



# Meta-analysis approach to study the prevalence of chronic obstructive pulmonary disease among current, former and non-smokers



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## ABSTRACT

Comparative risk assessment for Chronic Obstructive Pulmonary Disease (COPD) among current, former and non-smokers categories remains controversial and not studied in detail. We conducted a meta-analysis to summarize all the relevant published studies on this topic and to update the association between smoking and prevalence of COPD in current, former and non-smokers. Identification, screening, eligibility and inclusion of articles for the study were conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Quality assessment of included studies was undertaken using a scoring sheet. Meta-analysis after the final synthesis of the selected studies was performed using the STATA and Comprehensive Meta-Analysis (CMA) software. Estimates from forty two independent studies reporting 547,391 individuals were identified. Twenty two studies were conducted in Europe, nine in America and ten in Asia and one from New Zealand. The meta-analysis showed that the prevalence of COPD was significantly higher in current smokers compared with former and non-smokers. However, owing to large heterogeneity among the estimates obtained from the studies, stratification was done with respect to continent, diagnostic criteria of COPD and study design which also showed similar results. The stratified analysis also revealed similar trend of results with prevalence of COPD being higher in current smokers as compared to former and non-smokers. The present meta-analysis highlights the positive association between smoking and COPD prevalence. There is an urgent need to implement more effective policies towards the restriction of tobacco use, to reduce the burden of COPD.

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## 1. Introduction

The Global Initiative for Chronic Obstructive Lung Diseases (GOLD) has classified Chronic Obstructive Pulmonary Disease (COPD) as a diseased 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]. According to the Global Burden of Disease (GBD), COPD is the third leading cause of death in the world after ischemic heart disease and stroke, with 2.75 million deaths worldwide and predicted to further increase the mortality in the coming years [2]. In 1990, COPD was ranked sixth among all causes of death worldwide and by 2030 it is projected to be at the third position [3]. COPD is responsible for 5.5% of deaths globally, and this percentage rises to 6.06% for developing countries, as opposed to 3.78% in the developed countries. GBD study also attributes 3.09% of total Disability Adjusted Life Years (DALYs) globally and 3.12% of the total DALYs in developing countries to COPD [4].

Tobacco smoke exposure is one of the most significant factors for COPD with 80–90% of all cases attributable to smoking [5]. Pipe and cigar smoking have also been found to be associated with increased COPD risk, but less threatening than cigarette smoking [1,6,7]. Though cigarette smoking is one of the most significant causes of COPD, it accounts for about 20% of clinically significant COPD [1,6–8]. Male gender, advanced age, occupational exposure and low socio-economic status are some of the other well-known risk factors of COPD [9,10]. In high and middle income countries, tobacco smoke is the prime risk factor, while in low income countries exposure to indoor air pollution, such as the use of biomass fuels for cooking and heating causes the burden of COPD [11]. Some developing countries have exhibited higher mortality levels among non-smokers, for example in China there is a much higher risk of death from COPD among non-smokers [12]. Data from the third National Health and Nutrition Examination Survey, carried out between 1988 and 1994, revealed that 24.9% (plus or minus 1.4%) Americans with COPD were never smokers. The United Kingdom and Spain reported similar findings of 22.9% and 23.4%, respectively. Never-smokers with COPD were 5.6% out of a study population of 4291 participants [13,14].

The development of COPD is multifactorial and genetic factors are important risk factors for COPD. Alpha1-antitrypsin deficiency is an established genetic cause of COPD especially in the young and it has been reported that  $\alpha$ 1-antitrypsin deficiency occurs in 1–2 per cent of individuals with COPD [15].

Considering the risk of current, former and non-smokers on the morbidity of COPD from earlier reports, we have conducted a meta-analysis to estimate the association between smoking and prevalence of COPD in general population based on different smoking criteria. To the best of our knowledge, this is the first evidence-based meta-analysis on the global comparison of COPD morbidity among current, former and non-smokers. The variations due to different diagnostic criteria of COPD, study locations and study designs have been analyzed in the present study. This study can be utilized by policy holders for the effectiveness of their policies towards reduction of COPD.

## 2. Material and methods

### 2.1. Search Strategy

We searched the publications listed in the electronic database (source: PubMed, January 1, 1990–June, 2014) and Google Scholar (source: <http://www.scholar.google.co.in>) using the following text and key words in combination both as MeSH terms and text word “COPD”; “smokers”; “health”; “risk” or “factors”; “diagnostic”; “burden”; “exposure”; “disease” or “prevalence” or “morbidity” or “disability”; “mortality”; “tobacco”; “smoking”; “smoke”. The search was limited only to articles in English. The search was limited to PubMed and Google Scholar due to the non-accessibility of Medline and Embase.

### 2.2. Study Selection

Identification, screening, eligibility, inclusion of articles and meta-analysis for the study follows Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [16]. The systematic review protocol for PRISMA was based on the information available at <http://www.prisma-statement.org/statement.htm>

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

1. Design of the study: case control, cohort and cross-sectional studies.
2. Studies that contained the minimum information necessary to estimate the number of subjects in the smoking groups (current, former and non-smokers).
3. Methodology details in publication with mention of sampling strategy, study design, approach of diagnosis and diagnostic criteria used by the investigators should be available in the literature.

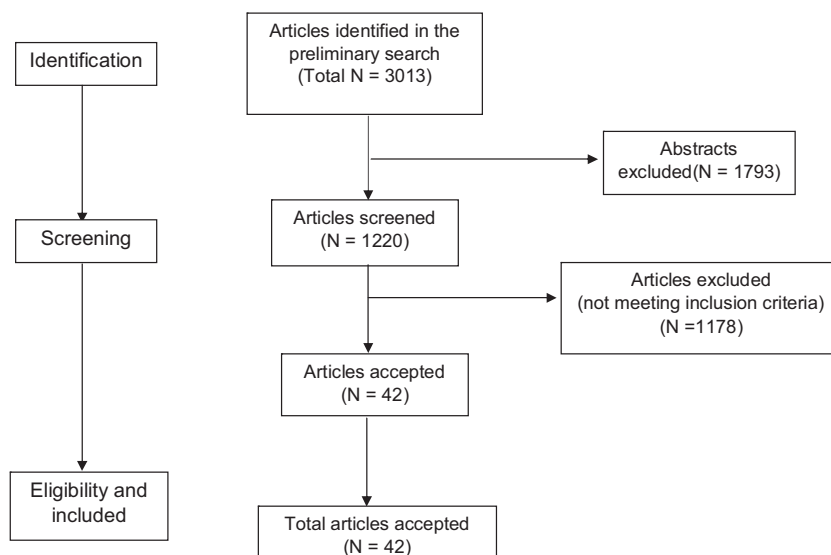


Fig. 1. Flow chart for the inclusion of articles in the study.

4. Availability of data on the number of COPD subjects in the smoking groups (current smokers, former and non-smokers).
5. Definition for smoking: current, former and non-smokers.
6. Studies with environmental tobacco smoke exposure were also included.

The exclusion criteria for the selection was following

1. Design of the study: randomized control trials, intervention study
2. Articles in languages other than English.
3. Subjects/patients with multiple diseases like COPD and TB, COPD and emphysema, alveolitis, SARS, HIV, metabolic disorders, cardiovascular disorders, gastrointestinal diseases and tumor.

### 2.3. Data abstraction

Articles were reviewed and cross checked independently by two authors (RK, CNK). Percentage agreement between the authors on the quality review ranged between 90% to 100%. Any disagreements were resolved by consensus of all authors. Data on the following characteristics were independently extracted: sample size, author's name, year of publication, study design, sample size, age group, study locations as continents (defined as Europe, America or Asia), occupation, gender category, number of COPD cases with respect to smoking status (current, former and non-smokers) and diagnostic criteria of COPD (Spirometry, patient reported diagnosis, physician diagnosis, questionnaire-based diagnosis). Information given above were collected and evaluated for quality and then cross-checked.

### 2.4. Quality assessment

Quality assessment of final included studies were conducted using a scoring sheet given as Table S1 (supplementary file) which was prepared by authors (RK, CNK) and independently analyzed and outcome results were discussed and reached a consensus.

### 2.5. Data analysis

Odds ratio was used to determine the association between smoking and the prevalence of COPD. The heterogeneity among the included studies was evaluated using the  $\chi^2$ -based Q statistic

test. In the case of heterogeneity, random effects model was used for the analysis or else a fixed effects model was used.

Subgroup analysis were performed to investigate potential sources viz., continent wise stratification (American, Asian and European), diagnostic criteria for COPD (Spirometry/Bronchodilator, Physician diagnosis/Questionnaire) and study design (Cross-sectional, Cohort and Case-Control), for analysis of between-study heterogeneity. The present study was approved and registered by the International Prospective Register of Systematic Reviews (PROSPERO), National Institute for Health Research (PROSPERO Registration No.: CRD42013005696). Meta-analysis was performed and forest plot were prepared using STATA (IC 13, StataCorp LP, TX, USA) and Comprehensive Meta-Analysis (CMA) software (USA, version 2.2.064). The criterion for significance was set at  $p < 0.05$ . Potential for publication bias was assessed with funnel plots, by Egger's regression asymmetry test [17] using CMA software.

## 3. Results

### 3.1. Study selection

With the search strategy, 3013 unique citations were initially retrieved. Of these, 1220 articles were considered of interest and full text was retrieved for detailed evaluation. 1178 of these 1220 articles were subsequently excluded and finally 42 articles were included in the meta-analysis. The detailed flowchart for the inclusion of articles is presented in Fig. 1.

### 3.2. Study characteristics

The characteristics (author's name, year, methodology, number of subjects, age group of study subjects and country) of the included articles in the study are shown in Table 1. Forty two studies reporting 547,391 individuals consisting of current, former and non-smokers were identified. Twenty two studies were based in Europe, nine in America, ten in Asia and one from New Zealand. After the final synthesis of literature, 42 articles were used for the meta-analysis (Table 1). Since there was only one case-control studies and one report based on hospital admission, these studies were not included due to constraints in stratified analysis. One study from New Zealand was not included in the stratified analysis.

**Table 1**  
Characteristics of the studies included in the meta-analysis.

Author name	Year	Gender	Method used	Country	No. of subjects	Age group
A. Johannessen [34]	1996	Male and Female	Spirometry	Norway	2235	15–70
A. Johannessen [35]	2004	Male and Female	Spirometry	Norway	908	Mean age 41.2
A. Menezes [36]	2005	Male and Female	Spirometry and Bronchodilator	Brazil	1000	>40
A. Menezes [36]	2005	Male and Female	Spirometry and Bronchodilator	Chile	1208	>40
A. Menezes [36]	2005	Male and Female	Spirometry and Bronchodilator	Mexico	1063	>40
A. Menezes [36]	2005	Male and Female	Spirometry and Bronchodilator	Uruguay	943	>40
A. Menezes [36]	2005	Male and Female	Spirometry and Bronchodilator	Venezuela	1357	>40
A. Caballero [37]	2008	Male and Female	Spirometry	Columbia	5539	>40
A. Lindgren [38]	2009	Male and Female	Questionnaire	Sweden	9319	18–77
A. Johannessen [39]	2012	Male and Female	Spirometry	Norway	758	40–79
A. Lindberg [40]	2006	Male and Female	Spirometry	Sweden	963	46–77
A. Lindberg [41]	2006	Male and Female	Spirometry	Sweden	1237	46–77
B. Lundback [42]	2003	Male and Female	Spirometry	Sweden	1282	>46
C. Iribarren [43]	1999	Male and Female	Questionnaire	USA	17774	30–85
D.M. Mannino [44]	2003	Male and Female	Spirometry	USA	7503	>17
D. Coultas [45]	2001	Male and Female	Spirometry	USA	5743	>45
D. Price [46]	2006	Male	Spirometry	UK	572	>40
D. S. Kim [47]	2005	Male and Female	Spirometry	Korea	3981	>45
D. S. Kim [48]	2006	Male and Female	Spirometry	Korea	9243	>18
FeiXu [49]	2005	Male and Female	Physician diagnosis	China	29319	>35
J.A. Dickinson [50]	1999	Male and Female	Spirometry	England	500	60–75
J. Hardie [51]	1998	Male and Female	Physician diagnosis	Norway	1649	>70
K. Tsushima [52]	2005	Male and Female	Spirometry	Japan	2246	mean age 53.7
K. M. Bang [53]	1993	Male and Female	Spirometry	USA	585	mean age 47.8
L. Shahab [54]	2006	Male and Female	Spirometry	England	8215	>35
L. Trupin [55]	2003	Male and Female	Physician diagnosis	USA	2061	55–75
M. Miravittles [56]	2009	Male and Female	Spirometry	Spain	4274	40–80
M. Miravittles [57]	2005	Male and Female	Spirometry	Spain	363	40–69
M. D. Eisner [58]	2005	Female	Physician diagnosis	USA	2113	55–75
M. P. Purdue [59]	2006	Male	Spirometry	USA	176997	>20
M. Bednarek [60]	2005	Male and Female	Spirometry	Poland	676	41–72
N. Zhong [61]	2007	Male and Female	Spirometry	China	20245	>40
P. Salameh [62]	2012	Male and Female	Questionnaire/Spirometry	Lebanon	833	>40
P. Vineis [63]	2005	Male and Female	Physician diagnosis	Europe	123479	35–74
P. Danielsson [64]	2012	Male and Female	Spirometry	Sweden	548	>40
P. S. Bakke [65]	1991	Male and Female	Spirometry	Norway	1275	15–70
P. Johnson [66]	2008	Female	Spirometry	India	900	30–70
R. de Marco [67]	2003	Male and Female	Spirometry	Europe	14855	20–44
R. Isoaho [68]	1994	Male and Female	Questionnaire	Finland	1196	>64
R.P. Young [69]	2009	Male	Spirometry	New Zealand	654	>40
S. Kojima [70]	2005	Male and Female	Spirometry	Japan	11460	25–74
S. Liu [71]	2007	Male and Female	Spirometry	China	3286	>40
T. Schikowski [72]	2005	Female	Spirometry	Germany	4757	54–55
U. Nihlen [73]	2003	Male and Female	Physician diagnosis/questionnaire	Sweden	4280	18–77
Y. Fukuchi [74]	2004	Male and Female	Spirometry	Japan	2343	>40
Z. J. Anderson [75]	2010	Male and Female	Hospital discharge register for their first hospital admission for COPD	Denmark	52799	50–64

### 3.3. Quality assessment of included studies

The quality assessment of included studies showed high score for 36 studies out of 42 studies. Rest 6 studies are in the moderate category as per the quality assessment tool.

## 4. Comparison of COPD among current smokers and non-smokers

### 4.1. Pooled analysis

Forty one estimates were obtained to compare the COPD status in current and non-smokers (Fig. 2). Due to the marked heterogeneity among the ORs ( $p < 0.001$ ), a random effects model was used and showed that the prevalence of COPD was significantly higher in current smokers compared with non-smokers (overall OR = 3.26; 95% CI, 2.67–3.98;  $z = 11.51$ ,  $p < 0.001$ ) (Table 2 and Fig. 2). The forest plot analysis revealed the rhomboid of the overall effect showing higher prevalence of COPD in current smokers as compared to non-smokers.

### 4.2. Stratified analysis with respect to study locations (Continent)

Owing to the large heterogeneity in the pooled analysis, stratified analysis was performed according to different criteria to study the patterns of the results obtained. Using random effects model, a significantly higher prevalence of COPD was observed for current smokers as compared to non-smokers, for Asian studies (OR = 3.38; 95% CI, 2.37–4.90;  $z = 6.45$ ,  $p < 0.001$ ) (Table 2). Similar trend was observed in studies of American and European origin, showing significantly higher prevalence of COPD in current smokers, for American (OR = 2.21; 95% CI, 1.64–2.97;  $z = 5.24$ ,  $p < 0.001$ ) and for European (OR = 4.25; 95% CI, 3.06–5.9;  $z = 8.61$ ,  $p < 0.001$ ) studies. The forest plot analysis for Asian, American and European studies depicted a similar trend while studying the rhomboid of the overall effect, with the analysis results depicting higher prevalence in current smokers (Fig. S1).

### 4.3. Stratified analysis by diagnostic criteria of COPD

A random effects model was used for the analysis of the thirty two estimates identified using Spirometry/bronchodilator test for diagnosis of COPD due to significant heterogeneity ( $p < 0.001$ ). Significantly higher prevalence of COPD (OR = 2.91;

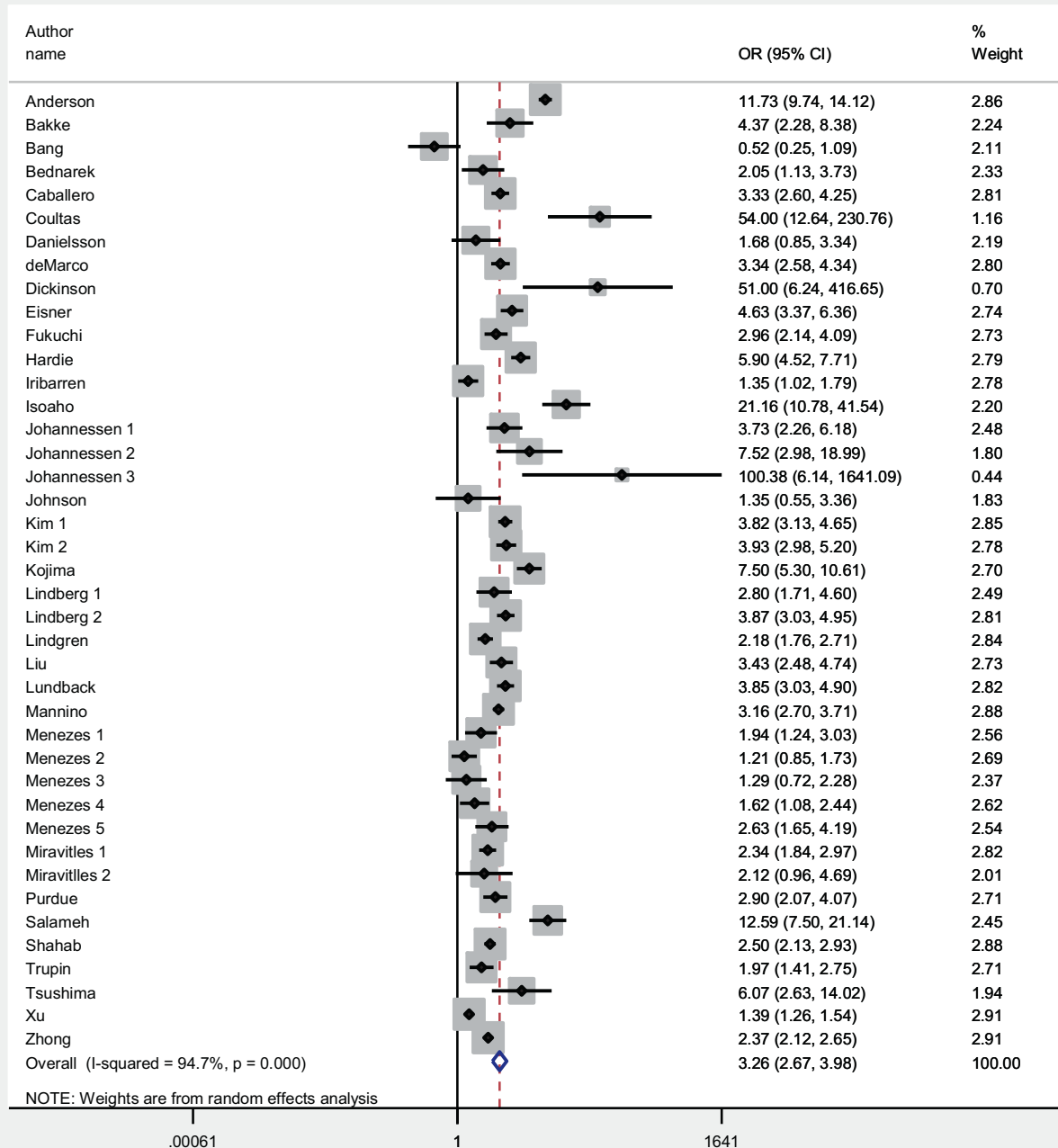


Fig. 2. Forest plot analysis for current v/s non-smokers (pooled data).

95% CI, 2.51–3.38;  $z=11.55$ ,  $p<0.001$ ) was observed in current smokers compared with non-smokers (Table 2). The random effects model used for the nine estimates from studies using physician diagnosis/questionnaire for the diagnosis of COPD showed significantly higher prevalence of COPD in current smokers (OR=4.36; 95% CI, 2.21–8.60;  $z=4.26$ ,  $p<0.001$ ) (Table 2). A similar trend was observed in the forest plot analysis of both the studies using Spirometry and bronchodilator test for the diagnosis of COPD. In the case of estimates from studies using physician diagnosis/questionnaire for the diagnosis of COPD, the rhomboid represented higher prevalence in current smokers (Fig. S1).

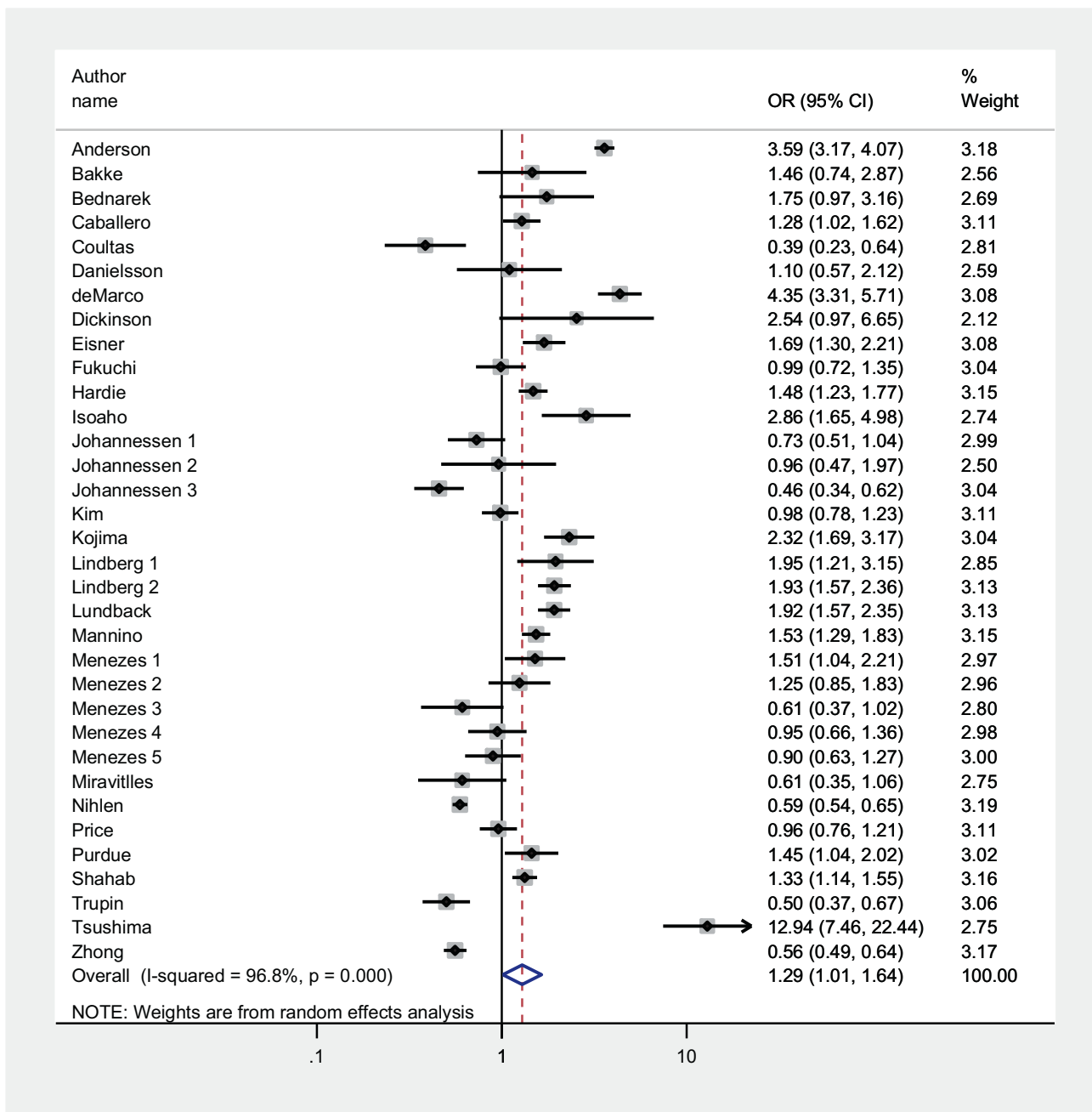
#### 4.4. Stratified analysis based on study design

Significant heterogeneity was observed among the thirty four cross-sectional estimates obtained. Using a random effects model for the analysis, the prevalence of COPD was found to be significantly higher in current smokers compared to non-smokers. (OR=2.97; 95% CI, 2.49–3.56;  $z=12.01$ ,  $p<0.001$ ) (Table 2). Five estimates from cohort studies were considered for the meta-analysis and heterogeneity was observed. A significantly higher prevalence of COPD in current smokers (OR=4.69; 95% CI, 1.51–14.57;  $z=2.67$ ,  $p<0.001$ ) was found using a random effects model (Table 2). The overall effect of studies based on the study

**Table 2**  
Comparison of prevalence of COPD between current and non-smokers.

	No. of estimates	Heterogeneity test (Q Test)	Current smokers v/s non-smokers		Pooled OR Test (z test)
			Odds ratio(OR)	95% C.I.	
All	41	758.17, $p < 0.001$	3.26	2.67–3.98	11.51, $p < 0.001$
Continent					
Asia	10	297.79, $p < 0.001$	3.38	2.37–4.90	6.45, $p < 0.001$
America	13	110.75, $p < 0.001$	2.21	1.64–2.97	5.24, $p < 0.001$
Europe	18	297.79, $p < 0.001$	4.25	3.06–5.90	8.61, $p < 0.001$
Diagnostic criteria					
Spirometry/Bronchodilator	32	184.36, $p < 0.001$	2.91	2.51–3.38	11.55, $p < 0.001$
Physician diagnosis/questionnaire	9	580.58, $p < 0.001$	4.36	2.21–8.60	4.26, $p < 0.001$
Study design <sup>a</sup>					
Cross sectional	34	426.97, $p < 0.001$	2.97	2.49–3.56	12.01, $p < 0.001$
Cohort	5	196.65, $p < 0.001$	4.69	1.51–14.57	2.67, $p < 0.01$

<sup>a</sup> 1Case control study and 1Hospital based study not included in stratified analysis by study design.



**Fig. 3.** Forest plot analysis for current v/s former smokers (pooled data).

**Table 3**  
Comparison of prevalence of COPD between current and former smokers.

	No. of estimates	Heterogeneity test (Q Test)	Current smokers v/s former smokers		
			Odds ratio(OR)	95% C.I.	Pooled OR Test (z test)
All	34	1019.5, $p < 0.001$	1.29	1.01–1.64	2.07, $p < 0.05$
Continent					
Asia	5	179.7, $p < 0.001$	1.69	0.77–3.69	1.32, $p = 0.19$
America	11	80.34, $p < 0.001$	1.02	0.78–1.33	0.13, $p = 0.89$
Europe	18	722.89, $p < 0.001$	1.41	0.97–2.04	1.82, $p = 0.07$
Diagnostic criteria					
Spirometry/Bronchodilator	29	608.06, $p < 0.001$	1.23	0.98–1.55	1.76, $p = 0.14$
Physician diagnosis/questionnaire	5	179.48, $p < 0.001$	1.66	0.84–3.26	1.47, $p = 0.09$
Study design					
Cross sectional	30	552.47, $p < 0.001$	1.17	0.95–1.45	1.47, $p = 0.14$
Cohort	4	160.29, $p < 0.001$	1.47	0.53–4.08	0.74, $p = 0.46$

designs using forest plot analysis showed the rhomboid depicting higher prevalence of COPD in current smokers (Fig. S1).

## 5. Comparison of COPD among current smokers and former smokers

### 5.1. Pooled analysis

Thirty four estimates obtained were compared for the COPD status in current and former smokers (Fig. 3). Owing to the large heterogeneity among the ORs ( $p < 0.001$ ), a random effects model was used which showed significantly higher prevalence of COPD (OR = 1.29; 95% CI, 1.01–1.64;  $z = 2.07$ ,  $p < 0.05$ ) in current smokers compared with former smokers (Table 3 and Fig. 3). The forest plot analysis revealed the rhomboid of the overall effect depicting higher prevalence of COPD in current smokers compared to former smokers.

### 5.2. Stratified analysis with respect to study locations (Continent)

Stratified analysis was performed to study the patterns of the results obtained due to large heterogeneity among results. Using random effects model, higher prevalence of COPD (OR = 1.69; 95% CI, 0.77–3.69;  $z = 1.32$ ,  $p = 0.19$ ) was observed in current smokers as compared to former smokers in case of Asian studies (Table 3). Similar trend was observed in studies of American and European origin, with higher prevalence of COPD in current smoker for American (OR = 1.02; 95% CI, 0.78–1.33;  $z = 0.13$ ,  $p = 0.89$ ) and for European (OR = 1.41; 95% CI, 0.97–2.04;  $z = 1.82$ ,  $p = 0.07$ ) studies. The forest plot analysis for Asian, American and European studies depicted a similar trend while studying the rhomboid of the overall effect, with the analysis results showing higher prevalence of COPD in current smokers (Fig. S2).

### 5.3. Stratified analysis by diagnostic criteria of COPD

A random effects model was used for the analysis of the twenty nine estimates identified using Spirometry/bronchodilator test for diagnosis of COPD due to significant heterogeneity ( $p < 0.001$ ). The prevalence of COPD was higher in current smokers compared with former smokers (OR = 1.23; 95% CI, 0.98–1.55;  $z = 1.76$ ,  $p = 0.14$ ) (Table 3). The random effects model used for the five estimates from studies using physician diagnosis/questionnaire for the diagnosis of COPD showed higher prevalence of COPD (OR = 1.66; 95% CI, 0.84–3.26;  $z = 1.47$ ,  $p = 0.09$ ) in current smokers as compared to former smokers (Table 3). Similar trend was observed in the forest plot analysis with the rhomboid of overall effect representing higher prevalence in current smokers (Fig. S2).

### 5.4. Stratified analysis based on study design

Significant heterogeneity was observed among the odds ratio obtained from the estimates. Using a random effects model, higher prevalence of COPD (OR = 1.17; 95% CI, 0.95–1.45;  $z = 1.47$ ,  $p = 0.14$ ) was observed in current smokers compared to former smokers in cross sectional studies (Table 3). Four estimates from cohort studies were considered for the meta-analysis, which showed the prevalence of COPD to be higher in current smoker (OR = 1.47; 95% CI, 0.53–4.08;  $z = 0.74$ ,  $p = 0.46$ ) using a random effects model (Table 3). The rhomboid of the overall effect of studies based on the study designs using forest plot analysis represented higher prevalence of COPD in current smokers (Fig. S2).

## 6. Comparison of COPD among former smokers and non-smokers

### 6.1. Pooled analysis

Thirty two estimates obtained were compared for the COPD status in former and non-smokers (Fig. 4). A random effects model was used, owing to the large heterogeneity among the ORs ( $p < 0.001$ ), which showed significantly higher prevalence of COPD in former smokers compared with non-smokers (OR = 2.68; 95% CI, 2.22–3.23;  $z = 10.35$ ,  $p < 0.001$ ) (Table 4). The rhomboid of the overall effect obtained from the meta-analysis showed higher prevalence of COPD in former smokers as compared to non-smokers.

### 6.2. Stratified analysis with respect to study locations (Continent)

Stratified analysis was performed due to large heterogeneity among results. Using random effects model, a significantly higher prevalence of COPD (OR = 3.89; 95% CI, 3.43–4.42;  $z = 21.14$ ,  $p < 0.001$ ) was observed in former smokers as compared to non-smokers in case of Asian studies (Table 4). Similar trend was observed in studies from America and Europe, where prevalence of COPD was significantly higher, for American (OR = 2.32; 95% CI, 1.74–3.09;  $z = 5.72$ ,  $p < 0.001$ ) and for European (OR = 2.65; 95% CI, 1.96–3.58;  $z = 6.34$ ,  $p < 0.001$ ) studies, in former smokers compared with non-smokers. The forest plot analysis for Asian, American and European studies depicted a similar trend with the rhomboid showing higher prevalence in former smokers (Fig. S3).

### 6.3. Stratified analysis by diagnostic criteria of COPD

A random effects model was used for the analysis of the twenty six estimates identified using Spirometry/bronchodilator test for diagnosis of COPD due to significant heterogeneity ( $p < 0.001$ ). Prevalence of COPD was significantly higher (OR = 3.63; 95% CI,

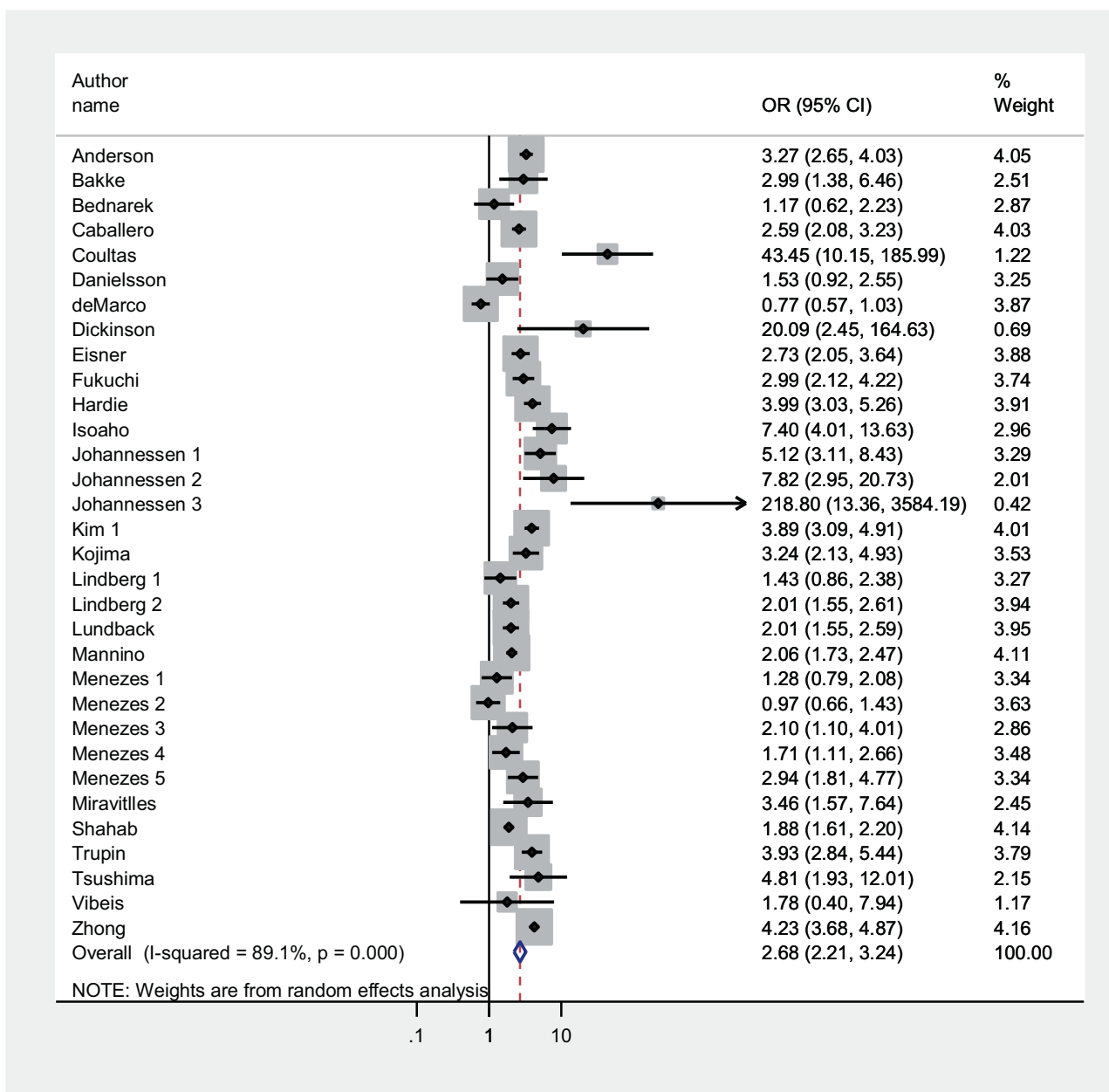


Fig. 4. Forest plot analysis for former v/s non-smokers (pooled data).

Table 4  
Comparison of prevalence of COPD between former and non-smokers.

	No. of estimates	Heterogeneity test (Q Test)	Former smokers v/s non-smokers		Pooled OR Test (z test)
			Odds ratio(OR)	95% C.I.	
All	32	283.7, $p < 0.001$	2.68	2.22–3.23	10.35, $p < 0.001$
Continent					
Asia	5	4.51, $p = 0.34$	3.89	3.43–4.42	21.14, $p < 0.001$
America	10	57.92, $p < 0.001$	2.32	1.74–3.09	5.72, $p < 0.001$
Europe	17	145.46, $p < 0.001$	2.65	1.96–3.58	6.34, $p < 0.001$
Diagnostic criteria					
Spirometry/Bronchodilator	26	247.11, $p < 0.001$	3.63	2.92–4.51	8.05, $p < 0.001$
Physician diagnosis/questionnaire	6	11.16, $p < 0.05$	2.49	2.0–3.11	11.67, $p < 0.001$
Study design					
Cross sectional	27	262.29, $p < 0.001$	2.64	2.15–3.24	9.29, $p < 0.001$
Cohort	5	19.80, $p < 0.001$	3.13	1.24–7.87	2.42, $p < 0.05$



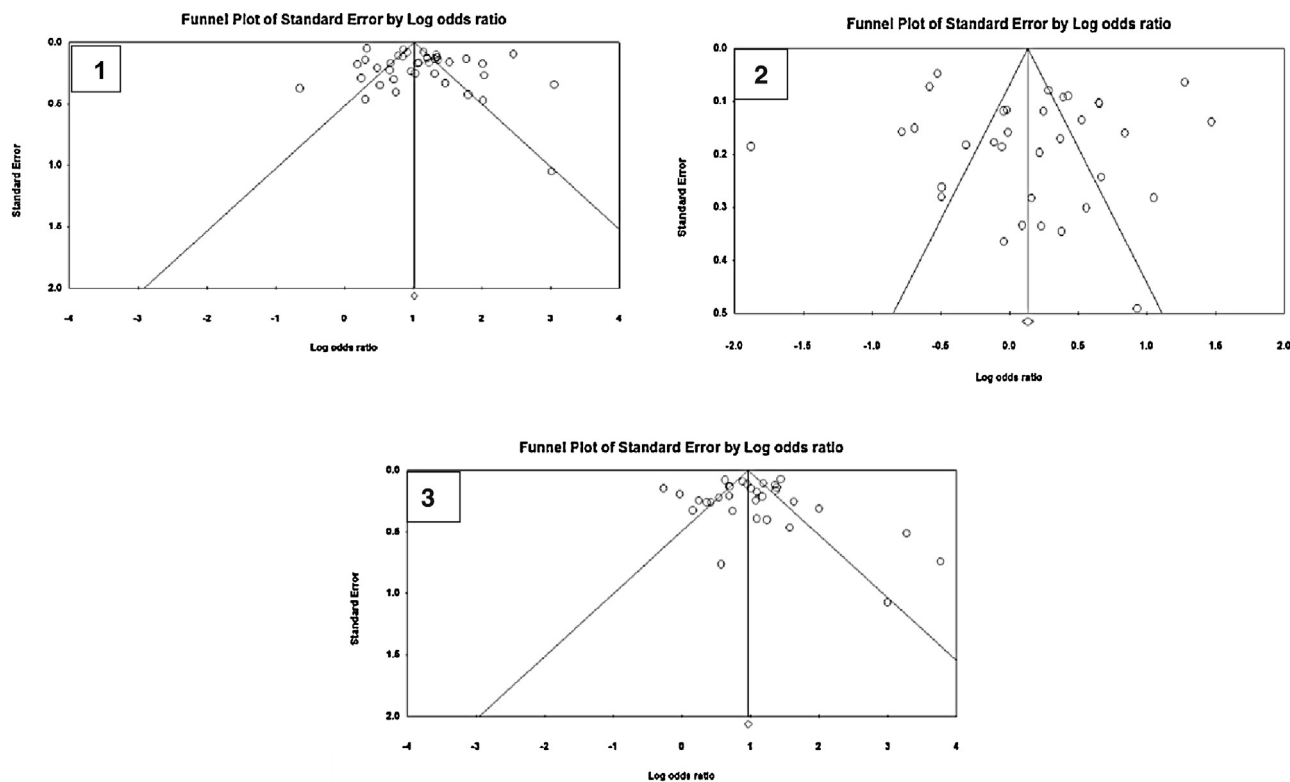


Fig. 5. Funnel plot analysis.

1: Current v/s non-smokers; 2: current v/s former smokers; 3: former v/s non-smokers.

2.92–4.51;  $z=8.05$ ,  $p<0.001$ ) in former smokers as compared to non-smokers (Table 4). The random effects model used for the six estimates from studies using physician diagnosis/questionnaire for the diagnosis of COPD showed significantly higher prevalence of COPD, (OR=2.49; 95% CI, 2.0–3.11;  $z=11.67$ ,  $p<0.001$ ) in former smokers as compared to non-smokers (Table 4). Similar trend was observed in the forest plot analysis with the rhomboid representing the overall effect of higher COPD prevalence in former smokers (Fig. S3).

#### 6.4. Stratified analysis based on study design

Using a random effects model, significantly higher prevalence of COPD (OR=2.64; 95% CI, 2.15–3.24;  $z=9.29$ ,  $p<0.001$ ) was observed in former smokers compared with non-smokers in cross sectional studies (Table 3). Five estimates from cohort studies were considered for the meta-analysis, which showed significantly higher prevalence of COPD in former smokers (OR=3.13; 95% CI, 1.24–7.87;  $z=2.42$ ,  $p<0.05$ ) using a random effects model (Table 4). The overall effect of studies based on the study designs using forest plot analysis showed the rhomboid representing higher prevalence of COPD in former smokers (Fig. S3).

#### 6.5. Funnel plot analysis

Funnel plot analysis was conducted to check for publication bias among the estimates from the studies selected for the final synthesis. Fig. 5 shows the funnel plot of the natural logarithms of OR estimates against their standard errors for all three comparisons among the smoking groups. Using the Egger's test of publication bias  $p=0.15$  was obtained for current and non-smokers,  $p=0.74$  for current and former smokers and  $p=0.90$  for former and non-smokers. Since many studies fall outside the funnel plot, there is a possibility for publication bias among the studies.

## 7. Discussion

The present meta-analysis, involving 547,391 participants from forty two studies found a positive association between smoking and prevalence of COPD for current smokers as compared to former and non-smokers. The results of the pooled analysis also show large heterogeneity among the different studies with respect to study location, diagnostic criteria and study designs. The publication bias was also observed among studies for current, former and non-smokers across studies from different locations. Further, this bias can be attributed to different study design, sample size, study protocols, criteria followed for current, former and non-smokers and COPD diagnosis in the final synthesized studies.

Smoking and age are widely known as major risk factors for COPD [18]. A recent study found that the prevalence of COPD among current smokers (22.4%) and former smokers (24.6%) were higher than the prevalence among non-smokers (7.0%). Additionally, individuals with  $\geq 20$  pack-years exhibited a 3-fold increased prevalence of COPD as compared to non-smoking individuals after adjusting for sex and age [19]. Smoking is the main cause of chronic bronchitis and emphysema, and it is estimated that 80–90% of the risk to develop COPD is due to smoking [20]. The population attributable fraction for smoking as a cause of COPD ranges from 9.7 to 97.9% [21]. Reports from a Swedish cohort study had observed population attributable fraction for smoking a cause of COPD to be 76.2% [22], whereas another cohort study from Denmark reported the same to be 74.6% [23]. Swedish Obstructive Lung Disease in Northern Sweden (OLIN) and National Health and Nutrition Examination Survey (NHANES III) studies reported that the population-attributable risk of COPD from smoking in these countries was 45% and 44%, respectively [24,25].

Active smoking is a major risk factor for COPD and the mechanism of action of components of cigarette smoke on lung tissue and parenchyma are multiple [26]. Histological analyses of bronchial biopsies from patients with mild to moderate COPD show the pres-

ence of an infiltrate of CD8+ lymphocytes in proximal airways. Neutrophils are present in high concentrations in the sputum of patients with COPD [27]. Cigarette smoke directly stimulates various types of cells, in particular macrophages [28,29] and epithelial cells of the airways, thus contributing to increased production of mediators and cytokines that participate in maintaining the inflammatory reaction [30]. A series of receptor-mediated signal transduction pathways are activated by reactive oxygen species and tobacco components, resulting in impairment of a variety of cell signaling and cytokine networks, subsequently leading to chronic airway responses with mucus production, airway remodeling, and alveolar destruction [30].

Different diagnostic criteria for COPD are followed in Global Occupational Lung Disease GOLD [76], American Thoracic Society (ATS), European Respiratory Society (ERS) [31] British Thoracic Society (BTS) [32] and National Institute for Health and Care Excellence (NICE) [33]. Diagnosis of COPD is confirmed by FEV<sub>1</sub>/FVC ratio <0.7 as per ATS/ERS guidelines and GOLD. BTS criteria for COPD include both FEV<sub>1</sub>/FVC <0.7 and FEV<sub>1</sub> <80% predicted values. BTS guidelines also state asthma with chronic obstruction may be included in COPD. In the NICE guidelines, a FEV<sub>1</sub> <80% of the predicted value was used for COPD diagnosis. To further fulfill the COPD definition in NICE guidelines, an FEV<sub>1</sub>/VC ratio <0.7 is also required.

Strengths of this meta-analysis include the strict inclusion criteria, high score for 86% studies in study quality assessment, the large number of subjects analyzed for current, former and non-smokers and the representation of study locations across the globe. Another strength of the present study is the analysis of COPD prevalence across various smoking groups (current, former and non-smokers). The stratification of the selected studies by location, study design and diagnostic criteria also adds to the strength of the present study. Inclusion of different types of studies into one meta-analysis may also introduce heterogeneity into the results. Limitations of the present study are (1) retrospective design, (2) lack of individual data sets from each study and (3) non availability of data on socio-economic status.

In conclusion, the results from this meta-analysis suggest a positive association between current smokers and the prevalence of COPD compared with former and non-smokers. The findings of the study shows evidence of smoking as a major risk factor for COPD prevalence. The results of the analysis also highlight the disparities in the diagnostic criteria of COPD across various studies and smoking status, resulting in high heterogeneity among results. The results assert the need for common global criteria for diagnosis of COPD and smoking status in epidemiological and clinical studies, for a better assessment of this research problem.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.toxrep.2015.07.013>

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