 558 individuals who completed the study (Table 3). The R5 was elevated (>ULN) in 138 (29.3%), R_{5-19} was elevated (>LLN) in 109 (23.3%), and X5 was elevated (<LLN) in 100 (21.2%) subjects. The FOT results were abnormal in 177 subjects (37.7%). The gender-wise no significant difference in abnormality of any FOT parameters was observed (Table 3).

Table 3. The distribution of abnormality in Forced Oscillation Technique according to gender

Variables	**Male (=242), n (%)**	**Female (=229), n (%)**	**p-value**	**Total (=471), n (%), (95% CI)**
R5 > ULN	65 (26.9)	73 (31.9)	0.14	138 (29.3) (25.4 - 35.6)
X5 < LLN	47 (19.4)	53 (23.1)	0.19	100 (21.2) ((17.8 – 25.2)
R_{5-19} > ULN	54 (22.4)	55 (24.3)	0.66	109 (23.3) (19.6 – 27.2)
Abnormal FOT	87 (36.1)	90 (39.3)	0.50	177 (37.7) (33.3 – 42.0)

R5: Whole-breath resistance at 5 Hz; X5: Whole-breath reactance at 5 Hz; R_{5-19}: Frequency-dependence resistance; ULN: upper limit of normal; LNN: lower limit of normal.

4.4. Spirometry

Acceptable spirometry was performed by 452 (81%) individuals out of 558 who completed the study. The normal, obstructive, and restrictive spirometry was observed as 46.2%, 26.1%, and 27.7%, respectively (Table 4). The obstructive spirometry was more common in males as compared to females (31.3% vs. 20.3%, p<0.05). The mild airflow obstruction contributed 45.8% of total obstructive spirometry. The restrictive patterns in spirometry were significantly more in females as compared to males (22.5% vs. 33.5%, p<0.05). The mild and moderate restrictions were responsible for the majority (68.8%) of restrictive spirometry.

Table 4. The distribution of spirometry abnormality and severity of abnormality according to gender

Variables	Male (=240), n (%)	Female (=212), n (%)	Total (=452), n (%)
Normal spirometry	111 (46.3)	98 (46.2)	209 (46.2) (95% CI: 41.7-50.9)
Obstructive pattern	75 (31.3)	43 (20.3)*	118 (26.1) (95% CI: 22.3-30.4)
Mild airflow obstruction	36 (48)	18 (41.9)*	54 (45.8)
Moderate airflow obstruction	13 (17.3)	8 (18.6)	21 (17.8)
Moderately severe airflow obstruction	12 (16.0)	11 (25.6)	23 (19.5)
Severe airflow obstruction	12 (16.0)	6 (14.0)	18 (15.3)
Very severe airflow obstruction	2 (2.7)	0	2 (1.7)
Restrictive pattern	54 (22.5)	71 (33.5)*	125 (27.7) (95% CI: 23.7-31.9)
Mild restriction	15 (27.8)	27 (38.0)	42 (33.6)
Moderate restriction	22 (40.7)	22 (31.0)	44 (35.2)
Moderately severe restriction	9 (16.7)	16 (22.5)	25 (20.0)
Severe restriction	8 (14.8)	4 (5.6)	12 (9.6)
Very severe restriction	0	2 (2.8)	2 (1.6)
MMEF<LLN[#]	99 (41.4)	44 (30.8)*	143 (30.6) (95% CI: 26.6-34.9)

*p<0.05; CI: confidence interval, MMEF: mid expiratory flow rate; LLN: lower limit of normal; [#]: MMEF data were available for 468 subjects

The age-group wise lung function abnormalities are compared in Table 5. The risk of elevated X5, R_{5-19}, obstructive, and restrictive spirometry was significantly higher in the older age group (age ≥ 55 years). The risk of elevated X5 and R_{5-19} and restrictive spirometry in the older age group remained significant even after adjusting for smoking.

Out of 558 subjects, 386 (69.2%) subjects performed both acceptable FOT and spirometry. Table 6 illustrates the relationship of FOT parameters with spirometry outcomes of these subjects. The R5, $R_{5-19,}$ and X5 were elevated in 17.7%, 15.1%, and 8.1% subjects with normal spirometry. The subjects with obstructive spirometry had a higher risk of elevated FOT parameters as compared to those with restrictive pattern in spirometry. Among all FOT parameters, the risk of having elevated X5 was the highest for both obstructive and restrictive spirometry.

Table 5. The age group-wise distribution of lung function abnormality

Variables	**Age group**		**Odds ratio, (95% CI)**	
	< 55 years (=213) n (%)	**≥ 55 years (=258) n (%)**	**Un-adjusted**	**Adjusted***
R5>ULN	58 (27.2)	80 (31.0)	1.20 (0.80 - 1.79)	1.17 (0.78 - 1.53)
X5<LLN	29 (13.6)	71 (27.5)	2.41 (1.49 - 3.88)#	2.26 (1.39 - 3.66)#
R_{5-19}>ULN	37 (17.6)	72 (28.0)	1.82 (1.16 - 2.85)#	1.66 (1.05 - 2.62)^
Obstructive pattern	46 (20.6)	72 (31.6)	1.78 (1.16 - 2.74)#	1.49 (0.95 – 2.33)
Restrictive pattern	50 (22.3)	75 (32.9)	1.71 (1.12 - 2.59)^	1.89 (1.23 - 2.89)#
MMEF <LLN@	72 (50.3)	71 (49.7)	0.91 (0.61 - 1.35)	0.74 (0.49 – 1.12)

* Adjusted for smoking; R5: Whole-breath resistance at 5 Hz; X5: Whole-breath reactance at 5 Hz; R_{5-19}: Frequency-dependent resistance; ULN: upper limit of normal; LNN: lower limit of normal; MMEF: Maximum mid-expiratory flow rate; @ acceptable MMEF was obtained from 468 cases; #p <0.01; ^p<0.05.

Table 6. The distribution of FOT abnormality with spirometry results

Variables	Normal spirometry (=186) n (%)	Obstructive pattern (=92) n (%)	Restrictive pattern (=108) n (%)
R5 > ULN	33 (17.7)	47 (51.1)	33 (30.6)
Adjusted Odds ratio* (95% CI)	1	4.88 (2.71-8.77)	2.02 (1.15-3.54)
X5 < LLN	15 (8.1)	38 (41.3)	31 (28.7)
Adjusted Odds ratio* (95% CI)	1	6.66 (3.31-13.42)	4.07 (2.06-8.07)
R_{5-19} > ULN	28 (15.1)	36 (40.4)	28 (25.9)
Adjusted Odds ratio* (95% CI)	1	3.09 (1.67-5.73)	1.82 (0.99-3.31)
Abnormal FOT	47 (25.3)	53 (58.2)	43 (39.8)
Adjusted Odds ratio* (95% CI)	1	3.93 (2.24-6.89)	1.90 (1.14-3.18)

*Adjusted for age and smoking status; R5: Whole-breath resistance at 5 Hz; X5: Whole-breath reactance at 5 Hz; R_{5-19}: Frequency-dependence of resistance; ULN: upper limit of normal; LNN: lower limit of normal.

Relationship of respiratory symptoms with lung function parameters

Table 7 illustrates the relationship of respiratory symptoms with an abnormality in FOT and spirometry. The adjusted odds for breathlessness with elevated R5 (OR: 1.81; 95% CI: 1.13 – 2.91) and abnormal FOT (OR: 1.73; 95% CI: 1.12 - 2.68) were statistically significant. The adjusted odds for a cough for all FOT parameters were statistically non-significant. The adjusted odds for breathlessness with obstructive spirometry (OR: 2.26; 95% CI: 1.29-3.95) and low MMEF (OR: 2.35; 95% CI: 1.42-3.87) were also statistically significant. Among all spirometry parameters, cough complaints showed a significant association with low MMEF (OR: 3.04; 95% CI: 1.74-5.34) only.

Table 7. The association of respiratory symptoms with an abnormality in FOT and spirometry parameters

Variables	Breathlessness				Cough			
	Breathless n (%)	Not breathless n (%)	Odds ratio, (95% CI)		Cough n (%)	No cough n (%)	Odds ratio, (95% CI)	
			Un-adjusted	Adjusted*			Un-adjusted	Adjusted*
R5 > ULN	109 (32.9)	29 (20.7)	1.88 (1.18-3.0)	1.81 (1.13 – 2.91)	24 (34.3)	114 (28.4)	1.31 (0.77-2.25)	1.24 (0.72 -2.15)
X5 < LLN	80 (24.2)	20 (14.3)	1.91 (1.12 – 3.27)	1.60 (0.92 – 2.78)	18 (25.7)	82 (20.4)	1.35 (0.75 – 2.43)	1.08 (0.58 – 2.0)
R_{5-19} > ULN	84 (25.7)	25 (17.9)	1.59 (0.96 - 2.62)	1.34 (0.81 -2.24)	18 (26.1)	91 (22.9)	1.19 (0.66 – 2.14)	0.95 (0.51 – 1.75)
Abnormal FOT	138 (41.8)	39 (27.9)	1.86 (1.21 – 2.86)	1.73 (1.12 - 2.68)	29 (41.4)	148 (37.0)	1.20 (0.72 – 2.02)	1.01 (0.99 – 1.03)
Obstructive pattern	99 (30.7)	19 (14.7)	2.56 (1.49-4.39)	2.26 (1.29 – 3.95)	29 (43.9)	89 (23.1)	2.62 (1.52 – 4.49)	1.02 (0.99 – 1.04)
Restrictive pattern	97 (30.0)	28 (21.7)	1.55 (0.95- 2.51)	1.55 (0.95 -2.53)	21 (31.8)	194 (26.9)	1.27 (0.72 – 2.23)	1.36 (0.76 – 2.43)
MMEF<LLN	116 (35.0)	27 (19.7)	2.19 (1.36 -3.54)	2.35 (1.42 – 3.87)	35 (53.8)	108 (26.8)	3.19 (1.87-5.44)	3.04 (1.74-5.34)

*Adjusted by smoking status and age R5: Whole-breath resistance at 5 Hz; X5: Whole-breath reactance at 5 Hz; R_{5-19}: Frequency-dependence of resistance; ULN: upper limit of normal; LNN: lower limit of normal.

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DISCUSSION

In this study, we characterized the respiratory symptoms of subjects from severely exposed cohort and assessed their lung functions simultaneously by FOT and spirometry. The majority of the subjects had at least one respiratory symptom, mostly breathlessness. The spirometry was abnormal in nearly half of our population. The FOT parameters also demonstrated a high prevalence of the abnormalities in small airway function.

The population-based studies are necessary following toxic inhalational disaster to understand the mechanisms of lung injury, clinical sequel, and appropriate medical management.[9] Besides the Bhopal gas disaster, the other two inhalational disasters where large numbers of subjects were affected were the Graniteville (South Carolina, USA) accident, exposure to chlorine gas; and the World Trade Centre (WTC) accident, exposure to a high concentration of cloud of dust. Extensive research and long term follow-up of the exposed population in both the disasters helped us to understand the pathogenesis of lung injury due to inhalation of toxic materials and identification of new syndrome, e.g. "WTC cough".[10]

Aftermath a disaster, over or under-reporting of symptoms in the exposed population, is expected due to various medical and non-medical reasons e.g., for easy access to compensation and rehabilitation packages, access to better healthcare facilities, and psychological state of mind, etc. Clark *et al.* observed under-reporting of respiratory symptoms after the Graniteville accident.[11] The authors opined that under-reporting of symptoms was due to a simple coping mechanism. Breathlessness is a cardinal and common symptom of various diseases, including cardiorespiratory diseases. Herzog *et al.* demonstrated observing breathlessness in others elicit mild-to-moderate breathlessness, negative effects, and increased brain responses in the absence of underlying abnormality.[12] More than three decades after the exposure, most of our population complain of respiratory symptoms, especially breathlessness. A high prevalence of self-reported breathlessness in the severe cohort may either be due to the negative effects of observing family members and neighbors suffering and dying from breathlessness or non-medical reasons. The morbidity of the cohorts of the ongoing long-term epidemiological study surveys was collected from the head of the family or available family members at the survey time.[3] Whereas, each individual's morbidity in the present study was collected from the subject him or herself by administering an elaborative questionnaire. Therefore, we observed a higher prevalence of respiratory morbidity as compared to the previous study.[3]

Inhaled agents penetrate deep inside the lung and damage the respiratory tract's lining epithelium starting from the upper airways to small airways (airways of <2 mm in internal diameter). The airway lumens get narrowed by inflammatory exudates, infiltration of the airway wall by inflammatory cells, constriction of airway smooth muscle, and peribronchiolar fibrosis. The respiratory epithelial cells are efficiently repaired from surviving basal epithelial cells, which serve as progenitor cells. The small airways are devoid of basal cells and are thus, their repair process is less efficient, leading to chronic inflammation and fibrosis.[13] Inflammation of the airways leads to airways' remodeling and, finally, increased airway resistance and abnormal lung functions. Several factors such as concentration, duration of exposure, whether exposure occurred in an enclosed space, particle size, and solubility of toxic chemicals, determine the degree of lung injury.[14] The degree of injury is also influenced by host factors such as extremes of age, metabolic rate, history of smoking, and pre-existing lung diseases. Depending on the factors mentioned above, individuals exposed to acute inhalational injury may recover, and some may develop long-term complications. Chronic pulmonary complications such as Reactive Airway Disease Syndrome, bronchiolitis obliterans, and cryptogenic organizing pneumonia may develop following acute inhalations.[14]

Spirometry is the most common and widely used test to diagnose lung function abnormalities. Evaluation of lung function is crucial to diagnose abnormality in individuals exposed to toxic agents. Immediately after the Bhopal gas disaster and subsequent 10-15 years, several studies were carried out to estimate the prevalence of respiratory symptoms and lung function abnormality of the exposed population. The prevalence of the type of lung function abnormality and severity of abnormality were widely variable across the studies.[15] The last published study on spirometry of the Bhopal gas disaster exposed population was a retrospective analysis of spirometry reports of individuals consulted in a hospital.[15] The study found the obstructive pattern in spirometry as the predominant abnormality (50.8%), followed by a restrictive pattern (13.3%). In contrary to the previous publications, more than half of our population had abnormal spirometry and the distribution of obstructive and restrictive patterns was nearly equal. Longitudinal spirometry over the sixteen years among workers and volunteers exposed to the WTC disaster demonstrated increasing the prevalence of restrictive patterns.[16] Cullinan *et al.* were first reported reduced MMEF, a subtle marker of small airway involvement in the spirometry in the exposed population of Bhopal Gas Disaster.[17] They observed those residing near the Union Carbide plant had significantly reduced MMEF. We observed 30.6% of our population had MMEF<LLN.

Following the WTC accident, the exposed subjects developed chronic respiratory morbidity, and their lung function continued to deteriorate over a long period.[16,17] Serial measurements of FEV_1 for nine years in WTC exposed fire workers failed to demonstrate a recovery in FEV_1.[18] During serial spirometry for more than thirteen years, no discernible recovery of spirometry in exposed emergency medical service workers of the WTC accident was observed, irrespective of their respiratory symptoms.[19] The leaked gases of the Bhopal gas disaster was more toxic and lethal as compared to other inhalational disasters. Therefore, persistent abnormality in the spirometry of our study population even more than thirty years after the exposure was not surprising. The subjects of age <55 years in our study had significantly fewer abnormality in both FOT and spirometry, signifies that those exposed in their early childhood might have recovered from the lung function abnormality to some extent. This finding was corroborated with our previous study.[3]

Spirometry may fail to detect complex heterogeneous pathology of airways, especially subtle underlying abnormality in small airways. FEV_1 predominantly reflects the dysfunction of large to medium-sized airways and a significant amount of small airway resistance required to be build up to make FEV_1 abnormal.[20,21] Forced Oscillation Technique (FOT) and Impulse Oscillometry (IOS) are two non-invasive techniques used in the clinical practice to assess small airway function.[20] The IOS is an improvised technique of FOT, where square pressure waves are superimposed on the tidal breaths. Both the techniques measure respiratory system resistance (Rrs) and reactance (Xrs), the main component of respiratory impedance. Rrs represents impedance to airflow, primarily reflecting overall airway caliber. Whereas, Xrs represents impedance to volume changes and encompasses both the respiratory system's inertial and elastic properties. The evaluation of small airway function in subjects exposed to inhalational disaster provides valuable information that is not often apparent in spirometry.[22,23] The involvement of small airways, i.e. bronchiolitis obliterans, was documented in the WTC disaster and these pathological changes were not apparent on the chest radiograph.[23,24] The lung autopsy of the gas exposed subjects also demonstrated severe tracheitis, bronchitis, and necrotizing bronchiolitis with denudation of the epithelium.[25] Oppenheimer *et al.* highlighted IOS as a better way of identifying small airway dysfunction in the WTC accident.[26] The IOS parameters were elevated in 68% of symptomatic with normal spirometry. Other investigators also identified the potential importance of assessing small airways functions in the population affected by the WTC accident. Friedman *et al.* compared spirometry and IOS parameters in persistent respiratory symptomatic and asymptomatic WTC exposed populations.[23] The R5 and R_{5-20} were elevated by 68%, and 36% of respiratory symptomatic with normal spirometry. The authors suggested that small airway dysfunction was responsible for the respiratory symptoms.[23] The present study is the first to investigate the small airway function in gas exposed population by FOT. In our study, 27.1% of the asymptomatic had abnormal FOT (elevated R5, R_{5-19}, and X5 in 19.5%, 21.1%, and 13.5%, respectively). The relatively lower prevalence of abnormal FOT parameters in our study as compared to subjects of the WTC accident may be due to either long lapse of time between exposure and evaluation or recovery in the meantime.

Several investigators established the association of small airways functions with respiratory symptoms in the WTC accident. Caplan-Shaw *et al*. observed persistent lower respiratory symptoms are due to the involvement of small airways.[27] The longitudinal analysis of lower respiratory symptoms in the WTC exposed population showed that symptom improvement was associated with improvement in IOS parameters and not with improvement in spirometry.[22] The restrictive pattern in spirometry of the WTC exposed population was also attributed to small airways involvements.[28] The small airways dysfunction causes closure of small airways at tidal volume, leading to a restrictive spirometry pattern. The abnormality of small airways function was also observed in our population with restrictive spirometry. Few cases of individuals with restrictive spirometry of the present study also undergone radiological evaluations; however, no evidence of obvious fibrosis or scarring was found in their chest X-ray.

LIMITATIONS AND STRENGTH OF THE STUDY

The present study's major limitation was its cross-sectional design, low participation, and recruitment was restricted to a severely exposed cohort. Nearly half of the recruited individuals completed the study. We also missed the individuals who are usually at work during our study visits. There was a potential risk of selection bias, as those with relatively fewer respiratory symptoms completed the study. The strength of this study was that individuals were recruited from the cohort of the long-term epidemiological study; therefore their exposure to the disaster was undoubted. The present study was carried out more than thirty years after the exposure, and the subjects were also exposed to occupational and environmental air pollution in subsequent periods. Though, we observed the abnormalities of the abnormality in lung functions were independent of smoking status. In the absence of longitudinal lung function assessments, the observed lung function abnormality cannot be attributed to disaster exposure only. Due to logistics issues, post-bronchodilator spirometry and FOT were not carried out in all cases. The lung volume estimation of cases with restrictive spirometry was also not carried out to confirm true restriction, i.e. reduced total lung capacity.

In conclusion, the present community-based cross-sectional study highlighted a high prevalence of self-reported respiratory symptoms, especially exertional breathlessness in the severely exposed cohort of the long-term epidemiological study. Breathlessness demonstrated a significant association with the abnormality of both FOT and spirometry. More than half of the study population had either obstructive or restrictive spirometry. About one-third of the studied population had abnormal FOT results, signifies persistent abnormality in small airway function. The age of individuals at the time of disaster is also a determinant of residual effects in lung function. A comprehensive assessment of lung function by both spirometry and FOT is indispensable in understanding the respiratory effects of inhalational injuries.

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STUDY QUESTIONNAIRE

1. Date of data collection______ /______ /________ Computer serial No._____________
2. ICMR ID__________________________
3. Name ____
4. Address____ Mobile no.__________________
5. Age (in years) _______________
6. Sex – Male______ Female______
7. Education of the Individual______________________________________
8. व्यवसाय: वर्तमान_________________________ वर्ष/ माह_______पिछला____________________________ वर्ष/ माह______
9. Socioeconomic status

	score
(A) Education of Head	
Profession or Honours	7
Graduate or post graduate	6
Intermediate or post high school diploma (XII Pass)	5
High school certificate (Class X Pass)	4
Middle school certificate (Class VIII Pass)	3
Primary school certificate (<Below VIII Pass)	2
Illiterate	1
(B) Occupation of Head	
Profession	10
Semi-Profession	6
Clerical, Shop-owner, Farmer	5
Skilled worker	4
Semi-skilled worker	3
Unskilled worker	2
Unemployed	1
(C) Family income per month (in Rs)	
>41000	12
20,000-40,999	10
15,000-19,999	6
10,000-14,999	4
6,000-9,999	3
2,000-5,999	2
<2,000	1

10. भोपाल गैस त्रासदी के समय निवास (स्थान का नाम)________________________

संयंत्र से निवास की लगभग दूरी < 1 km
2-5 km
6-10 km
>10 km

11. भोपाल गैस त्रासदी के 1 वर्ष के भीतर परिवार के किसी भी सदस्य की मौत हुई थी? हाँ/नहीं

यदि हाँ, तो वह आपका कौन था ______________________________

12. क्या आपको याद है कि भोपाल गैस त्रासदी के एक हफ्ते के दौरान आपने कोई भी लक्षण महसूस किया था? हाँ/नहीं

यदि हां, तो बहुत अधिक गंभीर लक्षण क्या थे_______________________________Eye , resp.

13. क्या आपको ऊपर के लक्षणों में से गैस रिसाव के एक हफ्ते के भीतर अस्पताल में भर्ती कराया गया था? हाँ/नहीं

14. क्या आप निम्न से पीड़ित हैं?

(i) मधुमेह (Diabetes) हाँ/नहीं
(ii) उच्च रक्तचाप (Hypertension) हाँ/नहीं
(iii) दिल की बीमारी (Cardiac Diseases) हाँ/नहीं
(iv) गुर्दे की बीमारी (Chronic kidney disease) हाँ/नहीं
(v) गंभीर यकृत रोग (Chronic liver disease) हाँ/नहीं

कोई अन्य बीमारियां (यदि कोई हैं तो कृपया बतायें)____

श्वास रोग लक्षण

कृपया हाँ या नहीं में उत्तर दीजिये ! यदि हाँ तो लक्षण की अवधि का ब्यौरा वर्षो में दीजिये !

छाती से सीटी जैसी आवाज आना तथा घुटन रहना Month/Years

15. क्या पिछले बारह महीनो में आपको कभी भी छाती से साँ-साँ की या सीटी जैसी आवाज आई है? हाँ/नहीं

16. क्या पिछले बारह महीनो में आप कभी सुबह छाती में घुटन या साँस लेने में कठिनाई के कारण उठे है? हाँ/नहीं

साँस लेने में कठिनाई

17.क्या पिछले बारह महीनो में आपको कसरत खेलकूद या ज्यादा घूमने के बाद साँस फूलने की तकलीफ हुई? हाँ/नहीं

18. क्या पिछले बारह महीनो में आपको कभी भी दिन के उस समय साँस लेने में कठिनाई हुई है जब आप कोई मेहनत का काम नहीं कर रहे थे? हाँ/नहीं

19.क्या पिछले बारह महीनो में आपको रात में साँस की तकलीफ के कारण नींद से उठाना पड़ा है? हाँ/नहीं

खांसी एव छाती में बलगम

20.क्या पिछले बारह महीनो में आपको रात में खांसी की वजह से नींद से उठना पड़ा है? हाँ/नहीं

21.क्या आपको सुबह उठने पर अक्सर खांसी आती है? हाँ/नहीं

22.क्या आपको सुबह उठते ही सबसे पहले छाती से बलगम निकलता है? हाँ/नही

23.क्या आपको एक साल में कम से कम तीन महीने से ज्यादा इसी तरह छाती से बलगम निकालनी पड़ती है? हाँ/नहीं

साँस लेना

24. इन तीन में से आपके लिए सबसे उचित क्या है?

(1) मुझे मुश्किल से कभी (या कभी भी नहीं) साँस लेने में कठिनाई होती है!

(2) मुझे साँस लेने में कठिनाई बार बार होती है पर हमेशा ठीक हो जाती है!

(3) मेरी साँस बिल्कुल ठीक कभी भी नहीं रहती है!

धूल,पंख एव पालतू जानवर

25. जब आप घर के धूल भरे भाग में या जानवरो (जैसे कुत्ते, बिल्ली, घोड़े) के साथ या पंखो, रजाइयों, तकियो आदि के पास होते है तो क्या आपको कभी?

(1) छाती में घुटन महसूस होती है! हाँ/नहीं

(2) साँस लेने में कठिनाई होती है! हाँ/नहीं

दमा

26.क्या आपको कभी भी साँस की तकलीफ के कारण अस्पताल में भर्ती कराया गया था**?** हाँ/नहीं

27.क्या आपको कभी भी दमा रहा है? हाँ/नहीं

28. क्या आप को पिछले बारह महीनो में दमे का दौरा पड़ा है? हाँ/नहीं

29. क्या आप साँस की तकलीफ के लिए किसी तरह की दवा (जैसे इन्हेलर, पंप, रोटहेलर, नैब्यूलाइजर, गोलियाँ आदि) ले रहे है? हाँ/नहीं

<u>एलर्जी एवं पारिवारिक लक्षण</u>

30.क्या आपकी त्वचा पर अक्सर चकते/निशान (urticaria) या खुजली (eczema) आदि हुआ है? हाँ/नहीं

जो होकर ठीक हो जाता है?

31.क्या आपकी नाक अक्सर बहती है या अक्सर छींके आती है? हाँ/नहीं

32.क्या आपकी आँखों में अक्सर खुजली रहती है? हाँ/नहीं

33.क्या आपके परिवार के किसी अन्य सदस्य को इन तीनो में से कोई तकलीफ है यदि हाँ तो किसे? हाँ/नहीं

दादा-दादी / माता-पिता / भाई / बहन / बच्चे / अन्य____________

34. क्या आपके परिवार के किसी अन्य सदस्य को दमे की तकलीफ है यदि हाँ तो किसे? हाँ/नहीं

दादा-दादी / माता-पिता / भाई / बहन / बच्चे / अन्य____________

35. क्या आपने वर्तमान या पूर्व में फेफड़े की टी.बी. का उपचार कराया है? हाँ/नहीं

<u>धूम्रपान एव तम्बाकू सेवन</u>

36.क्या आपने एक या उससे अधिक वर्ष तक धूम्रपान किया हैं? हाँ/नहीं

यदि हाँ तो अगले प्रश्न का उत्तर दें अन्यथा 42 पर जाये!

37.आप तम्बाकू का सेवन अक्सर किस तरह से करते हैं या करते थे?

1. सिगरेट 2. बीड़ी 3. हुक्का 4. सिगार 5.पाइप 6. अन्य

38.आप चौबीस घंटों में अक्सर कितनी सिगरेट, बीड़ी, हुक्का, सिगार या पाइप आदि का सेवन करते हैं या करते थे?

39.आपने किस उम्र में धूम्रपान शुरू किया था?

40.केवल एक उत्तर चुने जो आपके लिए उपयुक्त हो?

1.मैं अभी भी धूम्रपान करता हूँ!

2.मुझे धूम्रपान छोड़े एक वर्ष से कम समय हुआ है!

3.मुझे धूम्रपान छोड़े एक वर्ष से अधिक समय हो गया है!

यदि प्रश्न 40 का उत्तर 3 है तो अगले प्रश्न का उत्तर दे अन्यथा प्रश्न 42 पर जाये!

41.आपने कितने वर्षो से धूम्रपान छोड़ दिया है?

42.क्या आप धूम्रपान के अलावा तम्बाकू का किसी और रूप में सेवन करते हैं? हाँ/नहीं

43.आप तम्बाकू का सेवन अक्सर किस तरह से करते हैं?

1.जर्दा 2.खैनी 3.पान मसाला 4.गुटका 5.नसवार 6.अन्य (स्पष्ट करे) --------------------------------

44.आप कितने वर्षो से तम्बाकू का सेवन इस तरह कर रहे है?

45.आप एक दिन में कितनी बार तम्बाकू का सेवन इस तरह करते है?

प्रश्न 46 एव **47** के उत्तर तभी दे यदि **प्रश्न 36** का उत्तर नहीं हैं अन्यथा **48** पर जाये**!**

<u>पर्यावरण में तम्बाकू के धुंए के साथ संपर्क</u>

46. क्या आपके परिवार का कोई सदस्य (उसी घर में रहने वाले व्यक्ति) अक्सर आपकी उपस्थिति में धूम्रपान करते हैं या करते थे?

हाँ/नहीं यदि हाँ तो अगले **प्रश्न** का उत्तर दें अन्यथा **48** पर जायें **!**

47. परिवार के कौन से सदस्य आपके बचपन और वयस्क जीवन में अक्सर आपकी उपस्थिति में धूम्रपान करते हैं या करते थे?

शादी से पहले			तम्बाकू का प्रकार	घंटे प्रतिदिन	महीना/वर्ष
दादा	हाँ/नहीं				
दादी	हाँ/नहीं				
पिता	हाँ/नहीं				
माता	हाँ/नहीं				
भाई	हाँ/नहीं				
बहन	हाँ/नहीं				

अन्य (स्पष्ट करे)--------------------------------

शादी के बाद					
पिता/ ससुर	हाँ/नहीं				
माता/ सास	हाँ/नहीं				
भाई/ देवर	हाँ/नहीं				
बहन/ ननद/ भाभी	हाँ/नहीं				
बेटा	हाँ/नहीं				
बेटी	हाँ/नहीं				
पति / पत्नी	हाँ/नहीं				

अन्य (स्पष्ट करे)--------------------------------

तम्बाकू का प्रकार 1. सिगरेट 2. बीड़ी 3. हुक्का 4. सिगार 5. पाइप 6. अन्य____________

<u>भोजन पकाने का ईधन</u>

48. क्या आप नियमित रूप से भोजन पकाते है या थे? ☐

1. आजकल नियमित रूप से भोजन पकाते है!
2. पहले नियमित रूप से भोजन पकाते थे!
3. कभी नियमित रूप से भोजन नहीं पकाया

यदि उत्तर **3** है तो उत्तर यही समाप्त करे , अन्यथा अगले प्रश्न का उत्तर दें!

49. आपने किस उम्र से नियमित रूप से भोजन पकाना शुरू किया? ☐

50. आपने किस उम्र में नियमित रूप से भोजन पकाना बंद किया (यदि आप अब नहीं पकाते)? ☐

51. आप कितने नियम से भोजन पकाते हैं?

    1. प्रतिदिन
    2. महीने में ☐☐ दिन ☐☐

52. क्या आपके मकान में अलग से रसोई घर हैं? हाँ/नहीं

53. क्या आपकी रसोई में खिड़की या रोशनदान हैं? हाँ/नहीं

54. आप कितने घंटे रसोई में गुजारते है? ☐

55. आपके भोजन पकाने का मुख्य ईधन इनमें से कौन सा हैं और उसे आप कितने सालो से उपयोग कर रहे है? ☐

1.बिजली 2.गैस 3.मिट्टी का तेल 4.कोयला 5.लकड़ी 6.गोबर के उपले 7.धान फूस आदि 8.अन्य---------------

शोध परियोजना :

भूमिका :- यह शोध अध्ययन आई.सी.एम.आर.-राष्ट्रीय पर्यावरणीय स्वास्थ्य अनुसंधान संस्थान (निरेह) की दीर्घ-कालीन जनापदिक सर्वेक्षण में पंजीकृत व्यक्तियों में श्वसन तंत्र की जीर्ण बीमारियों का अध्ययन का आंकलन करने के लिए किया जा रहा है । हम आपको निम्नलिखित जानकारी देते हुए आपको इस अध्ययन का भागीदार बनने के लिए आमंत्रित करते हैं। अगर आपको इस संबंध में कोई अन्य जानकारी प्राप्त करनी हो तो आप शोध अन्वेषक से या शोध सहायक/फील्ड स्टाफ से प्राप्त कर सकते हैं ।

शोध का उद्देश्य :- ऐसा पाया गया है कि भोपाल गैस पीड़ित व्यक्तियों में श्वसन तंत्र की बीमारियों के लक्षण मिलते है। इस अध्ययन का उद्देश्य ऐसे व्यक्तियों में श्वसन तंत्र की बीमारियों का निदान हेतु आकलन करना है ।

शोध कार्य का तरीका :- इस शोध में हम आपसे आपके स्वास्थ्य-संबंधित कुछ जानकारी लेंगे एवं फेफड़ों की कार्यक्षमता का परीक्षण स्पाइरोमेट्री (Spirometry) एवं इंपल्स ऑसीलोमेट्री (Impulse oscillometry) द्वारा करेंगे ।

सहभागिता (स्वैच्छिक) :- इस शोध अध्ययन में आपका भाग लेना पूर्णतः स्वैच्छिक है। आप इस शोध अध्ययन में भाग लेने अथवा नहीं लेने के लिए पूर्णतः स्वतंत्र हैं । परन्तु यदि आप इस शोध अध्ययन में भाग लेने की सहमति देते हैं और यदि आपके फेंफड़ों में किसी भी प्रकार की असामान्यता पाई जाती है तो हम आपकी उचित चिकित्सा /बचाव हेतु मार्गदर्शन कर सकते हैं ।

शोध अध्ययन की विधि :- यदि आप इस शोध अध्ययन में भाग लेने की सहमति देते हैं तो हमारे शोध सहायक /फील्ड कार्यकर्ता आपसे आपके कार्य, आय, धूम्रपान की आदत एवं श्वसन तंत्र से संबंधित लक्षणों के बारे में जानकारी प्राप्त करेंगे । हम स्पाइरोमेट्री द्वारा फेंफड़ों की कार्यक्षमता का परीक्षण (Lung function test) करेंगे। तत्पश्चात् आपको 200/100µg सालब्यूटामॉल (Salbutamol) देंगे एवं स्पाइरोमेट्री द्वारा पुनः फेंफड़ों की कार्यक्षमता का परीक्षण करेंगे ।

जॉच प्रकिया की समयावधि :- प्रतिभागी की जॉच प्रकिया को पूरा करने में लगभग एक घन्टे तक का समय लगेगा ।

दुष्प्रभाव एवं जोखिम :- इस जॉच प्रकिया में किसी प्रकार का कोई दुष्प्रभाव एवं जोखिम नहीं हैं । फिर भी, यदि जॉच प्रकिया में आपको किसी प्रकार का कोई शारीरिक कष्ट महसूस होता है तो इस प्रकिया को रोक दिया जायेगा ।

लाभ :- इस शोध अध्ययन में भाग लेने पर प्रतिभागी को अपने फेफडों की स्वास्थ्य-स्थिति के बारे में महत्वपूर्ण जानकारी प्राप्त होगी जो आपके लक्षणों के निदान में सहायक होगी । इसके अतिरिक्त, आपकी सहभागिता से हमें शोध कार्य में अमूल्य योगदान प्राप्त होगा।

प्रतिपूर्ति/अनुदान :- इस शोध अध्ययन में भाग लेने वाले प्रतिभागी, किसी भी अनुदान/अन्य लाभ प्राप्त करने के पात्र नहीं होंगे।

गोपनीयता :- इस शोध.अध्ययन में संकलित की गई सारी जानकारी को गोपनीय रखा जायेगा एवं आपके बारे में एकत्रित की गई सारी जानकारी आपके एवं शोधकर्ता के अलावा किसी को भी ज्ञात नहीं करायी जायेगी ।

संपर्क हेतु :- यदि इस शोध.अध्ययन के संबंध में आपके अभी या अध्ययन के दौरान कोई प्रश्न हों अथवा आपको इस संबंध में कोई अन्य जानकारी प्राप्त करनी हो तो आप शोध सहायक अथवा प्रधान शोध अन्वेषक(Principal Investigator) डॉ० सजल दे वैज्ञानिक-ई, निरेह, भोपाल (दूरभाष संख्या-०७५५-२५३३१०६ ई-मेल sajalde@yahoo.com).

सहमति-पत्र

मैंने उपरोक्त सभी सूचनाऐं पढ ली हैं, अथवा मुझे पढ़कर सुनाई गईं हैं । मुझे इस संबंध में हर प्रकार के प्रश्न पूछने का अवसर दिया गया था और मेरे पूछे गये प्रश्नों का संतोषजनक उत्तर दिया गया है । मैं इस शोध अध्ययन में सहभागी बनने हेतु अपनी स्वेच्छा से अपनी सहमति दे रहा/रही हूॅ ।

प्रतिभागी का नाम -

प्रतिभागी का हस्ताक्षर -

दिनांक :-

शोध सहायक द्वारा घोषणा

मैं पुष्टि करता हूॅ कि प्रतिभागी को प्रश्न पूछने के उचित अवसर प्रदान किये गये हैं एवं प्रतिभागी द्वारा पूछे गये सभी प्रश्नों का सत्य एवं उचित उत्तर दिया गया है । मैं यह भी पुष्टि करता हूॅ कि प्रतिभागी पर किसी प्रकार का कोई दबाव नहीं था एवं उन्होंने अपनी सहमति स्वेच्छापूर्वक दी है।

शोध सहायक का नाम -

शोध सहायक का हस्ताक्षर -

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Original article

Respiratory morbidities and lung function abnormalities in survivors of Bhopal Gas Disaster: A cross-sectional study

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ABSTRACT

Background: Respiratory morbidities remained significant for the last four decades among the survivors of the Bhopal gas disaster. We hypothesized that lung function abnormalities, especially small airway dysfunctions, were responsible for the ongoing respiratory morbidities.

Methods: We conducted a cross-sectional study between 2018 and 2020 in the severely exposed cohort of the Bhopal gas disaster. A standardized questionnaire was used to record their respiratory symptoms. The forced oscillometry (FOT) and spirometry were utilized for assessing lung functions. Univariate and multivariate logistic regression analyses were used to examine the association.

Results: Of 916 enrolled individuals (men: 442, mean age: 55.2 ± 12.3 years), 558 participated in lung function assessments. Breathlessness was the most common complaint (71.7%), followed by cough (15.1%). The R5 > upper limit of normal (ULN), $R_{5\text{-}19}$ > ULN, and X5 < lower limit of normal (LLN) were observed in 29.3%, 23.3%, and 21.2% participants, respectively. Normal, obstructive, and restrictive spirometry was observed in 46.2%, 26.1%, and 27.7%, participants, respectively. FOT parameters were abnormal in 25.3% individuals with normal spirometry. Individuals with obstructive spirometry had the highest risk of having abnormal FOT parameters (adjusted odds ratio [adj OR]:3.93, 95% confidence interval [CI]: 2.24–6.89). Breathlessness showed a significant association with abnormal R5 (adj OR: 1.81; 95% CI: 1.13–2.91) and obstructive spirometry (adj OR: 2.26; 95% CI: 1.29–3.95).

Conclusions: Assessment of small airway functions along with spirometry are useful to identify complex lung function abnormalities in cases of toxic inhalation.

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1. Introduction

Bhopal gas disaster is one of the worst chemical disasters in the world. On December 3, 1984, toxic gases were leaked at Bhopal (capital of state Madhya Pradesh, India) from a nearby pesticide plant. Several thousand were exposed, and some of them died immediately and afterward. After the disaster, the Municipal Corporation of Bhopal categorized Bhopal city into gas-affected and non-affected areas (wards) based on the severity of symptoms observed in the residents of those areas [1]. The gas-affected areas were further stratified into mild, moderate, and severely affected areas based on the mortality rate between December 3 and 6, 1984 [1].

In 1985, the Indian Council of Medical Research (ICMR) initiated a long-term population-based epidemiological study to assess the long-term health effects of toxic gas exposure [1]. Cohorts for that epidemiological study were assembled by randomly recruiting individuals from both gas-affected and non-affected areas. The stratification of the exposed cohort into mild, moderate, and severely exposed was based on the recruited participants' residential addresses. Formation of cohorts and morbidity profile of these cohorts over the last 30 years had been published [1–3]. Respiratory morbidities continued to be one of the commonest morbidities of the exposed cohorts. We hypothesized that lung function abnormalities, especially small airway dysfunctions (SAD) were responsible for the ongoing respiratory morbidities.

Our study aimed (i) to characterize respiratory symptoms, (ii) to assess lung function by both forced oscillometry (FOT) and spirometry, and (iii) to assess the association of respiratory symptoms with lung function abnormalities in survivors of the Bhopal gas disaster.

2. Patients and methods

2.1. *Study population*

This community-based cross-sectional study was conducted from February 2018 to February 2020. The Institutional Ethics Committee of the National Institute for Research in Environmental Health approved the study protocol. The initial study plan was to recruit from all cohorts, but permission was granted to recruit only from the severely exposed cohort. Since its inception, the cohort size of the ICMR study remained highly variable on each survey due to the high attrition rates [1–3]. Before the initiation of the present study, 4170 severe cohorts were available during the most recent survey of the ICMR study. We decided to recruit all of them. The exclusion criteria were those who declined to participate or were unavailable on two attempts. Our previous study showed that individuals with age <20 years at the time of the disaster had lesser respiratory morbidity than those aged $\geq$20 years [3]. Therefore, we stratified the present study participants into two age groups: age $\leq$55 years (i.e., age was $\leq$20 years at the time of the disaster) and age >55 years (i.e., age >20 years at the time of the disaster) to verify the previous observation.

2.2. *Characterization of chronic respiratory symptoms*

We developed a questionnaire based on the Indian Study on Epidemiology of Asthma, respiratory symptoms, and Chronic Bronchitis (INSEARCH) questionnaire to characterize respiratory symptoms and smoking habits [4]. Data on admission to a hospital within one week after the exposure, the distance of residence from the pesticide plant at the time of exposure, self-reported comorbidities (e.g., diabetes, hypertension, coronary artery disease, chronic kidney diseases, etc.), and deaths of family members (living with the participants) within one year from the disaster were also collected. A trained technician administered the questionnaire during home visits. The principal investigator re-examined the responses. The complaint of breathlessness was defined as an affirmative response to at least one of the questions on breathlessness in different situations, i.e., a feeling of morning breathlessness, breathlessness on exertion, breathlessness without exertion, and breathlessness at night. The cough complaint was defined as an affirmative response to either having a cough in the morning or at night. The diagnosis of chronic bronchitis was based on the cough with expectoration for $\geq$3 months with an affirmative response to one of the two questions, i.e., cough in the morning and bring out phlegm from the chest in the morning.

2.3. *Forced oscillometry (FOT)*

The respiratory system resistance (Rrs) and reactance (Xrs) were measured by the Resmon Pro Full device (Restech Srl, Milan, Italy) at 5 Hz, 11 Hz, and 19 Hz sinusoidal signals. The equipment was calibrated daily before the procedure with reference impedance. FOT was performed in an upright sitting position, according to the European Respiratory Society's recommendation [5]. Each individual performed at least three FOT, and each test was continued until 15 accepted breaths were recorded. The mean of three acceptable tests was retained for the analysis. The FOT parameters included in this analysis were whole-breath respiratory system resistance at 5 Hz (R5), whole-breath respiratory system reactance at 5 Hz (X5), and frequency-dependence of resistance calculated as the difference of whole-breath resistance at 5 Hz and 19 Hz (R_{5-19}). We published the predicted values with the upper limit of normal (ULN) and lower limit of normal (LLN) of each FOT parameter for healthy Indian adults [6]. To date, the standards to describe the abnormality of FOT parameters have not been developed [7]. Therefore, we considered R5 and R_{5-19} were abnormal if the recorded values were higher than the ULN; and X5 was abnormal if the recorded values were lower than the LLN. An abnormal FOT was defined as abnormal R5 or $R_{5-19,}$ or X5, or all three parameters were abnormal.

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2.4. Spirometry

After FOT, spirometry was performed according to the ATS-ERS recommendation using PowerCube Diffusion+ (GANSHORN Medizin Electronic, Germany) [8]. Each participant performed at least three acceptable maximal forced expiratory maneuvers. The highest value of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) were recorded. The North Indian regression equations were used to estimate the predicted values of spirometry parameters, and the LLN was set at the 5th percentile [9]. If both $FEV_1/FVC \geq 0.70$ and FVC $\geq$ LLN, spirometry was categorized as normal spirometry. If $FEV_1/FVC < 0.70$, spirometry was categorized as an obstructive pattern according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline [10]. If $FEV_1/FVC \geq 0.70$ and FVC < LLN, spirometry was categorized as a restrictive pattern. The severities of obstruction and restriction were based on FEV_1% of predicted according to the ATS-ERS recommendation, i.e., mild (≥70); moderate (≥60 to <70); moderately severe (≥50 to <60); severe (≥35 to <50); and very severe (<35) [8]. If the maximum mid-expiratory flow rate (MMEF) was less than LLN; it was categorized as low MMEF.

2.5. Statistical methods

Categorical variables are summarized in counts and percentages. The proportions are presented with 95% confidence intervals (CI) and were compared by Pearson's chi-square test. The parametric variables are presented as mean ± standard deviation, and the Student's t-test was used to compare the two groups. Logistic regression analysis was performed to assess the association between respiratory symptoms and abnormalities in FOT and spirometry. The odds ratios (OR) with 95% CI were used to evaluate the associations. The significance (p-value) was set at the 0.05 level. Statistical analysis was carried out by IBM® SPSS® Statistics Version 23.

3. Results

3.1. Demographic characteristics

We could establish direct contact with 1695 severely exposed participants during the study period. Of them, 916 (55.7%) participated in this study. The reasons for the low recruitment are described in Fig. 1. The mean age of the study population was 55.2 ± 12.3 years. The majority (98.9%) mentioned that they were residing within 1 km from the plant during the disaster. The death of at least one family member within one year was reported by 20.7% of the participants. Admission to a hospital within one week after the exposure was reported by 24% of the participants. More than one year of tobacco smoking was reported by 18.4% of individuals, and most of them were current smokers (77.4%). Except for five women, all smokers were men. Smokers in the ≤55-year age group were fewer than those in the older age group (13.9% vs. 22.7%, $p < 0.01$).

The predominant self-reported comorbidity was systemic hypertension (37.0%; 95% CI: 33.9–40.2), followed by diabetes (14.4%; 95% CI: 12.3–16.8). Of 916, 558 participants (60.9%) took part in lung function testing. The demographic characteristics of those who took part in lung function testing and those who did not (n = 358) were similar (Table 1). Those who participated in lung function assessment reported fewer coronary artery diseases than those who did not (4.1% vs. 8.4%; $p < 0.01$).

3.2. Respiratory morbidities

The majority (79.6%; 95% CI: 76.9–82.1) reported having at least one respiratory symptom. The predominant respiratory symptom was breathlessness on exertion (76.6%; 95% CI: 73.7–79.2), followed by cough (21.2%; 95% CI: 18.7–23.9). Based on the questionnaire, the prevalence of chronic bronchitis was 15.5% (95% CI: 13.3–17.9). The individuals who participated in lung function assessment had less breathlessness (71.7% vs. 88.5%; $p < 0.01$), less cough (15.1% vs. 30.7%; $p < 0.01$), and less chronic bronchitis (9.9% vs. 24.3%; $p < 0.01$) compared to those who did not take part in lung function testing (Table 1).

The age group distribution between men and women in those who participated in the lung function assessment was similar (45.8% of men vs. 45.6% women had age ≤55 years). Women had more breathlessness (78.4% vs. 64.7%; $p < 0.01$), and less cough (11.7% vs.18.5%; $p = 0.03$) compared to men. Chronic bronchitis was more common in men than women (13.5%. vs. 6.4%; $p < 0.01$). The individuals aged ≤55 years had less breathlessness (75.9% vs. 80.6%; $p = 0.05$) and less cough (18.1% vs. 24.2%, $p = 0.02$) than individuals aged >55 years. However, chronic bronchitis in both age groups was comparable (14.3% vs. 16.6%; $p = 0.19$).

3.3. Forced oscillation technique

Acceptable FOT was performed by 471 participants. The R5 and X5 ≥ 150% predicted was observed in 24.2% and 28.9%, respectively (Fig. 2). The R5 > ULN was in 29.3%, $R_{5\text{-}19}$ > LLN was in 23.3%, and X5 < LLN was in 21.2% of participants (Table 2). We observed abnormal FOT parameters in 37.7% of participants. Both men and women had similar abnormalities in FOT (36.1% in men vs. 39.3% in women, $P = 0.27$).

3.4. Spirometry

A total of 452 participants performed acceptable spirometry. Normal, obstructive, and restrictive spirometry were observed in 46.2%, 26.1%, and 27.7% participants, respectively (Table 3). Obstructive spirometry was more common in men than in women (31.3% vs. 20.3%, $p < 0.05$). The severity of airflow obstruction was primarily mild (45.8%). The women had more restrictive spirometry than men (33.5% vs. 22.5%, $p < 0.05$). The severity of restrictive spirometry was mainly mild to moderate (68.8%).

The risk of abnormal X5, $R_{5\text{-}19}$, obstructive, and restrictive spirometry was significantly higher in the >55 years age group (Table 4). The risk of abnormal X5 and $R_{5\text{-}19}$ and restrictive spirometry in the older age group remained significant, despite adjusting for smoking.

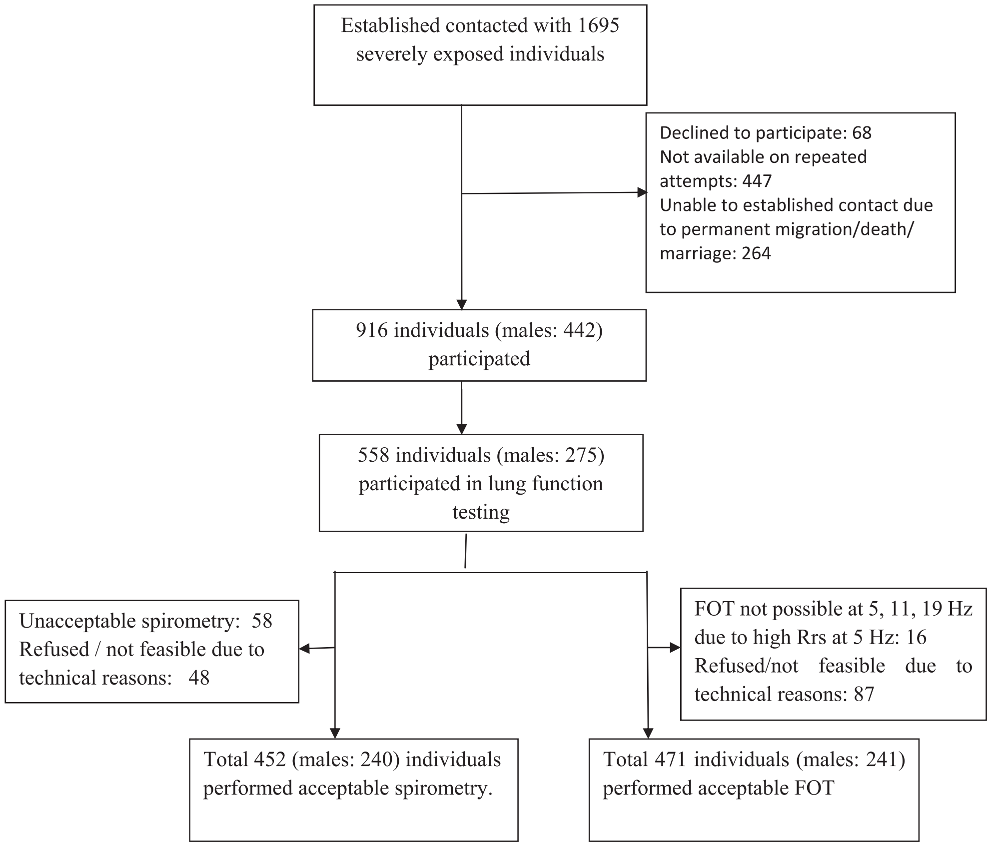

Fig. 1 – Flow chart of subject recruitment.

Table 1 – Demographic characteristics and respiratory symptoms of the study population.

Variables	Participated in lung function assessments (n = 558)	Not participated in lung function assessments (n = 358)	Total (N = 916)
Age (year), mean ± SD	55.8 ± 11.6	54.3 ± 13.2	55.2 ± 12.3
Men, n (%)	275 (49.3)	167 (46.6)	442 (48.3)
Smoked for >1 year, n (%)	107 (19.2)	61 (17.0)	168 (18.4) (95% CI: 15.9–20.9)
Comorbidities			
Diabetes mellitus, n (%)	75 (13.4)	57 (15.9)	132 (14.4) (95% CI:12.3–16.8)
Hypertension, n (%)	205 (36.7)	134 (37.4)	339 (37.0) (95% CI: 33.9–40.2)
Coronary artery disease n (%)	23 (4.1)	30 (8.4)*	53 (5.8) (95% CI: 4.5–7.5)
BMI (kg/m^2)	24.6 ± 5.2	–	–
Breathlessness, n (%)	400 (71.7)	317 (88.5)*	717 (78.3) (95% CI: 75.5–80.8)
Cough, n (%)	84 (15.1)	110 (30.7)*	194 (21.2) (95% CI: 18.7–23.9)
Chronic bronchitis, n (%)	55 (9.9)	87 (24.3)*	142 (15.5) (95% CI: 13.3–17.9)

BMI: body mass index; *p-value<0.01; CI: confidence interval.

Both acceptable FOT and spirometry were performed by 386 (69.2%) participants. The R5 > ULN, $R_{5\text{-}19}$ > ULN, and X5 < LLN were observed in 17.7%, 15.1%, and 8.1% of participants, respectively, with normal spirometry (Table 5). Individuals with obstructive spirometry had a higher risk of abnormal FOT parameters (adj OR: 3.93, 95% CI: 2.24–6.89). Participants with obstructive and restrictive spirometry had the highest risk of having abnormal X5.

3.5. *Relationship of respiratory symptoms with lung function parameters*

Among FOT parameters, breathlessness was significantly associated with abnormal R5 (OR: 1.81; 95% CI: 1.13–2.91) and abnormal FOT (OR: 1.73; 95% CI: 1.12–2.68; Table 6). Among spirometry parameters, breathlessness was significantly associated with obstructive spirometry (OR: 2.26; 95% CI:

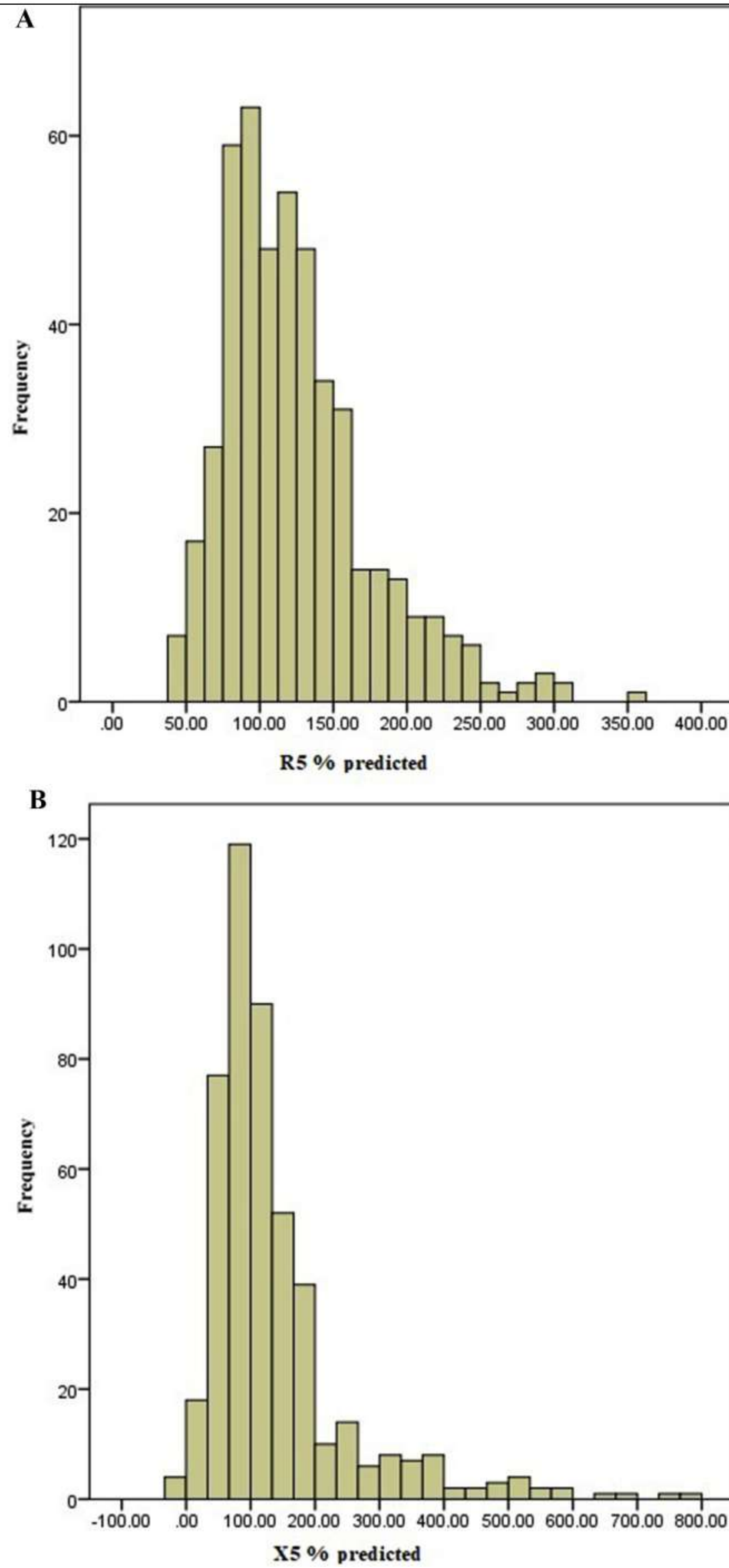

Fig. 2 – (A) Whole breath respiratory resistance at 5 Hz (R5) presented as percentage of predicted. (B) Whole breath respiratory reactance at 5 Hz (X5) presented as percentage of predicted.

Table 2 – The distribution of abnormality in Forced Oscillation Technique according to gender.

Variables	Men (=242) n (%)	Women (=229) n (%)	Total (=471), n (%), (95% CI)
R5 > ULN	65 (26.9)	73 (31.9)	138 (29.3) (25.4–35.6)
X5 < LLN	47 (19.4)	53 (23.1)	100 (21.2) (17.8–25.2)
$R_{5\text{-}19}$ > ULN	54 (22.4)	55 (24.3)	109 (23.3) (19.6–27.2)
Abnormal FOT	87 (36.1)	90 (39.3)	177 (37.7) (33.3–42.0)

R5: Whole-breath resistance at 5 Hz; X5: Whole-breath reactance at 5 Hz; $R_{5\text{-}19}$: Frequency-dependence resistance; ULN: upper limit of normal; LNN: lower limit of normal.

Table 3 – The distribution of spirometry abnormality and severity of abnormality according to gender.

Variables	Men (=240), n (%)	Women (=212), n (%)	Total (=452), n (%)
Normal spirometry	111 (46.3)	98 (46.2)	209 (46.2) (95% CI: 41.7–50.9)
Obstructive pattern	75 (31.3)	43 (20.3)*	118 (26.1) (95% CI: 22.3–30.4)
Mild airflow obstruction	36 (48)	18 (41.9)*	54 (45.8)
Moderate airflow obstruction	13 (17.3)	8 (18.6)	21 (17.8)
Moderately severe airflow Obstruction	12 (16.0)	11 (25.6)	23 (19.5)
Severe airflow obstruction	12 (16.0)	6 (14.0)	18 (15.3)
Very severe airflow obstruction	2 (2.7)	0	2 (1.7)
Restrictive pattern	54 (22.5)	71 (33.5)*	125 (27.7) (95% CI: 23.7–31.9)
Mild restriction	15 (27.8)	27 (38.0)	42 (33.6)
Moderate restriction	22 (40.7)	22 (31.0)	44 (35.2)
Moderately severe restriction	9 (16.7)	16 (22.5)	25 (20.0)
Severe restriction	8 (14.8)	4 (5.6)	12 (9.6)
Very severe restriction	0	2 (2.8)	2 (1.6)
MMEF < LLN#	99 (41.4)	44 (30.8)*	143 (30.6) (95% CI: 26.6–34.9)

*$p < 0.05$; CI: confidence interval, MMEF: mid expiratory flow rate; LLN: lower limit of normal.
#: MMEF: Maximum mid-expiratory flow rate, data were available for 468 subjects.

Table 4 – The age group-wise distribution of lung function abnormality.

Variables	Age group		Odds ratio, (95% CI)	
	<=55 years (=213) n (%)	>55 years (=258) n (%)	Un-adjusted	Adjusted*
R5 > ULN	58 (27.2)	80 (31.0)	1.20 (0.80–1.79)	1.17 (0.78–1.53)
X5 < LLN	29 (13.6)	71 (27.5)	2.41 (1.49–3.88)#	2.26 (1.39–3.66)#
$R_{5\text{-}19}$ > ULN	37 (17.6)	72 (28.0)	1.82 (1.16–2.85)#	1.66 (1.05–2.62)^
Obstructive pattern	46 (20.6)	72 (31.6)	1.78 (1.16–2.74)#	1.49 (0.95–2.33)
Restrictive pattern	50 (22.3)	75 (32.9)	1.71 (1.12–2.59)^	1.89 (1.23–2.89)#
MMEF < LLN@	72 (50.3)	71 (49.7)	0.91 (0.61–1.35)	0.74 (0.49–1.12)

* Adjusted for smoking; R5: Whole-breath resistance at 5 Hz; X5: Whole-breath reactance at 5 Hz; $R_{5\text{-}19}$: Frequency-dependent resistance; ULN: upper limit of normal; LNN: lower limit of normal; MMEF: Maximum mid-expiratory flow rate.
@ acceptable MMEF was obtained from 468 cases.
#$p < 0.01$.
^$p < 0.05$.

1.29–3.95) and low MMEF (OR: 2.35; 95% CI: 1.42–3.87). The adjusted odds for having cough with abnormalities in FOT parameters were non-significant. Among spirometry parameters, cough showed a significant association with MMEF (OR: 3.04; 95% CI: 1.74–5.34) only.

4. Discussion

In this study, we characterized the respiratory symptoms in the Bhopal gas disaster survivors and assessed their lung functions by both FOT and spirometry.

After any toxic inhalational disaster, population-based studies are crucial for understanding the pathophysiological mechanisms of lung injuries, long-term sequel, and developing appropriate medical management. Many individuals were also exposed to the dust of building materials during the World Trade Center (WTC) terrorist attacks. Extensive research and long-term follow-up of the exposed population in the WTC attacks helped us to understand the pathogenesis of lung injury following toxic inhalation. However, long-term follow-up lung function in the Bhopal gas disaster survivors is lacking.

The morbidity data of the ongoing long-term epidemiological study of the ICMR are collected either from the head of

Table 5 – The association of FOT abnormalities with spirometry results.

Variables	Normal spirometry (=186) n (%)	Obstructive pattern (=92) n (%)	Restrictive pattern (=108) n (%)
R5 > ULN	33 (17.7)	47 (51.1)	33 (30.6)
Adjusted Odds ratio* (95% CI)	1	4.88 (2.71–8.77)	2.02 (1.15–3.54)
X5 < LLN	15 (8.1)	38 (41.3)	31 (28.7)
Adjusted Odds ratio* (95% CI)	1	6.66 (3.31–13.42)	4.07 (2.06–8.07)
R_{5-19} > ULN	28 (15.1)	36 (40.4)	28 (25.9)
Adjusted Odds ratio* (95% CI)	1	3.09 (1.67–5.73)	1.82 (0.99–3.31)
Abnormal FOT	47 (25.3)	53 (58.2)	43 (39.8)
Adjusted Odds ratio* (95% CI)	1	3.93 (2.24–6.89)	1.90 (1.14–3.18)

*Adjusted for age (continuous variable) and smoking status (binary variable); R5: Whole-breath resistance at 5 Hz; X5: Whole-breath reactance at 5 Hz; R_{5-19}: Frequency-dependence of resistance; ULN: upper limit of normal; LNN: lower limit of normal.

Table 6 – The association of respiratory symptoms with an abnormality in FOT and spirometry parameters.

Variables	Breathlessness				Cough			
	Breathless n (%)	Not breathless n (%)	Odds ratio (95% CI)		Cough n (%)	No cough n (%)	Odds ratio (95% CI)	
			Un-adjusted	Adjusted*			Un-adjusted	Adjusted*
Abnormal R5 (R5 > ULN)	109 (32.9)	29 (20.7)	1.88 (1.18–3.0)	1.81 (1.13–2.91)	24 (34.3)	114 (28.4)	1.31 (0.77–2.25)	1.24 (0.72–2.15)
Abnormal X5 (X5< LLN)	80 (24.2)	20 (14.3)	1.91 (1.12–3.27)	1.60 (0.92–2.78)	18 (25.7)	82 (20.4)	1.35 (0.75–2.43)	1.08 (0.58–2.0)
Abnormal R_{5-19} (R_{5-19} > ULN)	84 (25.7)	25 (17.9)	1.59 (0.96–2.62)	1.34 (0.81–2.24)	18 (26.1)	91 (22.9)	1.19 (0.66–2.14)	0.95 (0.51–1.75)
Abnormal FOT	138 (41.8)	39 (27.9)	1.86 (1.21–2.86)	1.73 (1.12–2.68)	29 (41.4)	148 (37.0)	1.20 (0.72–2.02)	1.01 (0.99–1.03)
Obstructive pattern	99 (30.7)	19 (14.7)	2.56 (1.49–4.39)	2.26 (1.29–3.95)	29 (43.9)	89 (23.1)	2.62 (1.52–4.49)	1.02 (0.99–1.04)
Restrictive pattern	97 (30.0)	28 (21.7)	1.55 (0.95–2.51)	1.55 (0.95–2.53)	21 (31.8)	194 (26.9)	1.27 (0.72–2.23)	1.36 (0.76–2.43)
MMEF < LLN	116 (35.0)	27 (19.7)	2.19 (1.36–3.54)	2.35 (1.42–3.87)	35 (53.8)	108 (26.8)	3.19 (1.87–5.44)	3.04 (1.74–5.34)

*Adjusted by smoking status (binary variable) and age (continuous variable). R5: Whole-breath resistance at 5 Hz; X5: Whole-breath reactance at 5 Hz; R_{5-19}: Frequency-dependence of resistance; ULN: upper limit of normal; LNN: lower limit of normal.

the family or any adult family member available during the surveys [1–3]. In contrast, the morbidity data of the current study were collected through face-to-face interaction. This might be a possible reason for which we observed higher respiratory morbidities.

Lung function assessment is essential to evaluate the adverse effects of toxic inhalations. Immediately after the disaster and subsequently, several studies were conducted to estimate the lung function abnormalities in survivors of the Bhopal gas disaster. Spirometry was used in most studies. The type, severity, and distribution of abnormalities in spirometry were widely variable across those studies [11]. We also reported the development of new abnormalities and rapid decline in lung function in symptomatic survivors [12]. The most recent publication on lung function of the Bhopal gas disaster survivors was a retrospective analysis of spirometry reports of those who consulted a particular hospital for their respiratory problems [11]. That study reported obstructive patterns as the predominant abnormality (50.8%), followed by restrictive patterns (13.3%). The current study being community-based might be the reason for the different distribution of abnormalities in spirometry. Cullinan et al. were the first to report reduced MMEF in the Bhopal Gas Disaster exposed population, a subtle marker of SAD in spirometry [13]. They observed that those who were living near the pesticide plant had significantly reduced MMEF. However, they had not reported the prevalence of MMEF abnormalities. Approximately one-third of our population had MMEF < LLN.

The individuals exposed to the WTC attack also had persistent respiratory morbidity and lung function abnormalities over decades [14,15]. The gases of the Bhopal gas disaster were lethal compared to the dust of the WTC attack. Therefore, lung function abnormalities in the exposed population of the Bhopal gas disaster, even over 34 years after the exposure, were not surprising. We observed that the lung function abnormalities were less in younger participants than in older ones. This was possibly due to the wane of exposure effects as the children grew.

FEV_1 predominantly reflects the obstruction of medium to large-sized airways. A significant amount of small airway resistance must be built to make FEV_1 abnormal [16]. Spirometry fails to detect complex heterogeneous airway pathologies, especially if subtle abnormalities are present in the small airways. FOT and impulse oscillometry (IOS) are two noninvasive techniques used to assess SAD. Oppenheimer et al. highlighted IOS as a better way of identifying SAD in participants exposed to the WTC attack [17]. The small airway function in participants exposed to WTC attacks provided valuable information that was not apparent in their spirometry [14,15]. The association of SAD with persistent respiratory symptoms in the exposed population of the WTC attack is well established [14,18]. Breathlessness in the present study showed a significant association with the abnormalities of both FOT and spirometry. Similar to the WTC attack exposed population, we also found abnormalities in FOT parameters independent of spirometry abnormalities. Sriramachari documented the histopathological involvement of small airways in lung autopsies of the exposed people of the Bhopal gas disaster [19]. Our study is the first to investigate and document SAD in survivors of the Bhopal gas disaster.

The restrictive spirometry of the WTC disaster was attributed to the involvement of small airways [20]. SAD closes small airways at tidal volume, leading to restrictive spirometry. We also observed the presence of SAD in participants with restrictive spirometry. Few individuals with restrictive spirometry underwent further radiological evaluations; however, no evidence of fibrosis or scarring in lung parenchyma was observed.

The major limitations of this study were cross-sectional design, low participation, no comparator arm, i.e., recruitment only from the severely exposed cohort, few radiological examinations were carried out, and approximately half of the recruited individuals participated in lung function assessment. Therefore, the observation of this study may not be generalized to the survivors of the Bhopal gas disaster. The causes of low participation could be the following: preoccupation with their livelihood, lack of interest, no financial benefits for participation, change of residence, local migration, etc. We were also unable to establish contact with individuals who are usually at work during our study visits, and they were probably healthier. There is a potential risk of selection bias, as those with fewer respiratory symptoms participated in lung function assessments. This study was conducted over 34 years after the exposure, and they were also exposed to occupational and ambient air pollution in the succeeding years. Therefore, we cannot attribute the observed lung function abnormalities due to exposure only in the absence of longitudinal lung function data. Post-bronchodilator spirometry and FOT were not performed due to logistic issues. Lung volume estimation of participants with restrictive spirometry was also not performed to confirm reduced total lung capacity. The strength of this study was that participants were part of the original cohort of the long-term epidemiological study. Therefore, their exposure to the disaster was undoubted.

5. Conclusions

In conclusion, the present study highlights the high prevalence of self-reported respiratory morbidity and abnormalities in lung function. The small airway dysfunctions were independent of abnormalities in spirometry. A comprehensive lung function assessment is indispensable in assessing the effects of toxic inhalation.

Authors contribution

SD: Conceived the study, interpretation of data, and manuscript writing. NB: Data collection. YS: Data interpretation. All authors read and approved the final manuscript.

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Ethics approval statement

The Institutional Ethics Committee of the National Institute for Research in Environmental Health approved the study protocol (NIREH/BPL/1EC-prj.19/2017-18/1458).

Data sharing/data availability

Data can be shared for review only.

Grant/award number

Not applicable.

Conflict of Interest

All authors declare non-competing interests.

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