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Distribution of COPD-related symptoms in the Middle East and North Africa: Results of the BREATHE study

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Summary
Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide. However, its epidemiology in many developing countries is poorly characterised. The objective of this analysis was to evaluate respiratory symptoms which could be COPD-related in a large sample of individuals aged ⩾40 years in ten countries in the Middle East and North Africa (Algeria, Egypt, Jordan, Lebanon, Morocco, Saudi Arabia, Syria, Tunisia, Turkey and United Arab Emirates), together with Pakistan, using a standardised methodology. A random sample of 457,258 telephone numbers was contacted. A screening questionnaire was administered to each eligible participant, which included six questions relating to respiratory symptoms. Of 65,154 eligible subjects, 62,086 agreed to participate and 61,551 provided

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usable data. The age- and gender-adjusted prevalence of symptoms (persistent productive cough or breathlessness or both) was 14.3% [95% CI: 14.0–14.6%], ranging from 7.2% in UAE to 19.1% in Algeria. Symptoms were more frequent ($p < 0.0001$) in women (16.7%) than in men (12.2%). The adjusted prevalence of COPD according to the "epidemiological" definition (symptoms or diagnosis and cigarette use $\geqslant$10 pack·years) was 3.6% [95% CI: 3.5–3.7%] (range: 1.9% in UAE to 6.1% in Syria). COPD was more frequent ($p < 0.0001$) in men (5.2%) than in women (1.8%). The frequency of symptoms was significantly higher in cigarette smokers ($p < 0.001$), as well as in waterpipe users ($p < 0.026$). In conclusion, the prevalence of COPD in this region seems to be lower than that reported in industrialised countries. Under-reporting and risk factors other than smoking may contribute to this difference.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is characterised by chronic inflammation of the lung with consequent respiratory impairment and distress.[1,2] The most common symptoms of COPD are breathlessness, excessive sputum production, and a chronic cough.[3] The Global Initiative for Obstructive Lung Disease (GOLD) recommends that the diagnosis of COPD should be based on clinical symptoms of chronic bronchitis (cough and sputum production for at least 3 months/year for at least two years) or emphysema (breathlessness and coughing), and/or a history of exposure to risk factors for the disease, especially cigarette smoking, confirmed by obstructed airflow measured with spirometry.[4,5]

In 2005, the World Health Organisation (WHO) estimated that 210 million people had COPD and three million people died of COPD that year. Total deaths from COPD are projected to increase in the next twenty years, making it the third leading cause of death in the world unless urgent action is taken to reduce underlying risk factors, especially tobacco use and air pollution.[6] In the USA, the NHANES III survey was conducted in a sample of 16,084 adults from the general population. Fourteen percent of the adult population fulfilled the GOLD criteria for a diagnosis of COPD, which would correspond to 24 million individuals nationwide.[7]

Most of the available information on the prevalence of COPD symptoms has come from industrialised countries. However, available epidemiological data underestimate the total prevalence of COPD, because the disease is usually not diagnosed until it is clinically apparent and moderately advanced.[3] For example, a Swedish study has estimated that only 20–30% of subjects with COPD who met the GOLD criteria had been diagnosed as having COPD.[8] In the Middle East and North Africa (MENA) region, epidemiological data on COPD are either limited or localised to small regions and do not necessarily represent national prevalence estimates. Community-based prevalence surveys are rare due to the high cost and complexity of organising them.

For these reasons, we performed an international survey (BREATHE) in the general population of eleven countries of the MENA region in order to describe the prevalence of symptoms that could be COPD-related (persistent productive cough and breathlessness) in each country.

Methods

This was a cross-sectional epidemiological survey of COPD conducted in a random sample of the general population of eleven countries: Algeria, Egypt, Jordan, Lebanon, Morocco, Pakistan, Saudi Arabia, Syria, Tunisia, Turkey and UAE, between June 2010 and December 2011. This analysis estimates the prevalence of symptoms which could be COPD-related in these countries. The methodology used in the study has been described in detail in the methodology article.[9]

Study sample

A general population sample of at least 10,000 subjects in each country or zone was generated from random telephone numbers. A structured interview was carried out with all eligible subjects by telephone. All subjects aged $\geqslant$40 years who agreed to participate in the study were eligible. Subjects not domiciled in the country or those of foreign origin who had been resident in the country for < 6 months at the time of the interview as well as those who had comorbid mental illness were excluded.

Data collection

When the contact was established, the interviewer explained to the interviewee the goal of the study and the next steps. If the subjects agreed to participate in the study, they were invited to complete two questionnaires. The first "screening questionnaire" collected data on demographics, potential respiratory symptoms and smoking habits. The items related to respiratory symptoms were the occurrence and frequency of productive cough or breathlessness, and known respiratory disease (Table 1). The second, more detailed questionnaire was administered to the screened population with symptoms. This documented risk factors, comorbidities, respiratory disease history, clinical symptoms, impact on daily life and disease management. The present article presents the results from the screening questionnaire; data from the second questionnaire are presented elsewhere in this supplement.[10–12]

Case definition

Subjects were considered to have symptomatic COPD if they fulfilled the "epidemiological" definition of COPD used in this study, which includes two criteria. The first criterion was EITHER a diagnosis of COPD, emphysema or chronic

Table 1
Items used to document respiratory symptoms in the screening questionnaire

5.	**Do you suffer from persistent bronchitis or coughing with phlegm or sputum from the chest for the last 2 years or more?**
	Yes
	No
6.	**How many MONTHS in the past 12 months have you had bronchitis or chronic coughing with phlegm/sputum from the chest?**
	⌊_⌊_ Number of months per year
7.	**For how many years have you had bronchitis or chronic coughing with phlegm/sputum from the chest for at least 3 months?**
	⌊_⌊_ Years with repeated bronchitis
8.	**At what age did you first develop bronchitis or coughing with phlegm or sputum?**
	⌊_⌊_ Years old
9.	**Have you been repeatedly short of breath over the past 12 months?**
	Yes
	No
10.	**At what age did you first develop shortness of breath?**
	⌊_⌊_ Years old

bronchitis OR the presence of coughing with phlegm or sputum (productive cough), breathlessness or symptoms consistent with chronic bronchitis. The second criterion was a lifetime smoking exposure of $\geqslant$10 pack·years. The number of pack·years of cigarette exposure is defined as (number of cigarettes smoked per day/20) × (number of years smoked). Subjects were considered to have chronic bronchitis if they fulfilled the GOLD definition, namely "the presence of cough or sputum production for at least 3 months in each of two consecutive years".[5] The potential relationship between the presence of respiratory symptoms and smoking was also assessed. Subjects with diagnosed α_1-trypsin deficiency who reported the above respiratory symptoms were also assigned to the COPD group, regardless of smoking status.

Statistical analysis

Frequency rates were calculated together with their 95% confidence limits, and adjusted for age and gender unless otherwise specified. Missing data were not replaced and the relatively few subjects for whom data were missing were excluded from the calculation of frequency rates.

Associations between cigarette smoking and respiratory symptoms were quantified using odds ratios and were tested using the χ^2 test. Associations between waterpipe use and symptoms were assessed after adjustment for cigarette smoking. Adjusted odds ratios were used to quantify the association and the Cochran–Mantel–Haenszel statistic was used to test the null hypothesis.

Results

Study sample

A total of 62,086 subjects were interviewed regarding smoking habits. There were equal numbers of men and women (sex ratio: 1.04; 31,673 were men). Overall, 46.4% of subjects (n = 28,815) were aged between 40 and 49 years, 29.7% (n = 18,427) from 50 to 59 years and 23.9% (n = 14,844) aged $\geqslant$60 years.

Prevalence of COPD-related respiratory symptoms

The respiratory symptoms assessed during the screening phase were self-reported productive cough and breathlessness. Of the subjects enrolled in the study, 8,850 reported at least one of these symptoms. The age- and gender-adjusted prevalence of these respiratory symptoms was thus 14.3% [95% CI: 14.0–14.6%] of the general population of the MENA region aged over forty years. The prevalence of symptoms adjusted by age and gender in each participating country is presented in Fig. 1. The lowest prevalence was in UAE (7.2% [95% CI: 6.4–8.1%]) and the highest in Algeria (19.1% [95% CI: 17.9–20.4%]). Breathlessness alone was the most frequently reported symptom in all study countries (~60% of all reports). The mean age at symptom onset was 43.3±12.1 years for productive cough and 43.9±11.4 years for breathlessness.

COPD-related respiratory symptoms were more frequently reported ($p < 0.0001$) by women (16.7% [95% CI: 16.3–17.1%]) than by men (12.2% [95% CI: 11.8–12.6%]) (Fig. 2). This difference was particularly observed for breathlessness alone which was reported by 10.0% of women compared to 6.8% of men ($p < 0.0001$).

Prevalence of chronic bronchitis

Subjects were considered to have chronic bronchitis when the reported respiratory symptoms fulfilled the GOLD definition of chronic bronchitis. A total of 1,600 subjects in the study population fulfilled this definition. Accordingly,

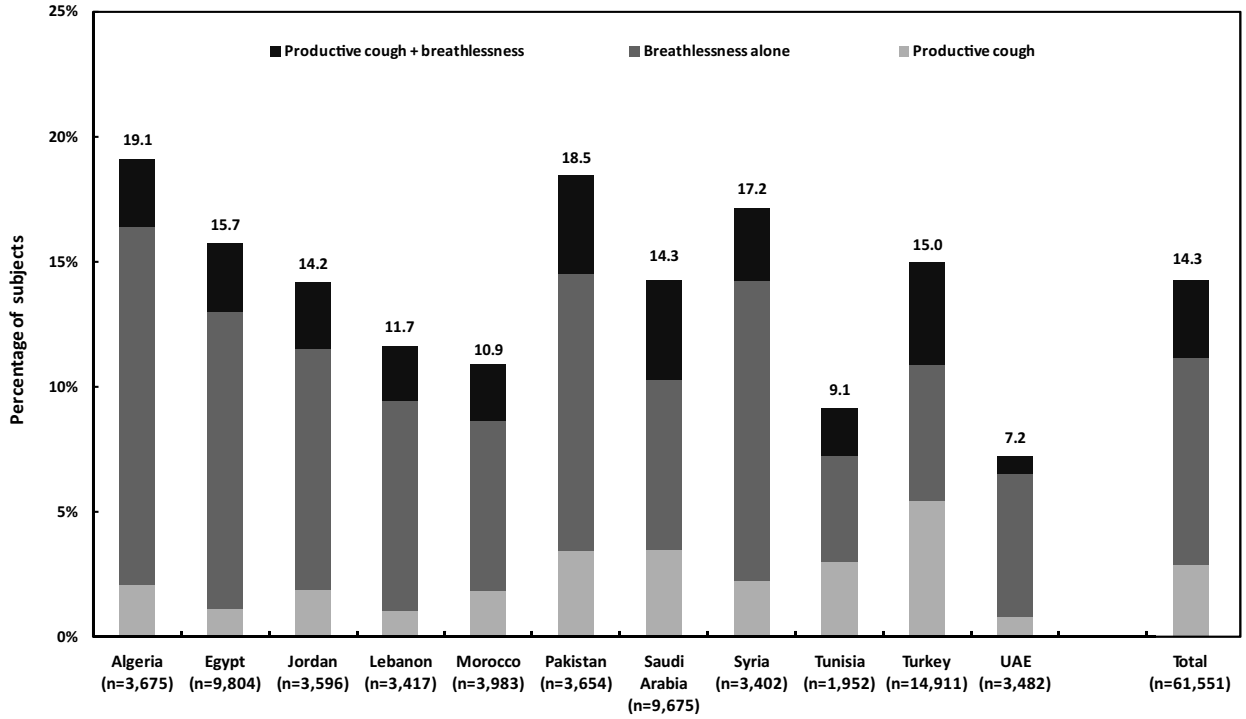

Figure 1. Age- and gender-adjusted prevalence of COPD-related symptoms in the general population aged over forty years in participating countries.

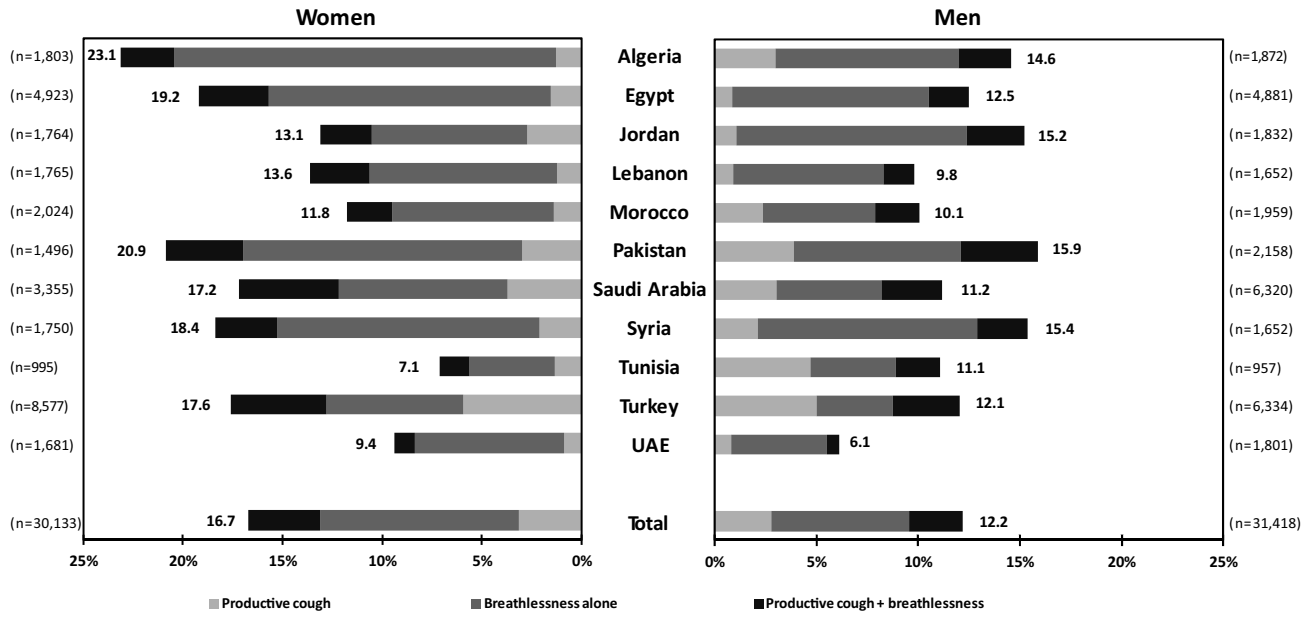

Figure 2. Age adjusted prevalence of respiratory symptoms.

the prevalence of chronic bronchitis in the general population was 2.6% [95% CI: 2.5–2.7%] (Fig. 3). Around one fifth (18.2%; 2.6/14.3) of subjects who reported some COPD-related respiratory symptoms and nearly half (42.6%; 2.6/6.1) of those who reported productive cough were considered to have chronic bronchitis. Overall, chronic bronchitis was more frequently documented ($p < 0.0002$) in women (2.8% [2.6–3.0%]) than in men (2.4% [2.2–2.5%]).

Prevalence of COPD

A total of 2,187 subjects fulfilled the "epidemiological" definition of symptomatic COPD as cited above. Accordingly, the prevalence of COPD adjusted by age and by gender in the general population of the MENA region was 3.6% [95% CI: 3.5–3.7%] ranging from 1.9% (95% CI [1.4–2.4%]) in UAE to 6.1% [95% CI: 5.3–6.9%] in Syria (Fig. 4).

Gender-specific COPD prevalence adjusted by age in each of the eleven countries is presented in Fig. 5. Overall, COPD

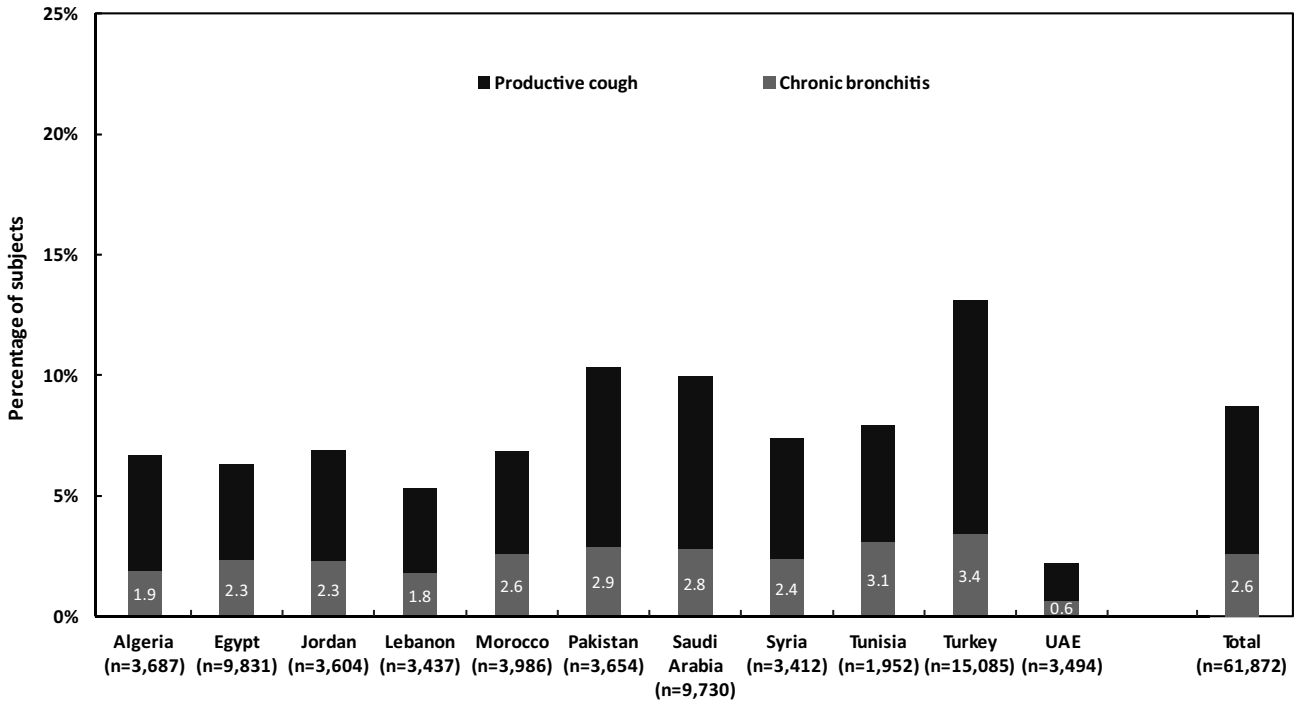

Figure 3. Prevalence of chronic bronchitis in subjects who fulfil the GOLD definition.

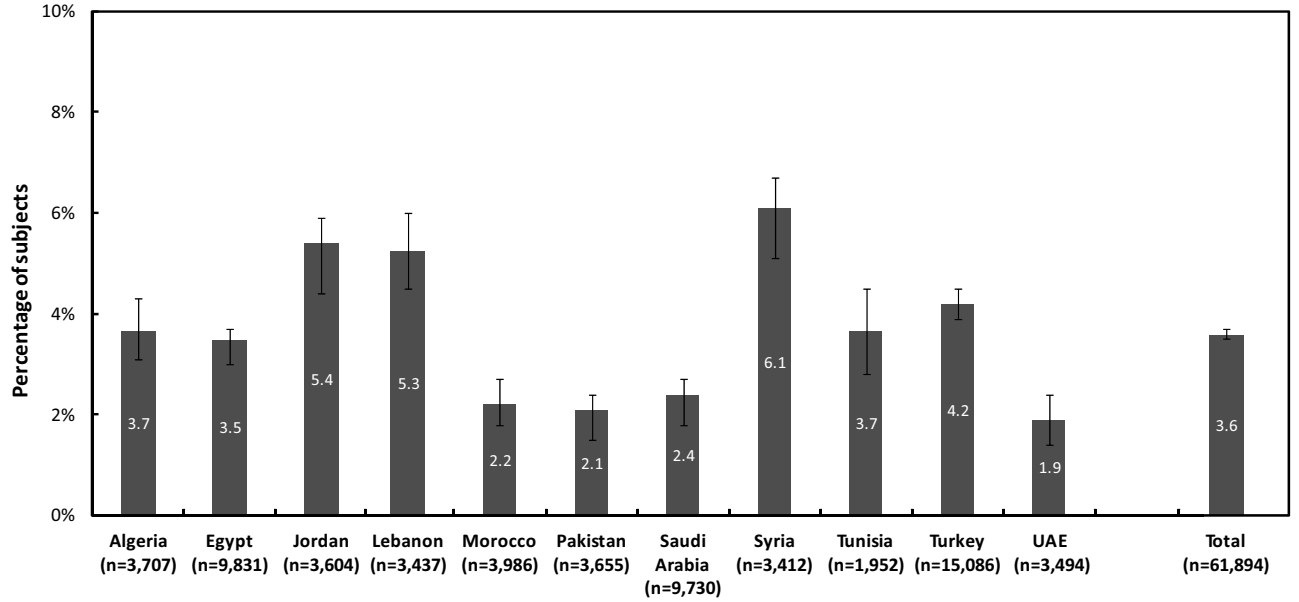

Figure 4. Prevalence of COPD according to the epidemiological definition in each participating country.

was more frequently documented ($p < 0.0001$) in men (5.2% [95% CI: 4.9–5.4%]) than in women (1.8% [95% CI: 1.7–2.0%]). The prevalence of COPD in men ranged from 2.6% [95% CI: 1.8–3.3%] in UAE to 9.7% [95% CI: 8.3–11.2%] in Syria. In women the highest rate was detected in Lebanon (4.7% [95% CI: 3.7–5.7%]).

The prevalence rate of COPD in subjects aged 40–49 years was significantly lower than that in the other age groups: 3.1% [95% CI: 2.9–3.3%] in subjects aged 40–49 years *versus* 3.9% [95% CI: 3.7–4.2%] in those aged 50–59 years and 3.8% [95% CI: 3.5–4.1%] in those aged $\geqslant$60 years ($p < 0.0001$). The highest prevalence rate was documented in Syrian subjects aged $\geqslant$60 years (7.2% [95% CI: 5.2–9.1%]).

History of known respiratory disease

In the study population, 1,872 subjects reported a previous respiratory diagnosis. This was most frequently chronic bronchitis (n = 1,446; 2.4% of the study population), COPD (n = 662; 1.1%), emphysema (n = 196; 0.3%), and α_1-antitrypsin deficiency (n = 107; 0.2%). The mean age at diagnosis was 43.0±11.7 years.

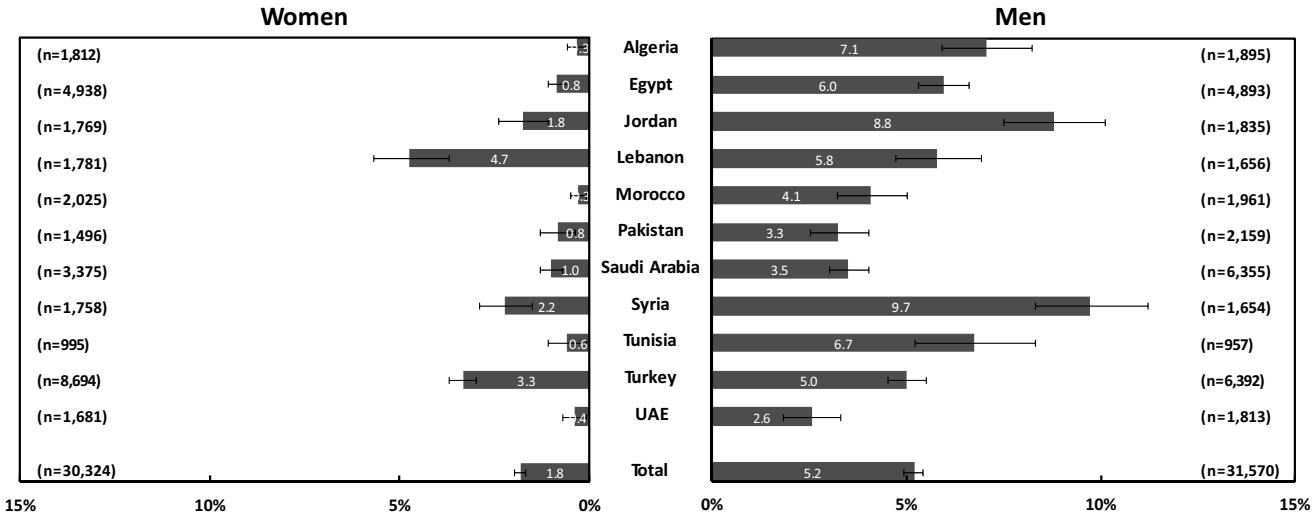

Figure 5. Gender-specific COPD distribution in the general population of the participating countries.

Table 2
Relationship between COPD symptoms and smoking

	No cigarette smoking (N = 42,923)	**< 10 pack·years (N = 4,307)**	**⩾10 pack·years (N = 13,284)**
Productive cough (N = 3,636)	2,204 (5.1%) OR = 1	283 (6.6%) OR = 1.30 [1.14–1.48] $p < 0.0001$	1149 (8.6%) OR = 1.75 [1.62–1.88] $p < 0.0001$
Chronic bronchitis (N = 1,562)	920 (2.1%) OR = 1	92 (2.1%) OR = 1.00 [0.80–1.24] NS	550 (4.1%) OR = 1.97 [1.77–2.20] $p < 0.0001$
Breathlessness (N = 6,961)	4,709 (11.0%) OR = 1	465 (10.8%) OR = 0.98 [0.89–1.09] NS	1787 (13.5%) OR = 1.26 [1.19–1.34] $p < 0.0001$
	No waterpipe use (N = 58,451)	**Waterpipe use (N = 2,173)**	
Productive cough (N = 3,640)	3,481 (6.0%) Adjusted OR[a] = 1	159 (7.3%) Adjusted OR[a] = 1.29 [1.09–1.51] $p = 0.007$	
Chronic bronchitis (N = 1,568)	1,496 (2.6%) Adjusted OR[a] = 1	72 (3.3%) Adjusted OR[a] = 1.42 [1.12–1.80] $p = 0.026$	
Breathlessness (N = 6,978)	6,695 (11.5%) Adjusted OR[a] = 1	283 (13.0%) Adjusted OR[a] = 1.18 [1.04–1.34] $p = 0.018$	

NS: not significant ($p > 0.05$)
[a] Adjusted for cigarette smoking.

Association between respiratory disease and smoking

The relationship between the presence of COPD-related respiratory symptoms and smoking status was assessed and is presented in Table 2. Firstly, the association between cumulative cigarette exposure and symptoms was evaluated. The frequency of all three symptom clusters evaluated (productive cough, chronic bronchitis and breathlessness) was significantly higher in cigarette smokers, and in particular in those individuals who had smoked over ten pack·years. Given that around half of waterpipe users also smoked cigarettes, the association between waterpipe use and symptoms was determined after adjusting for cigarette consumption. Again, a significant association was observed for all three symptom clusters. For both cigarette smoking and waterpipe use, the association was most robust for chronic bronchitis and weakest for breathlessness.

Discussion

The BREATHE study is to our knowledge the first large-scale international study of the prevalence of symptoms which could be COPD related (productive cough and breathlessness) in the general population of the MENA region aged over forty years. Our study showed that 14.3% of the general population of the eleven participating countries reported these respiratory symptoms which could be consistent with a diagnosis of COPD. Breathlessness alone was the most common reported symptom with a prevalence of 8.3%. Respiratory symptoms fulfilling the GOLD definition of chronic bronchitis were reported by 1,600 subjects (2.6%).

According to the "epidemiological" definition of COPD used in our study, COPD was reported by 2,187 subjects, corresponding to a prevalence of 3.6%. COPD was more frequent in men than in women (5.2% and 1.8% respectively), and was more frequently documented in subjects aged 50–59 years and $\geqslant$60 years than in those aged 40–49 years ($p < 0.0001$). For subjects with a diagnosed respiratory disease, the mean age at diagnosis was 43.3±12.1 years, which is close to the age at which respiratory symptoms were reported to have first appeared.

Comparison with published epidemiological data on the prevalence of COPD symptoms is difficult, as they vary considerably according to the methodology and the definition of COPD used. However, the *Confronting COPD* surveys in North America and Europe used a comparable methodology and the same COPD definition as that used in the BREATHE study. The proportion of subjects with symptomatic COPD in this large study was around 6.5% and was relatively homogenous between different countries.[13] The proportion that we observed in the BREATHE study (3.6%) was around half of this.

Several factors may contribute to this difference. Firstly, both smoking and respiratory symptoms may be under-reported in telephone interviews with members of the general population. As discussed in the accompanying article on smoking habits in the BREATHE population, potential under-reporting of smoking is a particular issue in women,[12] since it is not always regarded as socially acceptable for women to smoke in some participating countries. In this respect, it is pertinent that, while more women than men reported COPD-related symptoms in our study, inclusion of the smoking criterion in the epidemiological definition of COPD resulted in a threefold lower prevalence rate in women than in men. Under-reporting of productive cough may also occur, since some respondents may consider that coughing, at least when it is not severe, is a 'normal' behaviour in older people who smoke. The finding that productive cough was reported less frequently than breathlessness would be consistent with such under-reporting.

In addition, certain groups of subjects with COPD may not have been captured in our study. These include subjects with chronic airway obstruction who have been exposed to airborne risk factors other than smoking (see below), subjects with asymptomatic airway obstruction or mild symptoms that were not considered worthy of reporting, and those with COPD incorrectly diagnosed as asthma.

To our knowledge, few epidemiological studies have estimated the prevalence of chronic bronchitis using a methodology similar to that used in our study. The principal differences between this study and previous studies concern age and the selected study population. For example, a community-based study performed in the USA from 1971 to 2000 showed that the rate of self-reported lifetime chronic bronchitis in adults aged >18 years was 5.95%.[14] Another study conducted in eight European cities in 2004 in the same age group provided an estimate of 6.2%.[15] In contrast, the majority of epidemiologic studies on chronic bronchitis conducted in middle-income countries have been limited to specific population groups such as miners or hospitalised patients.[14] The prevalence of breathlessness found in the BREATHE study was similar to that reported in a French study performed in a large sample (n = 2,758) of individuals >40 years of age, which estimated the prevalence of breathlessness to be 9%.[16]

Our study shows that around two-thirds of subjects reporting symptoms evocative of COPD are not current smokers. These findings contrast with those of the *Confronting COPD* study in North America and Western Europe,[13] where around half were smokers, but are similar to those found in the literature with respect to middle-income countries. For example, a study performed in the general population aged 40–80 years in Abu Dhabi (UAE) in 2010, reported that 75% of subjects with COPD (according to the GOLD definition) were non-smokers.[12] In our study, it is particularly striking that, of the 1,607 subjects who fulfilled the GOLD symptom criteria for chronic bronchitis, which is one of the clinical phenotypes of COPD, 985 (61.3%) declared that they did not smoke cigarettes or reported a cumulative exposure <10 pack·years. If these 985 subjects are included for the estimation of the prevalence of COPD, the overall prevalence rate would rise to 5.2%. Nonetheless, we observed a clear association between cumulative cigarette exposure and the frequency of COPD-related symptoms, suggesting that this remains a major risk factor.

This suggests that COPD risk factors other than smoking, such as workplace pollution and indoor air pollution from biomass fuel may be involved.[17] Many studies performed in developing countries have shown that indoor air pollution from biomass fuel is an important risk factor for COPD particularly in rural non-smoking women in these countries.[17–21] Another specific risk factor in this region may be waterpipe use, and we observed a significant association between waterpipe use and the frequency of respiratory symptoms, independent of the risk associated with concomitant cigarette smoking. In this respect, a Lebanese survey performed in 2009 showed that waterpipe smoking may have the same harmful effect on health as cigarette smoking.[22] The epidemiological definition of COPD used in our study captures COPD related to cigarette smoking. While it is well known that this is the dominant risk factor in Western countries in COPD patients,[13] it is likely that a significant proportion of COPD in the developing countries and specifically in countries in the MENA region is more related to other risk factors such as indoor air pollution

from biomass fuel or waterpipe use. Therefore, a future epidemiological definition of COPD should take into account risk factors other than cigarette smoking.

The strength of our study resides in the large sample of subjects assessed using a homogeneous methodology in all participating countries. As COPD occurs mainly in adults and elderly subjects, our study include only subjects aged $\geqslant$40 years in order to limit potential inclusion bias which could lead to an underestimate of the COPD prevalence in these age groups. We also systematically documented smoking habits, since smoking represents a major risk factor for COPD.

However, our study has some limitations. It is possible that the prevalence of COPD was underestimated, since COPD symptoms may not be recognised by the subjects themselves and COPD is not necessarily diagnosed until it is moderately advanced. In addition, the case definition for COPD is problematic for developing countries, where the prevalence of tuberculosis is high and may be the origin of chronic irreversible airflow obstruction in a significant proportion of individuals.[14]

In conclusion, the BREATHE study showed that 3.6% of individuals in the general population of the MENA region fulfilled the epidemiological definition of COPD, lower than that reported in industrialised countries. In addition, causes of COPD other than cigarette smoking, such as waterpipe use, may be relatively more important in the MENA region.

Conflict of interest statement

MAT, SN, JAK, MB, BM, NMO, EU, AS and SW have received honoraria from GlaxoSmithKline Laboratories for their contribution to the BREATHE study. CN advised on the data management and statistical analysis of the results of the BREATHE study on behalf of GlaxoSmithKline Laboratories. NR and AEH are employees of GlaxoSmithKline Laboratories, which funded the BREATHE study and market a number of treatments for COPD.

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