Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide.

Aims: The aim of this study is to synthesize data on the worldwide prevalence and severity of COPD by geographical region, age-groups, and smoking status on a systematic review of the published medical literature.

Methods: A systematic search was performed following Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. International databases including PubMed, Scopus and Web of Science were searched for population–based studies that had reported the prevalence of COPD anywhere in the world and were published between January 2004 and May 2015. The prevalence of COPD was calculated based on World Health Organization (WHO) regions and sex and severity stages using metaprop. Meta-regression and subgroup analysis methods were applied to determine the sources of heterogeneity.
Results: In total 60 paper were screened with a combined subject sample size of 127 598. The prevalence of post-bronchodilator COPD was 12.16% (10.91–13.40%). The pooled prevalence of COPD was 15.70% (13.80–18.59%) in men and 9.93% (8.73–11.13%) in women. Among all the WHO regions, the highest prevalence was recorded for Region of the Americas (14.53%), and the lowest prevalence was recorded for South-East Asia Region/Western Pacific Region (8.80%). In meta-regression model variables included: sample size, regions, study quality score level of gathering data, publication year, and sampling methods that justify 29.82% of heterogeneity detected among COPD prevalence rates across the world.

Conclusions: It appears that the global prevalence of COPD among males is about 5% higher than females. The most prevalent stage of COPD is stage one.

Keywords: worldwide, epidemiologic characteristic, spirometry, GOLD criteria, systematic review, meta-analysis.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality globally worldwide. According to the Global Burden of Disease (GBD) study, COPD rose from the eighth to the fifth leading cause of Global Burden of Disease from 1990 to 2013. In 2013, COPD was the fourth cause of death globally, and it is predicted that COPD will become the third leading cause of death worldwide by 2020 (1).

Both emphysema and bronchitis can cause loss of daily function in many ways (2), and impose a massive and growing burden, both in direct and indirect costs on societies. For example, in 2010, the cost of COPD in the United States of America was estimated at about US$ 50 billion, which included US$ 30 billion of direct healthcare expenditures and US$ 20 billion of indirect costs (3). In Italy, as a European example, the total cost of a COPD patient has been calculated as €2706.70, of which €2460.40 is direct costs and €246.30 is indirect costs (4).
A recently published systematic review and meta-analysis which included studies based on different definitions of COPD without distinguishing between them reported the global prevalence of COPD (5), so the pooling of data based on these two different definitions is not reasonable. Thus, we undertook a new meta-analysis of COPD prevalence, according to data based on clinically distinct definitions separately. We analyzed the worldwide COPD prevalence according to the standard definition of Global Initiative for Chronic Obstructive Lung Disease (GOLD). Additionally, we estimated the COPD prevalence by geographic regions, clinical severity stages, age-groups, and smoking status.

Methods
Study Design

The study was designed as a systematic review of the published literature and meta-analysis. It was performed according to Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (7).

Definitions

There are several different definitions of COPD in the literature. In this study, we used the definition of Global Initiative for Chronic Obstructive Lung Disease (GOLD) (8): “the presence of a post-bronchodilator FEV1/FVC < 0.70”. Furthermore, stages were defined as follows (8):

Mild COPD or stage I: FEV1/FVC < 70% and FEV1 ≥ 80% predicted,

Moderate COPD or stage II: FEV1/FVC < 70% and 50% ≤ FEV1 < 80% predicted,

Severe COPD or stage III: FEV1/FVC < 70% and 30% ≤ FEV1 < 50% predicted,

Very severe COPD or stage IV: FEV1/FVC < 70% and FEV1 < 30% predicted.

Search Strategy

Searched databases: We searched PubMed, Scopus, and Web of Science (ISI) databases for
population-based studies that had reported the prevalence of COPD worldwide, between January 2004 and May 2015. The inclusion criteria and the exclusion criteria were applied to full-text articles. PubMed was searched using medical subject headings (MeSH) terms, and Scopus was searched using Emtree terms. We also considered all the references and related published systematic reviews in various regions. The Figure 1 depicts the search flow-diagram and the used search strategy is provided in Online Resource 1.

**Inclusion and exclusion criteria**

The study included total sampling population (i.e. survey respondents or general population, population-based cohort studies and population-based case-control studies. From all sampling articles just specific groups were excluded and also Studies published in languages other than English were excluded. Studies using a definition of COPD other than the GOLD definition were excluded. Studies conducted before 2004 were also excluded. If the full-text of a study was unavailable, up to three requests were emailed to the corresponding authors. The reference lists of related systematic reviews were also checked for further studies that might be eligible for inclusion. Two independent reviewers examined the titles and the abstract, then the full texts of the studies to see if they met the inclusion and exclusion criteria. In case of disagreement, the principal investigator made the final decision.

**Data extraction**

The data was extracted into a standardized Excel spreadsheet approved by the GBD investigators, including study variables such as the name of the first author, the year of publication, the study region, the total sample size, the response rate, the age and sex of the participants, the subjects number with COPD or point prevalence based on demographics and severity stages, and 95% confidence intervals of the point prevalence. All data was double-checked by other researcher to ensure it was accurate.

According to the definition of WHO region groups, the included studies (6,9–56) were from different regions: two about the African Region (AFRO), two about the South-East Asia Region (SEARO), 30 about the European Region (EURO), four about the Eastern Mediterranean Region (EMRO), thirteen about the Western Pacific Region (WPRO), and ten articles were about the Americas Region (AMRO). Also, one article that was conducted at the international level was included. Because of the scarcity of data, the Eastern Mediterranean Region was merged into the African Region, and South-East Asia Region was merged into the Western Pacific Region. The characteristics of the studies included are described in Table 1.

**Study quality assessment**
The quality of the studies was scored according to the GBD quality assessment checklist. The total study quality score could range from 1 to 24 and was based on summing up the level of gathering data (sub-district = 1, district = 2, provincial = 3, two or more provinces = 4, two or more subgroups = 5, and national = 6), sampling method (multilevel clustering random = 1, one level clustering random = 2, random simple sampling = 3, random stratified sampling = 4, and census = 5), sample size code (< 1000 = 1, 1000–5000 = 2, 5000–10000 = 3, > 10000 = 4), study design (case control = 1, cohort = 2, cross-sectional = 3), and response rate code (< 59% = 0, 60–74% = 2, 75–89% = 4, and > 90% = 6).

Statistical analysis

The aggregated prevalence of COPD was calculated based on WHO regions, sex, and severity stages using metaprop random effects analysis on Stata version 12. Forest Plots illustrated both the pooled data and individual data of the surveys. We used I-squared for calculating the heterogeneity among the studies included. Meta-regression and subgroup analysis methods were used to determine the sources of heterogeneity. We carried out meta-regression based on quality assessment score, WHO regions, sample size, level of gathering data publication year, and sampling methods. In addition, subgroup analysis was applied using regions, sex, and severity stages. In order to increase the data point, we estimated the post-bronchodilator COPD prevalence by cross-walking using regression model from pre-bronchodilator data.

Results

Characteristics of the studies included

The primary search recognized 61 588 published papers, including 22 639 in PubMed, 15 916 in Web of Science and 23 033 in Scopus. From those, 15 578 articles were eliminated after removal of duplicate articles. Thereafter, 45 503 studies were excluded after reading the titles and abstracts. Finally, a total of 60 papers, with a combined subject sample size of 127 598, met the inclusion criteria (Figure 1). However, 44 studies reported only the prevalence of COPD in terms of post-bronchodilator definition. 16 studies reported only the prevalence of COPD based on pre-bronchodilator definition, and 4 out of 60 papers have published both definitions.

Estimated prevalence of COPD

The prevalence of post-bronchodilator COPD was calculated using a cross-walking method for 16 papers. The R2 of the regression model was 0.97. Using the random effects method, the prevalence of COPD in terms of post-bronchodilator COPD was 12.16% (10.91–13.40%). By regions, COPD prevalence ranged from 8.80% in the combined South-East Asia and Western Pacific regions to 14.53% in the Americas Region. Also, the pooled prevalence of COPD according to sex was 15.70% in men and 9.93% in women (Table 2). The most common stage of COPD was stage 1 (7.05%) and the least common ones were stage 3 and 4 (1.61%) (Table 2).
The result of COPD prevalence among different stages, both sexes, and WHO regions is shown in Online Resource 2. Furthermore, the COPD prevalence was calculated according to age groups and smoking status. The prevalence of COPD was increased from 5.28% to 21.38% among age groups ‘50 years to 60 years’ (Table 4). In terms of smoking status, the least prevalence was found with the 'never smoked' groups (7.20%) and the highest prevalence was showed in the current smoker groups (18.36%) (Table 4).

**Meta-regression**

Univariate and multivariate meta-regression analysis were conducted to detect sources of heterogeneity. The variables used in the meta-regression models included: WHO regions, study design, level of collection data, publication year, sampling method, sample size, and quality assessment score. In the univariate models, significant factors were WHO regions, level of collection data, and sample size. None of the factors could justify the total heterogeneity in meta-analysis and the mentioned factors explained just 29.82% of the heterogeneity (Table 3).

**Discussion**

We found that more than 12% of the general population of the world suffered from COPD. Among all the patients, 44.16% had mild COPD, 44.22% had moderate COPD, and the rest had severe COPD. Our results indicate a higher global prevalence of COPD than previously published meta-analysis. The higher prevalence we calculated in our study may be due to the fact that we considered more recent studies than what the previous meta-analysis did. Although a meta-analysis of the global prevalence of COPD was published in 2015, the study did not distinguish between different COPD definitions (5). Moreover this study did not consider the severity of COPD, which is a critical point for causing specific mortality and COPD burden. The present study was designed and conducted to resolve these shortcomings. Another finding of this study was that with the aging of the population, the prevalence of COPD is increasing at a steady state with the aging of population. These findings are consistent with previous studies (57,58). Also, we observed that among the groups ever smoked, the prevalence of COPD was more than twice as high, if they never smoked. This finding confirms that one of the most important risk factors for COPD is smoking (59).

However, one strength of our study is using a standard definition of COPD to estimate the pooled global prevalence of COPD. This approach eliminates the role of the variable definitions of COPD in the heterogeneity of results in different studies. Another strength of our study is
reporting the severity of COPD stages.

It seems that the prevalence of COPD is increasing. The worldwide prevalence of 8.9% reported in 2006 (60) based on a meta-analysis of 37 papers which was lower than the most of recent report from Adeloye et al. (5). On the other hand, the difference could be a result of using different definitions of COPD. Furthermore, our results are consistent with the findings of some regional studies (61,62), in which the prevalence of COPD was reported to be closer to our results than other studies (5).

The prevalence of COPD is usually more common among men than women. Our meta-analysis also demonstrated a higher prevalence among men (63,64). This difference could be due to higher occupational risks (65) it could also be due to higher rates of smoking among men (66). The highest prevalence of COPD was observed in the Americas Region and the lowest prevalence in the South-East Asia Region / Western Pacific Region. These results are consistent with the results of Adeloye et al. (5). Our pooled estimation of the prevalence for the regions is also close to the prevalence reported by regional studies (61,62). This variability of the prevalence between the different regions is partially explained by the level of industrialization, the prevalence of smoking, the geographic situation, and the ethnicities of the populations (67–69). Martin et al. reported a higher rate of COPD among those of white ethnicity than among other ethnicities (70). Eisner et al. concluded that low socioeconomic communities were at higher risk of COPD. They also observed a higher prevalence of COPD among populations with low education or income (71).

A cohort study that followed a population with a sample size of more than 57 000 subjects for 35 years concluded that long-term exposure to traffic air pollutants may contribute to the increase in COPD (72). As a matter of fact, some researchers believe that COPD would not really exist in the absence of smoking (73).

Our study is a systematic approach for the estimation of COPD severity stages around the world. We found that most subjects with COPD were in stage 2 (moderate) by GOLD definitions. These findings are important for adjusting the estimation of the burden of COPD in the world, since the COPD years lived with a disability (YLDs) is calculated based on the years lost due to disability weight, which is substantially different among different COPD stages. For example, the weight of disability for COPD in GBD study in 2013 was 0.019 for stage 1 but 0.408 for stage 4 (74).
Our meta-analysis found a high level of heterogeneity among the studies included. Sub-group analysis by sex and region could not relieve this heterogeneity. Besides we found that the WHO region, the level of collection data, and the sample size of the studies were more associated with heterogeneity. However, after adjusting for all factors, we could only account for about 30% of the heterogeneity. This finding is similar to many other meta-analysis of prevalence studies (60,75). This high heterogeneity of the prevalence may be due to the variability of the prevalence in different populations and regions. It might also be due to differences between studies regarding the years they were conducted, their approach to population sampling and data collection methods. In meta-analysis of prevalence, heterogeneity is more than what expected for meta-analysis of relative risks. It would be due to significant real difference in the prevalence rates in various countries and regions (76).

**Limitations**

The main limitation of our study was the lack of data for some key regions and inconsistency between the numbers of studies conducted in different regions, which led us to merge the data of two WHO regions. The fact that we only included English papers was another limitation, since many papers discussed the subject in other languages. Moreover, the age group distribution was inconsistent between some papers so that we could not extract data for all of age groups, consequently we could not standardize the results for age and sex.

**Conclusion**

It seems that the prevalence of COPD is higher in the Americas Region than the other regions. Because of the lack of data in some regions such as the eastern Mediterranean Region and African Region, we recommend to conduct researches on the COPD prevalence, incidence, and mortality rate in these regions.

**Contributors**

All authors had full access to the data, reviewed and edited the manuscript, and take responsibility for its integrity and the accuracy of the analysis. FF, MV, FS, MD and EH contributed substantially to the study design, data analysis and interpretation. FS, MV, MD and EH wrote primary draft. FF, MV, FS, EH, MD and SSM revised manuscript.

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