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Chronic Obstructive Pulmonary Disease and Smoking in India: A Meta-Analysis

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ABSTRACT

WHO estimates show chronic obstructive pulmonary disease [COPD] as a growing major global cause of morbidity as well as mortality. COPD associated mortality is projected to grow by 160% in the decades ahead. Much of this projection holds pansexual cigarette smoking, improved life expectancy, bulging geriatric population and high levels of small particle pollution, as major causes behind increase in COPD case burden. The aim of the meta-analysis was to investigate association between COPD and risk factors by pooled and subgroup analysis. The publications listed in the NCBI PubMed and Cochrane library were searched using the following combination of the key words "COPD"; "smokers"; "health"; "risk" or "factors"; "diagnostic"; "burden"; "exposure"; "disease" or "prevalence" or "morbidity" or "mortality"; "tobacco"; "smoking"; "smoke", "India". Random effects meta-analysis was applied to generate pooled SMD by using CMA software. Main risk factors for COPD were higher age [SMD=0.53, CI= (0.0018-1.05)], total pack years of Smoking [SMD=13.83, CI (10.060-17.616)], FEV1 [SMD=-13.15, CI= (-16.234 to -10.085) and FEV/FVC ratio [SMD=0.915.CI= (0.767-1.063)]. Higher age, smoking, low values of FEV1 and FEV/FVC ratio is directly associated with high risk of COPD. The finding of the study shows evidence of smoking history in terms of pack of years as a major risk factor for COPD prevalence.

Keywords: Risk factors, Chronic Obstructive Pulmonary disease [COPD], Meta-analysis smoking

INTRODUCTION

The Global Initiative for Chronic Obstructive Lung Diseases (GOLD) has classified Chronic Obstructive Pulmonary Disease (COPD) as a disease state characterized by airflow limitation that is not fully reversible and which is also associated with abnormal inflammatory responses of the lungs to noxious particles or gases[1]. COPD is reported to have an estimated disease burden of 210 million people worldwide.[2]

Globally COPD was the fourth leading cause of death (5.1%) in 2004 and is projected to occupy the third position (8.6%) in 2030. COPD is a major cause of chronic morbidity; it was ranked 11th in 2002 and is projected to rise to seventh place in 2030[3].The prevalence of COPD in adults ranges between 0.2% in Japan and 37% in USA[4]. The Burden Obstructive Lung Disease (BOLD) group recently reported an average global COPD prevalence of 10.1% with wide variations across the participating countries[5]. Additionally, COPD contributes to the economic burden faced by patients as well as the healthcare infrastructure in the country, incurring 2–4-fold higher costs compared with asthma and ischemic heart disease (IHD).[6,7]

The WHO estimate suggests that 90% of COPD-related deaths occur in lower- and middle-income country. India and China constitute 33% of the total human population and account for 66% of the global COPD mortality[8]. Further, it has been estimated that COPD associated mortality is likely to grow by 160% in the Southeast Asian region in thecoming decades[9].

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Globally the increase in the burden of COPD has been attributed to cigarette smoking among men and women, longer survival of populations, and high levels of air pollution, particularly in developing countries[2,7]. Chronic obstructive pulmonary disease [COPD] is a major and growing cause of morbidity and mortality worldwide[10].

India is the large country comprising of people with varying socio-demographic profiles, cultural practices and ethnicities. Hence the risk factors for COPD are also likely to be different across various states and regions. Together COPD, asthma and other respiratory diseases are the second (10.2%) leading cause of death in the population aged 25–69 years in India, as reported in 2001–2003[11], and they account for 3% of disability adjusted life-years (DALYs) lost[12]. Of the CRD, COPD accounts forabout 500000 deaths in India, which is more than four times the number of people who die due to COPD in USA and Europe[13]. A recently completed nationwide questionnaire-based study estimated the prevalence of COPD at 3.49% in India[14].

The Greek word "meta" refers to "after" or "beyond" and therefore meta- analysis go beyond individual studies. The first definition of meta- analysis was given by Gene Glass[1976] as "the statistical analysis of a large collection of results from individual studies was the purpose of integrating the findings"[15]. Glass also called meta- analysis as "an analysis of analyses". Huque [1988] defined the term as "A statistical analysis that combines or integrates the results of several independent clinical trials considered by the analyst to be combinable"[16]

Search Strategy: We conducted the meta-analysis for COPD in India, to know the prevalence of COPD in the last five years [13th July 2012 to 20th June 2018] because thelast research paper published on 13th July 2012 regarding "PREVALENCE OF COPD IN INDIA: A SYSTEMATIC REVIEW"

METHODS

The publications listed in the NCBI PubMed and Cochrane library were primarily searched using the following combination of the key words "COPD"; "smokers"; "health"; "risk" or "factors"; "diagnostic"; "burden"; "exposure"; "disease" or "prevalence" or "morbidity" or "mortality"; "tobacco"; "smoking"; "smoke", "India". The search was limited only to articles in English. The search was limited to PubMed and additionally, the cross-references were also searched from the included papers to identify eligible articles. Studies considered were if they estimate the association between COPD and spirometer, smoking status, age, BMI, and gender parameters.

Data Extraction: The data extracted with following information: First author name, Publication year, Characters of population [Mean and SD of gender, age, pack of years, BMI, FEV1, FVC,FEV/FVC Ratio]. If the comparative references were not the same, for example, some references may record the mean age, but in some studies, they given in the 'N', in those cases if the available information is sufficient then we calculated the mean age of the study. Studies were considered if they estimate the association between COPD and spirometry, smoking status, age, BMI, and gender parameters.

Inclusion of the published articles for the study was based on the following criteria

Inclusion criteria

- Articles are confined to within India.
- Study type: Study subjects were human with COPD Case control group.
- Studies reporting at least 3 or more risk parameters like smoking pattern, Pack of years, FEV1, FVC, FEV/FVC, BMI, age and gender etc.;
- Provided method description of various parameters with means and standarddeviation.
- The literatures are collected from 22/12/2011 to 20/06/2018.
- Methodology details in publication with approach of diagnosis and diagnostic criteria used by investigators should be available in literature.
- Provided original data

Exclusion criteria

- Studies reporting other parameters with no numerical data or only graphicrepresentation.
- Studies reporting the parameters on diseases other than COPD
- Reports on various discussed parameters only in COPD without control group.
- Methodology details in publication with approach of diagnosis and diagnosticcriteria used by investigators should be available in literature.

The search resulted from 22, December, 2011 to 20, June, 2018 identified 29222 citations.28620 references were excluded by screening their titles and abstracts and 581remained for full text review to determine eligibility. Among 581 articles 567 full text papers as they failed to meet inclusion criteria or had in sufficient information for data extraction.

Fig 1: Flow chart for inclusion of articles in the study

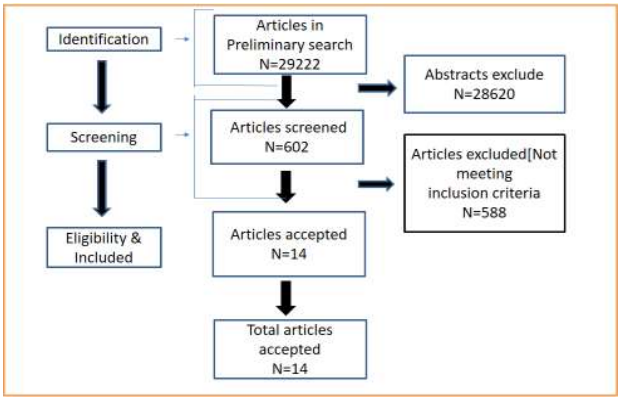


Table 1: Characteristics of studies

Sr. No	Authors Name	Year of Publication	Study type	Total Patients (N)	COPD Cases	Control Cases	Age, years* (M± SD) Case	Age, years* (M ±SD) Control	Smokers/ Nonsmokers (N) Case	Smokers/ Nonsmokers (N) Control	Pack years† (M±SD) Case	Pack years† (M±SD) Control	FEV1 (Mn±SD) Case	FEV1 (M ± SD) ontrol	FEV1/FVC (M±SD) Case	FEV1/FVC (M ± SD) control
1'	A. Ahmad et al.	2013	CC	215	140	75	45.48±1.26	41.67±1.87	98/44	25/50	16.09±0.61	4.35±0.80	47.88±1.76	84.20±1.26	70.14±1.31	97.56±0.71
2.	Almira Akparova et al.	2017	CC	107	55	52	53.81±9.00	53.27±6.17	37/18	6/46	20.6±7.9	1.3±0.5	61.02±18.1	94.6±8.2	67.o±0.13	80.0±0.03
3.	Prashant Mani Tripathi etal.	2017	CC	202	101	101	55.6±0.9	52.9±1.1	73/28	33/68	32.8±1.8	18.7±1.3	37.6±1.0	89.8±0.7	61.2±0.7	101.6±0.7
4.	Jyoti Bajpai et al.	2017	CC	260	180	80	57.3±20.58	48.3±18.2	_	_	17.56±13.83	NA	_	_	_	_
5.	Priti Lokesh Meshram et al.	2018	CC	100	50	50	46.28±48.16	70.9±23.8	_	_	_	_	_	_	_	_
6.	S. Singh et al.	2016	CC	250	150	100	57.95±10.43	52.06±11.89	118/32	45/55	146.4±1.7	33.7±1.2	_	_	55.06±9.51	99.0015.78
7.	Arja Cholendraet al.	2013	CC	386	236	150	63.19±8.79	60.97±8.95	97/139	147/3	42.44±38.22	52.05±56.22	36.68±11.89	71.2±14.78	55.52±8.08	86.35±6.72
8.	Rajlaxmi Sarangi et al.	2017	CC	85	39	46	62.97±1.30	48.76±12.71	_	_	_	_	_	_	_	_
9.	Virendra C et al.	2012	CC	200	100	100	53.24±11.03	45.82±8.39	_	_	_	_	_	_	80.95±14.36	87.62±7.219
10.	Nishant Nayyaret al.	2017	CC	144	84	60	61.29±6.51	56.18±7.72	_	_	_	_	_	_	_	_
11.	Prem Parkash Gupta et al.	2013	CC	80	40	40	57.25±9.07	56.9±9.21	_	_	39.95±20.94	_	_	_	_	_
12.	Sujoy Mukherjee et al.	2017	CC	550	260	290	35.07±13.02	43.89±11.33	40/220	100/190	_	_	99.05	99.05	81.51±29.18	92.23±30.14
13.	Prem Parkash Gupta et al.	2018	CC	80	40	40	60.2±11.2	62.3±7.8	_	_	30.8±15.7	28.5±12.8	_	_	50.0±0.009	56.0±0.10
14.	Avi Kumar et al.	2017	CC	27	11	14	54.5±10.3	56.5±8.81	_	_	29±19.3	29.8±29.6	_	_	50.9±13.8	50.7±8.7

CC- Case Control Study;
M ± SD - Mean ± Standard Deviation

A total of 14 articles met the inclusion criteria. The Meta-analysis include these 14 studies of case control study. The flow chart for the inclusion of articles is represented in fig 1.

About smoking history in terms of pack of years of the subjects 6 studies were included, 14 studies provided data for age parameter. Analysis by spirometry diagnostic criteria ofCOPD, 10 studies for FEV1, 8 studies for FVC and 9 studies for FEV/FVC ratio are included. Of the 14 papers reviewed, one was published in the 2012s, three in the 2013s, one in 2016s, seven in 2017, and two in 2018s.Summary of the 14 eligible articles is presented in table 1.

Statistical analysis

Studies were included in the final analysis when they had considered COPD as an airflow limitation that is not fully reversible [assessed by post bronchodilator spirometry], according to the American Thoracic Society Criteria[17] [Post bronchodilator forced expiratory volume in 1s (FEV1) /Forced vital capacity(FVC) ratio <0.70) or the Global Initiative for obstructive lung DiseaseCriteria[18]] [Presence of a post bronchodilator FEV1/FVC ratio <0.70] or the method of FEV1/FVC below the lower limit of normal value. In the meta- analysis, the mean and SD values of risk factors like age, smoking history in terms of pack of years, FEV1, FVC, and FEV/FVC were compared between COPD patients and controls. Standardized mean difference (SMD) and its 95% CI as a summary statistic for the difference of various defined parameter. The overall effect size SMD was presented as a Z-score. The Z-score with a p-value of ≤0.05 was considered statistically significant. Heterogeneity across studies was detected using I^2 statistics. A random effect model was applied when there is significant heterogeneity (I^2 > 45%). Subgroup analysis performed by using smoking parameter to understand the prevalence of individual risk factors among COPD patients and control. Risk of publication bias was adjudged using funnel plot. All analyses were performed using Comprehensive Meta-analysis.

RESULTS

Funnel plot analysis Funnel plot analysis was conducted to check for publication bias. We looked for a publication bias in age parameter associated with COPD case control studies. Fig 2 shows that the Standard error against standard in mean differences. Using Eggers test of publication bias p=0.00035 was obtained for age. Since some studies fall outside the funnel plot, there is possibility for publication bias among studies.

Pooled analysis

Comparison of COPD risk by age among case and control group [Fig: 2]

Pooled estimates on SMD shows that significantly higher age favor to COPD patients than controls [SMD=0.535, CI= [0.018-1.05], P<0.05]. Most of the studiesfound similar result as pooled. Heterogeneity test illustrates the significance variation between studies [I^2=97.4, P<0.001].

Comparison of COPD risk by smoking history in terms of pack of years among case and control group. [Fig: 4]

The studies were then stratified between smoke history in terms of pack of years of COPD case and control group participants [n=6]. The Pooled analysis estimateson SMD shows that the high risk of COPD was significantly seen in smoking parameter in terms of pack of years than controls [SMD=13.838, CI=[10.060- 17.616], P<0.001]. All the studies found similar result as pooled. Heterogeneity testillustrates the significance variation between studies [I^2 =99.620], P<0.001].

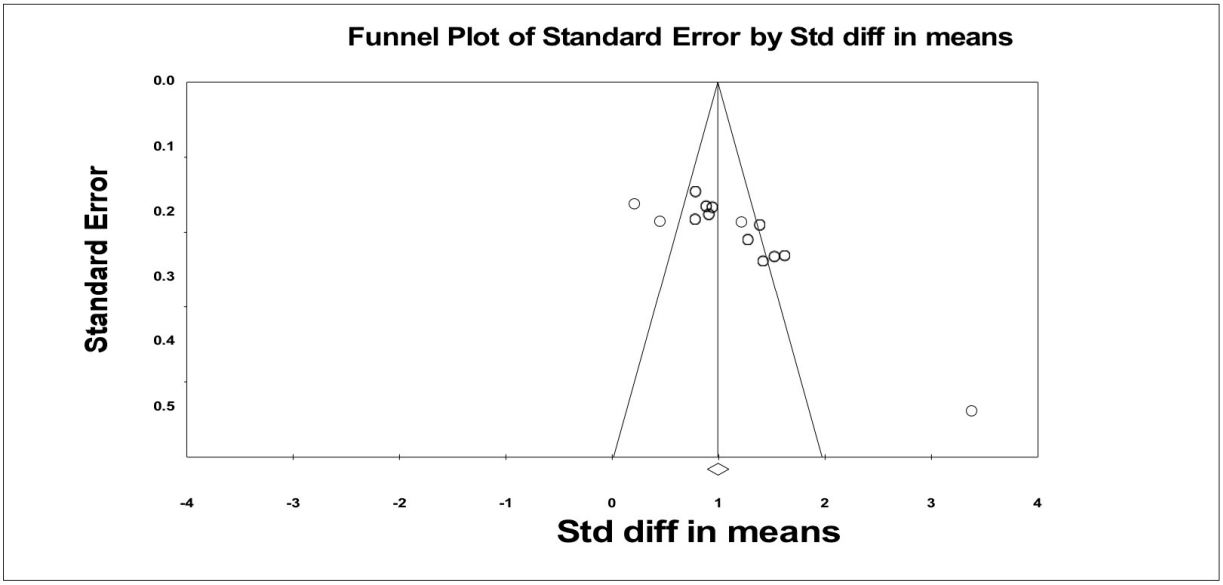
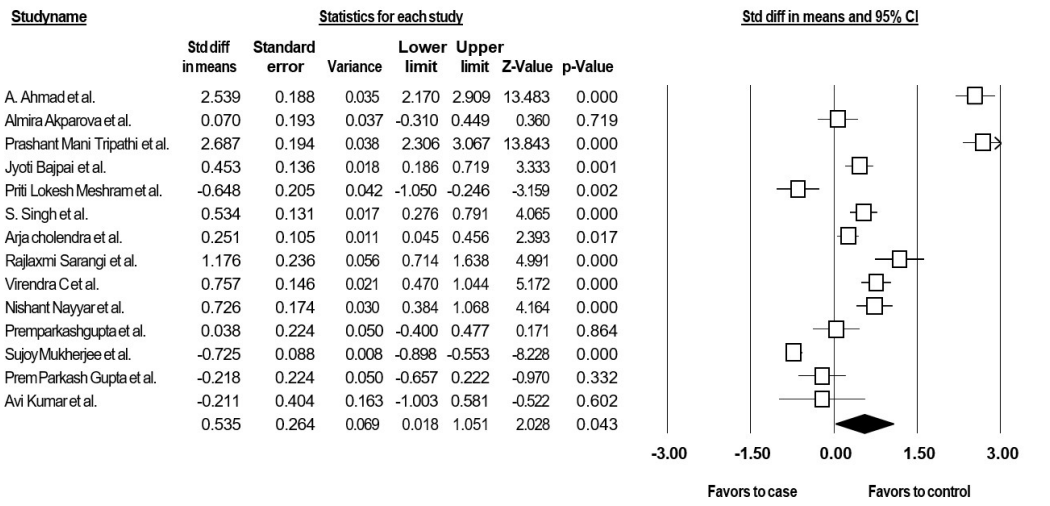
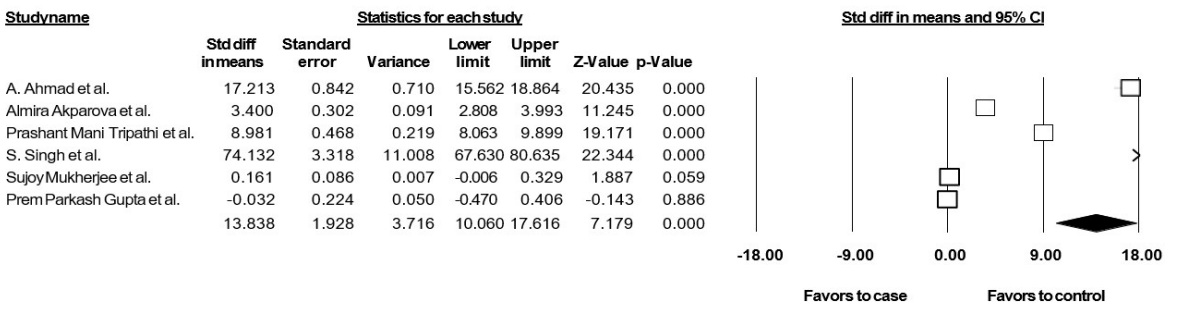


Figure 2: Forest plot showing COPD risk by age parameter compared with control.



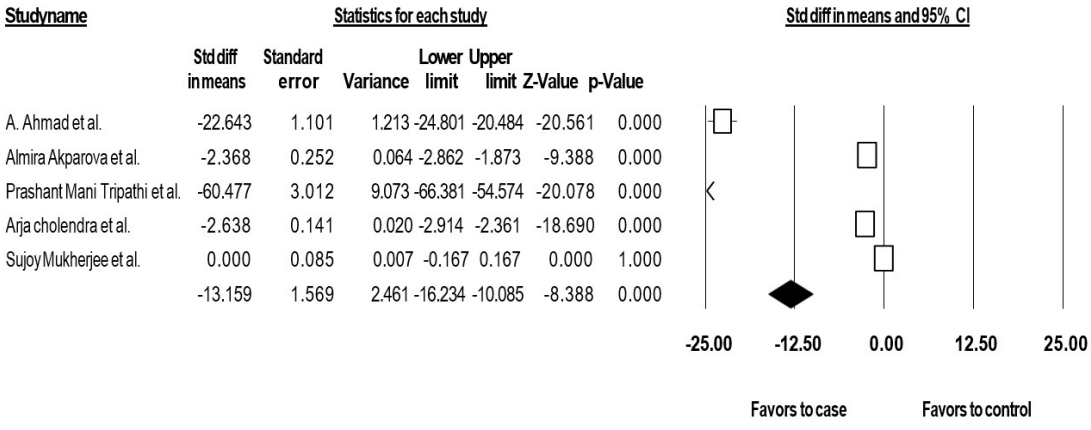
I-Sq=97.36 Q-Sq=492.71

Figure 3: Forest plot showing age parameter of COPD case compared with control



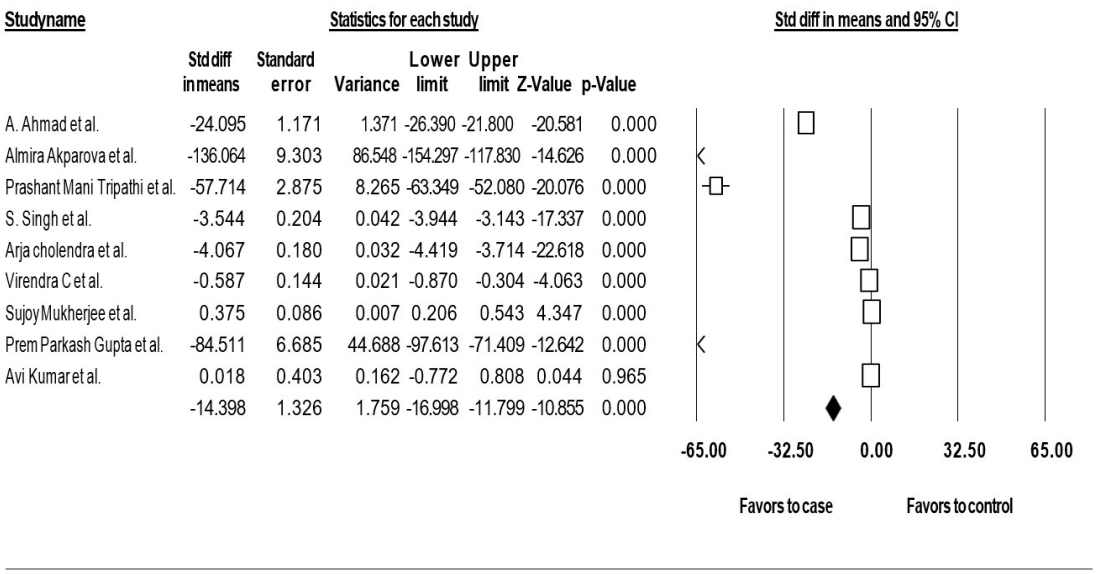
I-Sq=99.620 Q-Sq=492.71

Figure 4: Forest plot showing COPD due to exposure to smoking in terms of pack of years compared with control.



I-Sq=99.629 Q-Sq=1076.889

Figure 5: Forest plot showing diagnostic criteria FEV1 of COPD group is comparingwith control group



I-Sq=53.924 Q-Sq=17.563

Figure 6: Forest plot showing diagnostic criteria FEV/FVC ratio of COPD group iscomparing with control group

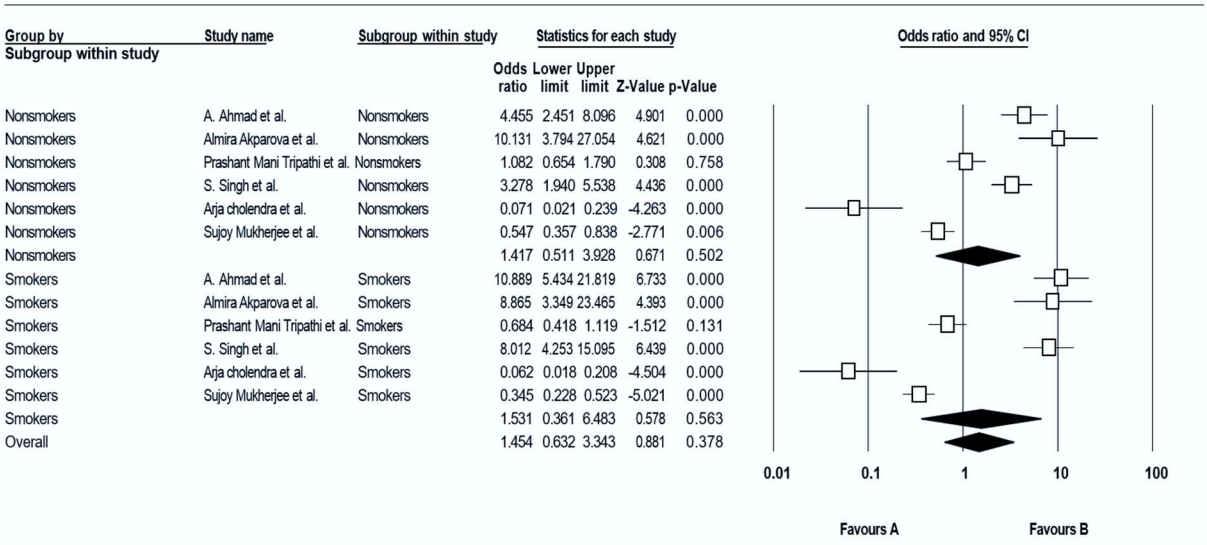


Figure 7: Forest plot showing COPD group in terms of smoking status [smokers:Non-smokers] compared with control group

Comparison of COPD risk by diagnostic criteria [Spirometry =FEV1, & FEV/FVC ratio] of COPD.

FEV1 diagnostic parameter [Fig: 5]

Among five studies in case of COPD group FEV1 ranges between 30% to 65% less than normal range and in control group FEV1 ranges between 70% to 95%, in case of control group FEV1 value is normal, but in one study in case of COPD group FEV1 value is showing normal (Table1). Pooled estimates on SMD shows that significantly diagnostic parameter FEV1 is directly associated with COPD patients than controls. Significantly lower values of FEV1 were found in COPD patients than control group [SMD=-13.159], CI= [-16.234 to -10.085], P<0.001] Most of the studies found similar result as pooled. Heterogeneity test illustrates the significance variation between studies [I^2=99.62], P<0.001].

FEV/FVC ratio diagnostic parameter [Fig: 6]

Most of studies in case of COPD group FEV/FVC ratio is < 70%, less than normal range and FEV/FVC ratio is >70% in case of control group is normal (Table). Pooled estimates on SMD shows that significantly diagnostic parameter FEV/FVC is directly associated with COPD patients than controls. Significantly lower

ratio of FEV/FVC was found in COPD patients than control group. [SMD=-11.799], CI= [- 16.998 to -11.799], P<0.001]. All the studies found similar result as pooled. Heterogeneity test illustrates the significance variation between studies [I^2 =53.92], p<0.001.

Subgroup analysis

Subgroup analyses were performed with by smoking status [Smokers: Non-smokers], in this case former smokers considered as smokers. The studies were then stratified between smokers and non-smokers of COPD case and control group participants [n=6]. The subgroup analysis estimates on OD shows that the high risk of COPD was seen in smokers [OR=1.531, CI=0.361-6.483, p=0.563] than non-smokers [OR=1.47, CI=0.511-3.938, p=0.502]. Heterogeneity test illustrates the significance variation between studies [I^2=95.2, P<0.001]. [Fig.6]

LIMITATIONS

Such analysis can be done at global level to see variation by risk factors association with COPD. Several studies reported additional comparisons of risk factors between case and control; examples include education, income, co-morbidities, region and some clinical parameters other than spirometry. However due to in consistent data, we could not pool these estimates across the studies.

DISCUSSION

In developing countries, lung disorders are one of the primary causes of death. The third largest cause of death worldwide was chronic obstructive pulmonary disease (COPD) [19]. Chronic respiratory disorders (CRDs) accounted for 4.7 percent of all Disability Adjusted Life Years worldwide (DALY). 2 CRDs can harm people and health systems if they are not detected, treated, and managed properly. However, in low- and middle-income countries, chronic respiratory disorders (CRDs), particularly asthma and COPD[20], have received little attention. India is a substantial and growing contributor to worldwide COPD mortality[22]. According to a comprehensive review, the prevalence of chronic bronchitis in rural India is between 6.5 percent and 7.7 percent. The study also highlights the scarcity of community-based research in India that estimate the incidence of chronic respiratory illnesses[21]. High CAL prevalence is linked to a family history of respiratory disease and a lack of education. Improved access to education is seen as one of the most important social strategies for tackling the high burden of non-communicable diseases (NCDs)[23]. As people get older, their lung functions diminish. the cumulative increase in environmental and occupational hazards the burden of chronic respiratory illnesses, and other risk factors are anticipated to rise. With a lifespan of more than 100 years, Kerala state has an average age of 71 years and a fertility rate of 1.6. The elder age group is growing, whereas the younger age group is diminishing. According to the 2011 Census, around 12% of Kerala's population are elderly population.

For assessing the prevalence of chronic respiratory disorders, we employed meta-analysis, as in many other similar research, depending on the sensitivity and specificity of articles of the data and the disease condition. There are various advantages to our systematic review.

To begin, we used data from a total of 14 papers in the meta-analysis, the majority of which were population-based studies of good quality. In people with persistent airflow limitation on spirometry, the presence of respiratory symptoms and GOLD grade III or IV disease severity were substantially linked to a previous diagnosis of COPD[24,25]. The results were variable definitions of chronic airflow limitation are reasonably consistent across analysis methods and definitions. The methods employed to assess disease severity, respiratory symptoms, and smoking history were very uniform among trials, allowing the results to be pooled. Finally, we ran various pooled analysis to see how sensitive our findings were to different definitions of COPD. The results from pooled analysis of this meta-analysis study provides the confirmation that exposure to smoke parameter in terms of pack of years and ages positively associated with COPD. The findings of the study show evidence of smoking history in terms of pack of years as a major risk factor for COPD prevalence. Clinical parameter FEV1 and FEV/ FVC ratio is also associated with COPD. By subgroup analysis it can be seen that the overall effect reflects higher prevalence of COPD in smokers as compared to non-smokers. The study reflects that there is high risk of COPD in smokers, with great concern for the mankind with the need to reduce smoking.

A large number of people with COPD in the community had never smoked. External risk factors such as secondary smoking and indoor air pollution from the combustion of biomass fuels may be the cause of COPD in people who have never smoked. The increased prevalence of chronic respiratory disorders could be due to indoor air pollution from home fuel combustion. Females have a similar high prevalence, emphasising the significance of addressing risk factors other than smoking. Although India has developed programmes to tackle cancer, diabetes, heart disease, and stroke, no such programme has been developed for chronic respiratory illness. Given the high frequency of COPD and their contributions to morbidity and death, a comprehensive approach to combat them is required. the most important COPD burden-reduction strategy approach is the control of tobacco smoke exposure. The most recent efforts to reduce smoking behaviours using a variety of methods, Government of Canada Anti-Tobacco legislation and campaigns of India deserves praise. The problem of smoking and passive smoking still exists and need to be resolved. There is need of awareness pro-

gram of this problem to reduce raising disease burden over the next decade.

Furthermore, research is needed on COPD prevalence and incidence associated with other chemical exposure, to identify how to effectively reduce the risksfrom exposure to smoking.

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