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ORIGINAL RESEARCH

Impact of active and passive smoking as risk factors for asthma and COPD in women presenting to primary care in Syria: first report by the WHO-GARD survey group

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Yousser Mohammad[1]
Rafea Shaaban[1]
Bassam Abou Al-Zahab[2]
Nikolai Khaltaev[3]
Jean Bousquet[4,5]
Basim Dubaybo[6]

[1]National Center for Research in Chronic Respiratory Diseases, Tishreen University School of Medicine, Latakia, Syria; [2]Ministry of Health, Damascus, Syria; [3]Global Alliance Against Chronic Respiratory Diseases, World Health Organization, Geneva, Switzerland; [4]Department of Respiratory Diseases, University Hospital, Hôpital Arnaud de Villeneuve, Montpellier, France; [5]Inserm, CESP Centre for Research in Epidemiology and Population Health, U1018, Respiratory and Environmental Epidemiology Team, Villejuif, France; [6]Department of Internal Medicine, Wayne State University School of Medicine, Detroit, MI, USA

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Correspondence: Yousser Mohammad
National Center for Research in Chronic Respiratory Diseases, Tishreen University, PO Box 1479, Latakia, Syria
Tel +963 93 375 5240
Email ccollaborating@gmail.com

Background: The burden of chronic respiratory disease (CRD) is alarming. International studies suggest that women with CRD are undersurveyed and underdiagnosed by physicians worldwide. It is unclear what the prevalence of CRD is in the general population of Syria, particularly among women, since there has never been a survey on CRD in this nation. The purpose of this study was to investigate the impact of different patterns of smoking on CRD in women.

Materials and methods: We extracted data on smoking patterns and outcome in women from the Global Alliance Against Chronic Respiratory Diseases survey. Using spirometric measurements before and after the use of inhaled bronchodilators, we tracked the frequency of CRD in females active and passive narghile or cigarette smokers presenting to primary care. We administered the questionnaire to 788 randomly selected females seen during 1 week in the fiscal year 2009–2010 in 22 primary care centers in six different regions of Syria. Inclusion criteria were age >6 years, presenting for any medical complaint. In this cross-sectional study, three groups of female subjects were evaluated: active smokers of cigarettes, active smokers of narghiles, and passive smokers of either cigarettes or narghiles. These three groups were compared to a control group of female subjects not exposed to active or passive smoking.

Results: Exposure to active cigarette smoke but not narghile smoke was associated with doctor-diagnosed chronic obstructive pulmonary disease (COPD). However, neither cigarette nor narghile active smoking was associated with increased incidence of spirometrically diagnosed COPD. Paradoxically, exposure to passive smoking of either cigarettes or narghiles resulted in association with airway obstruction, defined as forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) < 70% according to the Global initiative for chronic Obstructive Lung Disease criteria; association with FEV_1 < 80% predicted, evidencing moderate to severe GOLD spirometric grade, and doctor-diagnosed COPD. Physicians tend to underdiagnose COPD in women who present to primary care clinics. Whereas around 15% of enrolled women had evidence of COPD with FEV_1/FVC < 70% after bronchodilators, only 4.8% were physician-diagnosed. Asthma did not appear to be a significant spirometric finding in these female subjects, although around 11% had physician-diagnosed asthma. One limitation is FEV_1/FVC < 70% could have also resulted from uncontrolled asthma. The same limitation has been reported by the Proyecto Latinoamericano de Investigacion en Obstruccion Pulmonar (PLATINO) study.

Conclusion: Contrary to popular belief in developing countries, women exposed to tobacco smoke, whether active or passive, and whether by cigarettes or narghiles, like men are at increased risk for the development of COPD, although cultural habits and taboos may decrease the risk of active smoking in some women.

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Recommendations: These findings will be considered for country and region strategy for noncommunicable diseases, to overcome underdiagnosis of CRD in women, fight widespread female cigarette and narghile smoking, and promote behavioral research in this field.
Keywords: passive smoking, women, COPD, asthma, narghile, water pipe, behavior

Background and rationale

Chronic respiratory disease (CRD), including asthma and chronic obstructive pulmonary disease (COPD), constitutes a global public health problem that has reached pandemic proportions. Recent estimates indicate that around 300 million patients suffer from asthma and 210 million from COPD worldwide.[1,2] Despite the high prevalence of these disorders, several issues relating to pathogenesis and management remain elusive. For example, whereas the role of active cigarette smoking in the pathogenesis of COPD has been established,[1,3] its role in asthma onset is controversial, with evidence suggesting that it may only play a role as an aggravating factor.[4] Similarly, passive smoking has been identified as a risk factor for COPD,[1] but its role in asthma onset is inconclusive. Epigenetic asthma studies[5] demonstrate a possible link, while epidemiological ones remain inconclusive.[6–8]

Another controversial issue is sex differences in susceptibility to COPD.[9,10] As smoking patterns in women change to resemble those of men, the prevalence of chronic respiratory disorders in women is changing. It is unclear whether these changes may be influenced by sex-specific issues, such as menopausal status. COPD has historically been considered a disease of men.[1,3,10] Recent evidence, however, showed a growing epidemic of women smoking in the past few decades in Western countries, and recently in developing countries.[10,11] This change in behavior led to a rise in COPD prevalence among women in the West, and we are expecting the same for women in developing countries. Few studies have been done in developing countries,[1] especially in women.[9]

Many authorities believe that COPD is not properly diagnosed or treated worldwide,[12–14] and that it is especially underdiagnosed in women.[9,10] This may be related to the fact that proper diagnosis requires spirometric measurements that may not be universally available. COPD is diagnosed by lung-function measurements (spirometry), especially forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and FEV_1/FVC ratio.[1,15] Unfortunately, diagnosis is hampered by very limited use of spirometry within primary care worldwide,[13] particularly in developing countries.[14] Asthma is also underdiagnosed, and prevalence based on wheezing reported in the last 12 months, as defined by the International Study of Asthma and Allergies in Childhood (ISAAC) and the European Community Respiratory Health Survey,[16] is not applicable for clinical practice and clinical research.[7,16]

In an attempt to address these controversies, a global initiative using a standardized survey is being undertaken. The Global Alliance Against Chronic Respiratory Diseases (GARD) World Health Organization (WHO) survey is a multicenter survey that aims to track chronic respiratory symptoms, the frequency of CRD, and their associated risk factors in patients visiting primary health care centers (PHCs).[12] The survey also addresses issues related to treatment with inhalers of either corticosteroids or long- or short-acting bronchodilators, risk factors, and spirometry to measure FVC, FEV_1, and FEV_1/FVC ratio after bronchodilator use. In our survey, we adopted the definitions established by the Global initiative for chronic Obstructive Lung Disease (GOLD).[1] Specifically, we used the ratio of $FEV_1/FVC < 70\%$ after bronchodilators to signify airway obstruction[1] (although other spirometric definitions are available).[12,15] $FEV_1 < 80\%$ predicted is considered abnormal. These definitions are also used by the European Coal and Steel Community (ECSC) for reference equations.[1,3,15,17] To ascertain reversibility of airway obstruction, we measured FEV_1 after inhalation of a bronchodilator. Improvement in FEV_1 after bronchodilator use is a hallmark of asthma, but can also be found in COPD.[1]

There are no previous surveys in Syria on CRD prevalence and risk factors in patients managed at PHCs. Syria is the first country in the eastern Mediterranean region to administer this GARD multicenter survey to collect data and implement evidence-based interventions on prevention and control of CRD. The GARD survey is a particularly useful tool to study the role of smoking as a risk factor in females 6 years and older presenting to primary care in Syria. In addition to risks associated with cigarettes, the GARD survey allowed us to explore the health effects of smoking waterpipes, locally called narghiles,[18–20] and the role of passive smoking of either narghiles or cigarettes in females, who in this society tend to spend the majority of their day indoors.

Objectives

This study aimed to measure the prevalence of asthma and COPD in patients presenting to PHCs, to identify their

risk factors, and to explore the effect of active and passive smoking of either narghiles or cigarettes on respiratory symptoms, CRD as diagnosed by primary care general practitioners (GPs), and lung function in women presenting to PHCs.

Materials and methods

Source data

This was an observational prospective study. Female patients 6 years of age or older were randomly recruited from 22 centers in six of the 14 different regions of Syria (designated officially as departments).

Data collection

The GARD survey core questions were used as previously reported.[12] We introduced two additional survey questions specific to the local tradition of smoking narghiles. These were:

1. Do you smoke narghiles?
2. Are you exposed daily to environmental smoke of cigarettes or narghiles?

And to the GARD spirometry form, we added a question:

1. Have you ever undergone peak-flow measurement or a spirometry test?

Responses to this question helped us optimize training of individuals administering and interpreting spirometric measurements.

Spirometric measurements

Lung-function measurements were performed using a flow/volume-measuring portable office automatic calibrated spirometer (Spirobank II®; Medical International Research, Rome, Italy)[21] to track FEV_1, FVC, and FEV_1/FVC. Rules of European Respiratory Society (ERS) measurements were observed.[1,3,17,22] For each participant, flow–volume loops were repeated several times until three reliable tracings were obtained. The best two tracings for FEV_1 and FVC within 5% or 100 mL of each other were examined, and the highest values were retained for the study analysis, as per recommendations of the ERS.[17,21–23]

Then, a reversibility test (by inhalation of 400 µg of salbutamol via AeroChamber Plus* Flow-Vu*[Trudell Medical International, London, ON, Canada]) was performed when FEV_1 was <80% predicted, or FEV_1/FVC < 70%, and was considered positive if FEV_1 improved by 12% and 200 mL.[1] We referred to predictive values of the ECSC.[15,17]

Training

One GP in each center was trained to do spirometry for an entire day, then worked under supervision of the trainer for another day. Furthermore, for quality control the spirometric tracings were reviewed by the trainer every day during the week of the survey. Trainers were chest physicians certified for spirometry. For children, two certified pulmonary pediatricians performed spirometry.

Statistical analysis

Data were expressed as percentages for discrete variables and as means (standard deviations) for continuous variables. The chi-square test and *t*-test were used when analyzing differences between groups. Analysis of variance was used to compare continuous variables between the three studied groups. Logistic regression models were fitted using respiratory symptoms or diseases or lung functions as the dependent variable and active or passive smoking as the independent variable. All possible interactions between the explanatory variables were tested and found to be statistically nonsignificant. We considered $P < 0.05$ to be significant. Statistical analysis was carried out using the Stata software package (version 6; StataCorp, College Station, TX, USA).

Results

During the study period, a total of 788 women were enrolled. The characteristics of these women are shown in Table 1. Mean body mass index (BMI) was 24.5 kg/m^2 (standard deviation [SD] 6.6 kg/m^2). Almost 80% of the women were nonsmokers. Asthma frequency was 11.0%, and COPD frequency was 4.8% in women visiting the PHCs, as diagnosed by GPs. Baseline mean FEV_1 percent predicted was 79.9% (SD 23.1%), and the FEV_1/FVC ratio after bronchodilators was 82.7% (SD 14.1%). FEV_1/FVC ratio was less than 70% in more than 15% of the women examined.

Adult women were classified into three categories by their active smoking status: nonsmokers, narghile smokers, and cigarette smokers (Table 2). Active cigarette-smoking women were slightly older than nonsmokers or narghile smokers. Cough, sputum, wheezing, and COPD were more common among cigarette-smoking women, while wheezing (ever) was more common among narghile smokers. There were no differences with regard to BMI, breathlessness, current asthma, or lung functions (FEV_1, FEV_1/FVC after bronchodilators) among all groups.

A multiple logistic regression model was used to assess the relationship between active smoking status

Table 1 Characteristics of women by age

	6–19 years	20–44 years	>44 years	Total	*P*-value
n (%)	280 (35.5)	300 (38.1)	208 (26.4)	788	
BMI, mean (SD)	19.3 (3.9)	26.1 (5.2)	29.8 (6.3)	24.5 (6.6)	<0.001
Region, n (%)					0.001
• Urban	241 (96.8)	201 (88.2)	147 (89.6)	596 (92.0)	
• Rural	8 (3.2)	27 (11.8)	17 (10.4)	52 (8.0)	
Active smoking, n (%)					<0.001
• Nonsmokers	268 (95.7)	206 (68.7)	138 (66.4)	657 (78.5)	
• Narghile smokers	9 (3.2)	44 (14.7)	12 (5.8)	69 (8.2)	
• Cigarette smokers	3 (1.1)	50 (16.7)	58 (27.9)	111 (13.3)	
Cough, n (%)	50 (18.0)	116 (39.1)	95 (46.1)	276 (33.3)	<0.001
Sputum, n (%)	31 (11.1)	98 (32.7)	87 (41.8)	229 (27.4)	<0.001
Breathless, n (%)	13 (5.1)	52 (21.4)	51 (30.9)	124 (18.3)	<0.001
Wheeze ever, n (%)	71 (25.7)	89 (30.4)	80 (39.0)	250 (30.4)	0.007
Current asthma, n (%)	21 (7.5)	37 (12.3)	31 (14.9)	92 (11.0)	0.029
COPD, n (%)	2 (0.7)	16 (5.3)	22 (10.6)	40 (4.8)	<0.001
FEV_1% predicted, mean (SD)	83.9 (23.7)	80.5 (22.2)	73.2 (22.2)	79.9 (23.1)	<0.001
FEV_1/FVC#, mean (SD)	85.5 (13.3)	83.2 (13.3)	78.2 (15.3)	82.7 (14.1)	0.12
FEV_1/FVC < 70%#, n (%)	25 (12.4)	28 (15.1)	30 (21.3)	86 (15.6)	0.08

Note: #After bronchodilators.
Abbreviations: SD, standard deviation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

and respiratory symptoms and COPD after controlling for center, region, age, and BMI. The adjusted odds ratio (OR) was still significant for wheezing but not sputum in narghile smokers, and for cough and sputum but not wheeze in cigarette smokers. The OR for COPD as diagnosed by GPs in cigarette-smoking women was 2.9 (95% confidence interval [CI] 1.1–7.6), whereas the corresponding OR for narghile-smoking women was 2.6 (95% CI 0.6–11.5) (Table 3).

Nonsmoking women in the whole sample (788 women, >6 years old) were classified into two categories: nonexposure and exposure to environmental tobacco smoke (ETS) of either narghiles or cigarettes (Table 4). The groups did not differ in age distribution, cough, sputum, breathlessness, or asthma prevalence. However, females exposed to passive smoking had slightly greater BMI and lower lung function than non-exposed ones. In addition, wheeze (ever) and COPD were more frequent in exposed females.

A multiple logistic regression model was used to assess the relationship between passive smoking status and wheeze (ever), COPD, and lung functions after controlling for center and age. The adjusted OR for COPD in exposed females

Table 2 Relation between active smokers and respiratory symptoms and functions in women aged ≥20 years

	Active smokers			
	Nonsmokers	Narghile smokers	Cigarette smokers	*P*-value
n (%)	389 (69.8)	60 (10.8)	108 (19.4)	
Age, mean (SD)	41.0 (14.5)	34.9 (12.1)	45.2 (10.9)	<0.001
BMI, mean (SD)	27.8 (6.1)	26.1 (5.0)	27.4 (6.1)	0.24
Cough, n (%)	137 (35.6)	21 (35.0)	68 (63.6)	<0.001
Sputum, n (%)	113 (29.1)	27 (45.0)	58 (53.7)	<0.001
Breathless, n (%)	74 (25.8)	12 (26.7)	25 (27.5)	0.95
Wheeze ever, n (%)	106 (27.9)	23 (38.3)	50 (47.2)	0.001
Current asthma, n (%)	47 (12.1)	6 (10.0)	18 (16.7)	0.36
COPD, n (%)	17 (4.4)	3 (5.0)	18 (16.7)	<0.001
FEV_1% predicted*, mean (SD)	77.4 (22.8)	81.8 (20.0)	76.5 (21.3)	0.19
FEV_1/FVC#, mean (SD)	81.6 (15.1)	80.7 (10.6)	80.6 (13.8)	0.82

Notes: *FEV_1 adjusted for age and height; #after bronchodilators.
Abbreviations: SD, standard deviation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 3 Relation between active smokers and respiratory symptoms by logistic regression

	Active smokers (≥20 years)				
	Nonsmokers	Narghile smokers		Cigarette smokers	
	Reference	Adjusted OR*	95% CI	Adjusted OR*	95% CI
Cough	1	0.9	0.4–2.3	1.9	1.0–3.8
Sputum	1	2.3	0.9–5.5	1.9	1.0–3.7
Wheeze ever	1	3.4	1.3–9.0	1.6	0.8–3.2
COPD	1	2.6	0.6–11.5	2.9	1.1–7.6

Note: *OR adjusted for age, center, region, and BMI.
Abbreviations: OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; BMI, body mass index.

was 3.2 (95% CI 1.1–9.2). It was 2.1 (95% CI 1.4–3.3) for FEV_1 percent predicted <80%, and 1.8 (95% CI 1.0–3.3) for $FEV_1/FVC < 70\%$ after bronchodilators (Table 5).

Discussion

We surveyed a representative sample of 788 women attending PHCs through 1 week. We demonstrated that the prevailing symptoms of these women were consistent with COPD, prompting GPs to make the diagnosis on clinical grounds. Furthermore, the clinical suspicion of COPD related to passive smoking was confirmed by spirometric evidence of airway obstruction($FEV_1/FVC < 70\%$ after inhaling with bronchodilators according to GOLD definition).[1] The clinical and spirometric diagnosis of COPD was made irrespective of whether the passive smoking was related to cigarette or narghile smoking. Interestingly, the GPs did not entertain asthma as a diagnosis in these women, whether they were exposed to active or passive smoking.

This is the first study to demonstrate a difference in spirometric findings between women who are active smokers and those who are exposed to passive smoking. Passive smoking is associated with $FEV_1/FVC < 70\%$ after bronchodilators, which confirms a role of passive smoking in airway obstruction. Passive smoking is also associated with $FEV_1 < 80\%$ predicted, which means moderate-to-severe airway obstruction following the GOLD criteria,[1] while active smoking is not. These paradoxical findings may be related to some sociological and cultural factors. Most women in our sample who report to free PHCs come from economically deprived areas with cultural taboos[20,24] and social inhibitions. In these societies, it is not acceptable for women to smoke in front of their husbands, or in public.[25] This may have resulted in lower pack-years for cigarettes and less spirometric impairment. In a general review, Ohar et al reported women to be more exposed to ETS than active smoking, and that they smoked fewer cigarettes than men.[10] In a former study in Turkey, women smoked fewer cigarettes compared to men.[26] The data for narghile smoking are more variable, with some studies demonstrating an effect on lung function, while others do not.[27] A recent study emphasizes the need for quantitative data to track the dose–effect relationship between active narghile smoking and COPD.[18]

Table 4 Relation between passive smokers and respiratory symptoms and FEV_1 in nonsmoking females

	Passive smokers		*P*-value
	No	Yes	
n (%)	368 (56.01)	289 (43.99)	
Age, mean (SD)	28.1 (18.2)	28.7 (18.1)	0.70
BMI, mean (SD)	23.1 (6.4)	24.7 (7.1)	0.02
Cough, n (%)	96 (26.3)	88 (30.8)	0.21
Sputum, n (%)	74 (20.1)	67 (23.2)	0.34
Breathless, n (%)	40 (15.6)	47 (17.0)	0.65
Wheeze ever, n (%)	86 (23.9)	90 (31.7)	0.03
Doctor diagnosed asthma, n (%)	33 (9.0)	35 (12.1)	0.19
COPD, n (%)	5 (1.4)	13 (4.5)	0.01
FEV_1% predicted*, mean (SD)	84.4 (20.8)	76.1 (25.2)	<0.001
$FEV_1/FVC^{\#}$, mean (SD)	85.1 (13.0)	81.6 (15.3)	0.01

Notes: *FEV_1 adjusted for age and height; #after bronchodilators.
Abbreviations: SD, standard deviation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 5 Relation between passive smoking and respiratory symptoms and functions in women by logistic regression

	Passive smoking			*P*-value
	Nonexposed	Exposed		
	Reference	Adjusted OR*	95% CI	
Wheeze ever	1	1.39	0.97–1.99	0.07
COPD	1	3.20	1.11–9.23	0.03
FEV_1% predicted, <80%	1	2.11	1.36–3.27	0.00
$FEV_1/FVC < 70\%^{\#}$	1	1.83	1.03–3.25	0.04

Notes: *OR adjusted for age and center; #after bronchodilators.
Abbreviations: OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

This study reveals a number of important findings. First, it is the first study to find an association between narghile smoking and wheezing (ever). Second, it demonstrates a difference in the rate of diagnosis of COPD by GPs between cigarette smokers and narghile smokers. COPD diagnosed by GPs in our survey was associated with active cigarette smoking with an OR of 2.9 (95% CI 1.1–7.9), while for active narghile smokers, the OR was 1.2 (95% CI 0.35–11). This confirms previously reported findings for cigarette smoking.[1,3,12] Third, it dispels the myth that COPD is primarily a male disease. Women exposed to smoking demonstrate the same symptoms and spirometric alterations as males. COPD was considered to be a male disease, reflecting the fact that the proportion of women who smoke was lower than men.[1,3,10,11] The past several decades have demonstrated an increase in the prevalence of women smokers and a concomitant increase in COPD among women.[1,3,9,10,28] This is also true in developing countries.[17,28] Previously published studies showed that active smoking of cigarettes causes alteration of lung functions in a dose-dependent manner.[1,3] It is universally accepted that active smoking is responsible for 85%–90% of COPD, but only 15% of smokers with genetic predisposition develop COPD.[1,3]

The effect of exposure to tobacco smoke, whether active or passive, on lung growth and function has been addressed previously. A review of the literature reveals considerable discrepancies. For example, Weiss et al using smoking machines,[29] reported respiratory symptoms in individuals exposed to ETS, but reduction in FEV_1 occurred only in a minority of patients labeled by the authors as "sensitive subjects." Similarly, in a general review on passive smoking of narghiles, Chaouachi[30] reported an increase in respiratory symptoms in children with ETS related to narghile smoking with a concomitant decrease in FEV_1. In contrast, Masi et al[31] found no relation between exposure to smoking and reduction in lung function in adults during a 7-year follow-up period. In this study, FEV_1 in men and women remained unchanged. Similarly, Masjedi et al[32] also reported no effect of passive smoking on respiratory functions of men or women. These discrepancies may be related to differences in the level of exposure, since the various study groups had varying degrees of exposure to active and passive smoking. Alternatively, the differences may be related to polymorphism, genetic predisposition, or environmental factors that need to be investigated.

An important study to mention is one conducted in Cape Verde,[12] which used the same GARD survey we administered to our subjects. The authors reported the diagnosis of COPD in 6.2% of 337 subjects. The authors utilized different methodology in their data interpretation. For example, they used the British Thoracic Society COPD diagnostic criteria ($FEV_1/FVC < 70\%$ and $FEV_1 < 80\%$), whereas we used the GOLD criteria ($FEV_1/FVC < 70\%$ after bronchodilator). In addition, they did not conduct reversibility tests. Despite these methodological differences, they found that active smoking was associated with COPD for both sexes, but the OR for active cigarette smokers and $FEV_1/FVC < 70\%$ was 3.21 (95% CI 0.79–12.95, $P = 0.1$). Like our current study, the Cape Verde study did not investigate the dose–effect relationship. In contradistinction to our study, the Cape Verde study was limited to active smoking of cigarettes, and found women to be less susceptible to lung-function changes.

Eleven percent of patients presenting to PHCs in our study have doctor-diagnosed asthma. The ISAAC study found current asthma defined as wheezing in the last 12 months to be 5.7% in children 13–14 years old in Syria.[33] In our GARD survey, we were dealing with patients older than 6 years presenting to PHCs and not adolescents in the whole community. In a former Syrian study, passive smoking was reported to be the most prevalent trigger for asthma attacks.[34]

In our GARD study, asthma did not appear to be a major contributor to morbidity. There was no association between the frequency of asthma cases as diagnosed by GPs, and either passive or active smoking. This finding has not been uniformly reported. In fact, there is considerable controversy in this area too, prompting the US Surgeon General to report that the role of ETS in the asthma epidemic is still inconclusive.[8] For example, Gilliland et al[35] conducted a prospective cohort study among 2,609 children with no lifetime history of asthma or wheezing followed annually in schools in California, and found that regular smoking was associated with increased risk of new-onset asthma, with a relative risk of 3.9 (95% CI 1.7–8.5) compared with nonsmokers. In a general review, Baena-Cagnani et al reported several studies showing association between ETS and asthma onset.[36] In contrast, Hancox et al[37] followed a cohort of subjects from birth to 32 years of age and found that exposure to smoking was not associated with an increase of asthma in atopic subjects. The authors suggested that this finding may be related to an allergic suppression effect of smoking. Similarly, the Epidemiological Study on the Genetics and Environment of Asthma (EGEA)[4] shows no association of active smoking with asthma. Here again, the role of genetics in explaining these discrepancies needs to be emphasized. The role of passive smoking in asthma onset is explained by epigenetic

changes in patients with susceptible genes,[5] which play a role in wheezing illnesses and allergy in childhood.[7] Recently the ISAAC study found a dose–response relationship between exposure to passive cigarette smoke and childhood asthma expressed as wheezing in the last 12 months, suggesting a causal role.[38]

It would be interesting to speculate on the variability seen among studies as described above and also within our study between cigarette and narghile smoking. The variability may be related to genetic factors, to differences in the inflammatory response, or to differences in the substances emitted by cigarettes and narghiles. Recent studies have demonstrated that there is a genetic predisposition for COPD and asthma,[1,7] with variants of 17q21 genes linked to asthma caused by ETS.[39] Epigenetic changes caused by ETS lead to altered gene expression, playing a role in asthma onset.[5] DNA oxidative damage caused by cigarette-smoke particles could affect transcriptional regulation of COPD-related genes, and thereby contribute to disease pathogenesis.[40] Changes in the endobronchial inflammatory response have been described.[41] Floreani and Rennard[41] reported a cascade of inflammatory events, cytokine release, and a T helper 2 secretion profile. The authors concluded that the intimate micromolecular mechanisms of such changes are still elusive. Interleukin 13 is also higher in children exposed to parent smoking.[42] These inflammatory changes may be related to differences in the composition of smoke emitted from cigarettes and narghiles. Cigarette ETS is more toxic than mainstream smoke inhaled by smokers (MSS), because particles are smaller and go deeper into the lungs.[43]

Chaouachi[30] described the characteristics of smoke emitted from tobacco. Tobacco smoke is composed of MSS and ETS inhaled by household members or coworkers. ETS of cigarettes is composed of smoke from the burning part of the cigarette between puffs and smoke exhaled by the smoker. However, for narghiles, ETS is composed only of exhaled smoke. Narghile smoke is rich in CO, glycerol, and water (probably around 80% or more). The fact that narghile smoke contains these substances, which are not known to cause airway damage, and the fact that the nicotine and particles may be partially filtered by water may explain some of the less pronounced changes in physiologic parameters reported in some studies on narghile smoking.

One limitation of our study is the possibility that some of the subjects may have had asthma rather than COPD. Although the GOLD criteria for COPD include $FEV_1/FVC < 70\%$ after bronchodilators, this definition in clinical surveys has limitations. In the Proyecto Latinoamericano de Investigacion en Obstruccion Pulmonar (PLATINO) study, which like us adopted the functional definition of GOLD for COPD, the authors acknowledge the limitation of this epidemiological definition for clinical research, because some asthma patients may meet the criteria for COPD.[28] In our study, it was not possible to exclude the diagnosis of asthma in some women labeled as COPD. Because our participants had never had lung-function tests, nor had they been treated with inhalers, alterations of $FEV_1/FVC < 70\%$ after bronchodilators could have resulted from either COPD or uncontrolled asthma, and $FEV_1 < 80\%$ could reflect moderate-to-severe COPD, but severe uncontrolled asthma as well.[1,7] We relied on trained GPs to make the clinical differential diagnosis. After reviewing the file and spirometry, the GPs in health centers made the clinical diagnosis of COPD in only 4.8%; among the 15% of women fulfilling the criteria of $FEV_1/FVC < 70\%$ after bronchodilators (Table 1), demonstrating a significant association of active cigarette smoking with COPD (OR 2.9, 95% CI 1.1–7.6) (Table 3).

It is worthwhile to mention another limitation regarding the GOLD definition of airway obstruction we adopted for our results: $FEV_1/FVC < 70\%$ after bronchodilators, because in older adults, especially in patients over 70 years, values of 65%–70% may be normal. The use of predicted values extrapolated from the younger population may result in overdiagnosis of COPD.

Conversely, in people under 45 years, using a ratio of 70% may result in underdiagnosis of airway obstruction. To avoid both of these problems, many experts recommend use of the lower limit of normal (LLN) values for each population. LLN are based on the normal distribution and defined as values less than the fifth percentile predicted.[44] However these LLN values compared to the fixed value of $FEV_1/FVC < 70\%$ after bronchodilator, are highly dependent of valid reference equations using post bronchodilator FEV_1.[1,44]

Other limitations include the fact that dose–effect relationships were not investigated, a limitation observed in many other studies.[1,3,28] Another limitation is the potential for recall bias.[29] To overcome this limitation and avoid confusion between asthma and COPD, and to improve the accuracy of diagnosis, GPs reviewed the patient file after subjects filled out the questionnaire, and performed spirometry and reversibility tests. It was only then that the GPs gave the final diagnosis. Another layer of confirmation was verification of the diagnosis by a chest specialist, as well as strict quality controls on the spirometry apparatus and tracing.

Our study is the first systematic assessment of CRD in women exposed to passive and active smoking in Syria using

the validated WHO GARD survey in the eastern Mediterranean region. Our findings of a significant rate of COPD in women (4.8%) confirm the belief that COPD is underdiagnosed among women, a finding previously reported by several other investigators. This may be related to the fact that many COPD patients report only to PHCs where spirometry is not routinely available. Similar observations have been reported from Africa[14] and in developed countries.[10,13,14] Varkey[9] and Ohar et al[10] reported that COPD in women is underdiagnosed by physicians, understudied, and research is needed to understand female susceptibility. Similarly, asthma is underdiagnosed worldwide too, and a standard definition for asthma in clinical research needs to be validated.[7,16]

Few published studies focus on CRD in women in developing countries. The aim of our study was to highlight the underdiagnosis of COPD and asthma, and their risk factors in PHCs, in order to give an evidence-based tool to health authorities. Our public health recommendations include the following:

- There should be increased awareness among health care providers about the prevalence of CRD in women and the need to conduct spirometry when suspected.
- Both asthma and COPD should be suspected and ruled out, as both are underdiagnosed in women.
- There is a need to strengthen smoking-cessation efforts for cigarettes and narghiles among women.
- Passive smoking is harmful in women, altering lung function, and should be considered in CRD-prevention programs.
- Future research is needed to address the challenging issues involved in how to implement international guidelines, including the evaluation of the WHO's practical approach to lung health and package of essential noncommunicable disease interventions, in accordance with the agenda of the WHO and the Non Communicable Diseases action plan.[45–47]
- Quantitative and qualitative research is needed in developing countries[9] to track women's patterns of smoking and to understand the behavioral, social, and traditional factors that influence smoking.
- The essential tools to diagnose CRD, such as peak-flow meters and spirometry, should be available to PHCs in developing countries.[48,49]

It is noteworthy that the same GARD survey has been conducted in several other countries.[50] In the Russian Federation (2010–2011), investigators reported asthma in 6.4% of their sample, while only 20% of COPD patients had an accurate diagnosis. These findings have prompted a national campaign to train GPs for spirometry and CRD. Another country where the GARD survey has been investigated is Georgia, where investigators found that the prevalence of COPD is far higher than that proposed by the Ministry of Health. Here again, a national campaign against CRDs was launched, which has recently been expanded to include the Transcaucasian region (Armenia, Azerbaijan, Georgia). Unlike our study, these two GARD surveys did not focus on women and did not address passive smoking.

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Disclosure

The authors report no conflicts of interest in this work.

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