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Sex differences in the clinical presentation and management of airflow obstruction

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ABSTRACT: The aim of the present study was to explore differences in the clinical expression, clinical diagnoses and management of airway diseases in a primary-care setting.

Patients aged ⩾35 yrs who had ever smoked were enrolled when they presented for any reason to one of eight rural primary-care practices. Respiratory symptom questionnaires and spirometry were administered. In total, 1,034 patients had acceptable and reproducible spirometry, of whom 550 (53%) were males and 484 (47%) were females.

Males smoked more than females (41.2 *versus* 29.2 pack-yrs) respectively, and were more likely to have a pre-bronchodilator forced expiratory volume in one second/forced vital capacity <0.70 at 22.4 *versus* 11.8%, respectively. However, more females than males reported breathlessness (51.0 *versus* 42.8%, respectively), a prior diagnosis compatible with airflow obstruction and taking respiratory medications (23.4 *versus* 14.9%, respectively).

In conclusion, the current results suggest that females are more likely than males to report breathlessness and be prescribed respiratory medications independent of differences in the severity of airflow obstruction.

KEYWORDS: Airflow obstruction, clinical practice, sex, spirometry, treatment

The most common causes of airflow obstruction in primary-care practices are chronic obstructive lung disease (COPD), characterised by progressive, partially reversible airway obstruction, and asthma, characterised by variable airflow limitation [1, 2]. Previous studies have shown that the clinical diagnosis of chronic bronchitis is made more commonly in females than males, and emphysema is more commonly diagnosed in males than females [3]. Hypothetical case presentations to primary-care physicians reveal that, for the same clinical history, males were more likely to be diagnosed with COPD and females with asthma [4]. Whether or not females are more susceptible to cigarette smoke than males is controversial. A recent study in a pulmonary clinic matched females to males on forced expiratory volume in one second (FEV_1) per cent predicted [5]. Compared with males, females were younger, smoked less, were more breathless and reported poorer quality of life scores. The present study explores differences in clinical expression of airway disease, diagnoses and management in a primary-care setting. The study group was not selected based on the presence or absence of respiratory symptoms or known lung disease.

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METHODS

Geographical location

Primary-care practices were recruited from rural Eastern Ontario, Canada. They had to be within a 2-h driving distance of the Ottawa Hospital (Ottawa, ON, Canada), which allowed the hospital-based research assistants to drive to the practices each day to perform spirometry. Several rural communities were selected to assess variability between practices. The practices were sent letters of invitation and then contacted *via* telephone. The first eight practices that agreed were included in the study.

Subjects

Eligible subjects were all patients presenting to their primary-care practitioners for any reason, who were aged ⩾35 yrs, and who had smoked ⩾20 packets of cigarettes in their lifetime. The patients were given a brief questionnaire by the clinic receptionist to determine their age and smoking history, and were asked whether they would agree to participate. Patients who were eligible and agreed to participate were approached by the research assistant and signed informed consent forms. Patients who could not perform spirometry were excluded. The study was approved by the Ottawa Hospital Human Ethics Committee.

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Baseline data collection

Interviewer-administered questionnaires included questions about smoking, respiratory symptoms and diagnosed respiratory illnesses, and were taken from the American Thoracic Society (ATS) Questionnaire [6], which has been standardised and tested for reliability.

Spirometry was performed in the primary-care practice building by trained research assistants using a Microlab 3500® (Micro Medical Ltd, Kent, UK). Testing was carried out with the subjects seated. A maximum forced exhalation was carried out for a minimum of 6 s. A minimum of three and a maximum of eight forced vital capacity (FVC) manoeuvres were performed to obtain at least three acceptable loops, two of which were reproducible within 200 mL. The reference values for FEV_1 and FVC were those of KNUDSON *et al.* [7]. Post-bronchodilator FEV_1 was measured 20 min after 200 μg of salbutamol in those with an FEV_1/FVC <70% pred or an FEV_1 <80% pred. All spirometry tests were reviewed by an independent senior cardiopulmonary technologist and two respirologists to ensure acceptability.

Statistical analysis

Two different criteria were used for determining the prevalence of airflow obstruction. The first was an FEV_1/FVC <70% pred, the clinical threshold criteria popularised by the Global Initiative for Chronic Obstructive Lung Disease guidelines for the diagnosis of airflow obstruction [8]. The second definition was a pre-bronchodilator $FEV_1/FVC1$ less than the lower limits of normal (LLN), based on reference equations determined by the third National Health and Nutrition Examination Survey spirometric data [9]. Results were stratified by sex and differences were tested either with an independent unpaired t-test or Chi-squared statistics.

RESULTS

The study included eight communities with populations between 1,206 and 4,406, of which 1,046 subjects were enrolled. A total of 1,034 subjects had acceptable and reproducible spirometry, of whom 550 (53%) were males and 484 (47%) were females. There was no significant difference in prevalence of airflow obstruction between the eight study sites (Chi-squared, $p=0.17$). The mean±SD age of the study patients was 59±12.7 yrs, with patients having a smoking history mean±SD of 35.5±28.5 pack-yrs.

To determine the degree to which the study group was representative of all eligible subjects, the entire clinical population that visited the eight primary-care practices was surveyed for several days. Of the 1,800 subjects who were 100% sampled, 561 were ⩾35 yrs of age and had ever smoked. Compared with all of those eligible (aged ⩾35 yrs and had ever smoked), the group studied using spirometry differed as follows: 1) aged 2 yrs younger; 2) 1% more males; and 3) 1 yr extra smoking.

In the study group of 1,034, males were on average 5.5 yrs older and had smoked for 12 pack-yrs more than females ($p<0.0001$; table 1). Females reported dyspnoea ($p=0.008$) and wheeze ($p=0.031$) more frequently. Based on responses to the ATS Questionnaire [6], females were twice as likely to have been diagnosed with asthma, 20 *versus* 10% ($p<0.0001$), respectively, and two-thirds more likely to have been diagnosed with chronic bronchitis, 19 *versus* 11% ($p=0.001$), respectively. The prevalence of airflow obstruction was higher in males than females. This was statistically significant when defined by FEV_1/FVC <70% pred, but not significant when defined by the LLN criteria. In total, 123 (22%) males and 57 (12%) females had an FEV_1/FVC <70% pre-bronchodilator ($p<0.0001$). FEV_1/FVC less than LLN was present in 76 (14%) males and 54 (11%) females ($p=0.20$). Females were also almost twice as likely to report using respiratory medications, 23 *versus* 15% ($p=0.0005$), respectively.

When the analysis was restricted to only those with obstruction defined by the LLN criteria, females had smoked less than males, 39 *versus* 53 pack-yrs ($p=0.0008$), respectively. They were also much less likely to report sputum, 17 *versus* 41%, respectively, (table 2). There were no significant sex differences in reported respiratory diseases and medications.

Respiratory medication use was stratified by severity of obstruction from none to severe (table 3). Females were twice as likely as males to be prescribed medications unless airway obstruction was severe. When severe, 70% of both males and females reported taking at least one respiratory medication.

TABLE 1 Characteristics of the1034 study subjects

Characteristics	Males	Females	p-value
Subjects	550 (53)	484 (47)	
Age yrs	61.7±12.4	56.2±12.5	<0.0001
Post-secondary education	139 (25.7)	111 (23.3)	0.3792
Smoking history pack-yrs	41.2±32.3	29.2±21.8	<0.0001
Symptoms			
Shortness of breath	235 (42.8)	247 (51.0)	0.0082
Cough	108 (19.7)	119 (24.6)	0.0570
Phlegm	126 (22.9)	95 (19.7)	0.2051
Wheeze	209 (38.0)	216 (44.6)	0.0307
Diagnoses			
Asthma	56 (10.2)	96 (20.0)	<0.0001
COPD	15 (2.7)	20 (4.2)	0.2097
Emphysema	20 (3.7)	12 (2.5)	0.2846
Chronic bronchitis	62 (11.4)	88 (18.7)	0.0010
FEV_1/FVC <0.70	123 (22.4)	11.8 (57)	<0.0001
Severe	29 (5.3)	11 (2.3)	
Moderate	69 (12.6)	36 (7.4)	
Mild	25 (4.6)	10 (2.1)	
FEV_1/FVC <LLN	76 (13.8)	54 (11.2)	0.2021
Severe	23 (4.2)	10 (2.1)	
Moderate	43 (7.8)	33 (6.8)	
Mild	10 (1.8)	11 (2.3)	
Respiratory medication	82 (14.9)	113 (23.4)	0.0005

Data are presented as n (%) or mean±SD, unless otherwise stated. COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; LLN: lower limits of normal.

TABLE 2 Characteristics of 130 subjects with a forced expiratory volume in one second/forced vital capacity less than the lower limit of normal based on the third National Health and Nutrition Examination Survey spirometry data

Characteristics	Males	Females	p-value
Subjects	76 (58)	54 (42)	
Age yrs	62.9±12.8	60.3±13.9	0.2807
Post-secondary education	17 (23.0)	11 (20.4)	0.7250
Smoking history pack-yrs	52.9±28.2	38.6±19.0	0.0008
Symptoms			
Shortness of breath	50 (65.8)	33 (61.1)	0.5843
Cough	32 (42.1)	14 (25.9)	0.0573
Phlegm	31 (40.8)	9 (16.7)	0.0033
Wheeze	46 (64.5)	32 (59.3)	0.5455
Disease			
Asthma	21 (27.6)	21 (40.4)	0.1312
COPD	9 (11.8)	6 (11.5)	0.9582
Emphysema	13 (17.3)	4 (7.7)	0.1166
Chronic bronchitis	14 (18.9)	13 (25.5)	0.3803
Medication	29 (38.2)	28 (51.9)	0.1210

Data are presented as n (%) or mean±SD, unless otherwise stated. COPD: chronic obstructive pulmonary disease.

To determine if airflow obstruction was more likely to be reversible in females than males, bronchodilator response was stratified by sex and severity of obstruction (table 4). No significant differences were found between the sexes.

DISCUSSION

Females were more likely than males to report respiratory symptoms, which is consistent with the recent findings of DE TORRES *et al.* [5]. In addition, the current authors found that females were more likely to have received a diagnosis of a chronic airway disease, and were more likely to be taking respiratory medications. One possible explanation is a sex difference in the severity or expression of the disease. More females than males reported breathlessness, which was not explained by age, smoking history or FEV_1. This relative increase in symptoms may explain the increased probability of being both diagnosed with lung disease and treated.

There also appears to be a sex-bias in the diagnosis of chronic bronchitis, which may influence population health statistics for respiratory disease. The defining symptom of bronchitis is mucus hypersecretion from the chest and does not require airflow obstruction to be present [10]. Although males generally reported more sputum production, consistent with this diagnosis, females in the present study were more likely to be labelled as having chronic bronchitis. American national population database studies have also reported a greater prevalence of chronic bronchitis in females compared with males [3]. The current results suggest that this observed difference may not reflect differences in mucus hypersecretion, but rather a physician diagnostic bias.

TABLE 3 Prevalence of taking at least one respiratory medication by sex and severity in obstructed patients

Degree of obstruction	Males:females	Definition of obstruction	Prevalence		p-value
			Males	Females	
None	474:429	$FEV_1/FVC \geqslant LLN$	53 (11.2)	84 (19.6)	0.0004
Mild	10:11	$FEV_1/FVC < LLN$; $FEV_1 \geqslant 80\%$	1 (10.0)	3 (27.3)	0.5865
Moderate	43:33	$FEV_1/FVC < LLN$; $50\% \leqslant FEV_1 < 80\%$	12 (27.9)	18 (54.6)	0.0185
Severe	23:10	$FEV_1/FVC < LLN$; $FEV_1 < 50\%$	16 (69.6)	7 (70.0)	1.0000

Data are presented as n or n (%), unless otherwise stated. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; LLN: lower limit of normal.

TABLE 4 Bronchodilator response by sex and severity of obstruction

Degree of obstruction	Males:females	Definition of obstruction	Mean bronchodilator response		p-value
			Males	Females	
Mild	5:7	$FEV_1/FVC < LLN$; $FEV_1 \geqslant 80\%$	5.1±5.5	1.6±2.7	0.1689
Moderate	40:33	$FEV_1/FVC < LLN$; $50\% \leqslant FEV_1 < 80\%$	7.0±10.3	7.7±12.1	0.7815
Severe	20:10	$FEV_1/FVC < LLN$; $FEV_1 < 50\%$	12.6±12.0	8.6±6.6	0.3457

Data are presented as n or mean±SD, unless otherwise stated. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; LLN: lower limit of normal.

It is not possible to determine if the prevalence of asthma was truly higher in the female study population or whether there was a reporting bias. Self-reported asthma and bronchial hyperresponsiveness are known to be more common in adult females than adult males [11, 12]. CHAPMAN *et al.* [13] reported that clinicians presented with hypothetical cases were more likely to diagnose asthma in females than males despite similar age, smoking histories and symptoms. The present results also suggest a sex-bias in diagnosing asthma. Females were twice as likely as males to be diagnosed with asthma although bronchodilator responsiveness did not differ between the two groups. Females have been reported to use primary-care services with greater frequency, but to receive fewer specialist referrals than males and to be less likely than males to be referred for invasive cardiac procedures [4, 14, 15]. These findings raise the expectation that females may also be relatively under-treated for respiratory disease. The current authors found the opposite to be true. Females were more likely to be prescribed respiratory medications until severe obstruction was present (table 3). Males may be relatively under-treated at milder stages of airflow obstruction.

The two different criteria used to define airflow obstruction affected males and females differently in the present study. The FEV_1/FVC ratio decreases with age among healthy adults. Elderly people without respiratory disease may have a FEV_1/FVC within the LLN defined by a healthy reference population, yet have a FEV_1/FVC <70% pred. This scenario occurred more often in males than females in the present study because the mean age of males was 62 *versus* 56 yrs for females.

In conclusion, the current authors found that sex differences in symptom reporting, diagnoses and management of respiratory illness exist in primary-care practices. Physician awareness of this issue may help reduce this presumably unintentional bias. It may stem from a difference in the prevalence of breathlessness, a subjective indicator. Perhaps increased use of spirometry, an objective measure, would reduce the sex-related biases and improve diagnosis and management of airway diseases in the primary-care practice setting.

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