Sex Differences in Severe Pulmonary Emphysema

Fernando J. Martinez[1], Jeffrey L. Curtis[1], Frank Sciurba[2], Jeanette Mumford[3], Nicholas D. Giardino[4], Gail Weinmann[5], Ella Kazerooni[6], Susan Murray[3], Gerard J. Criner[7], Donald D. Sin[8], James Hogg[8], Andrew L. Ries[9], MeiLan Han[1], Alfred P. Fishman[10], Barry Make[11], Eric A. Hoffman[12], Zab Mohsenifar[13], and Robert Wise[14], for the National Emphysema Treatment Trial Research Group*

[1]University of Michigan, Division of Pulmonary and Critical Care Medicine, Ann Arbor, Michigan; [2]University of Pittsburgh, Division of Pulmonary and Critical Care Medicine, Pittsburgh, Pennsylvania, [3]University of Michigan School of Public Health, Department of Biostatistics, Ann Arbor, Michigan; [4]University of Michigan, Department of Psychiatry, Ann Arbor, Michigan; [5]National Heart, Lung and Blood Institute, Division of Lung Diseases, Bethesda, Maryland; [6]University of Michigan, Department of Radiology, Ann Arbor, Michigan; [7]Temple University, Division of Pulmonary and Critical Care Medicine, Philadelphia, Pennsylvania; [8]University of British Columbia, Respiratory Department, Vancouver, British Columbia, Canada; [9]University of California, Department of Medicine, San Diego, California; [10]University of Pennsylvania, Office of Program Development, Philadelphia, Pennsylvania; [11]National Jewish Medical & Research Center, Division of Pulmonary Sciences and Critical Care Medicine, Denver, Colorado; [12]University of Iowa, Department of Radiology, Iowa City, Iowa; [13]Cedars-Sinai Medical Center, Division of Pulmonary Medicine, Los Angeles, California; and [14]Johns Hopkins University, Division of Pulmonary and Critical Care Medicine, Baltimore, Maryland

***Rationale*: Limited data on sex differences in advanced COPD are available.**

***Objectives*: To compare male and female emphysema patients with severe disease.**

***Methods*: One thousand fifty-three patients (38.8% female) evaluated for lung volume reduction surgery as part of the National Emphysema Treatment Trial were analyzed.**

***Measurements and Main Results*: Detailed clinical, physiological, and radiological assessment, including quantitation of emphysema severity and distribution from helical chest computed tomography, was completed. In a subgroup (n = 101), airway size and thickness was determined by histological analyses of resected tissue. Women were younger and exhibited a lower body mass index (BMI), shorter smoking history, less severe airflow obstruction, lower $D_{L_{CO}}$ and arterial P_{O_2}, higher arterial P_{CO_2}, shorter six-minute walk distance, and lower maximal wattage during oxygen-supplemented cycle ergometry. For a given FEV_1% predicted, age, number of pack-years, and proportion of emphysema, women experienced greater dyspnea, higher modified BODE, more depression, lower SF-36 mental component score, and lower quality of well-being. Overall emphysema was less severe in women, with the difference from men most evident in the outer peel of the lung. Females had thicker small airway walls relative to luminal perimeters.**

***Conclusions*: In patients with severe COPD, women, relative to men, exhibit anatomically smaller airway lumens with disproportionately thicker airway walls, and emphysema that is less extensive and characterized by smaller hole size and less peripheral involvement.**

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*A complete list of NETT members may be found before the REFERENCES.

Correspondence and requests for reprints should be addressed to Fernando J. Martinez, M.D., M.S., 1500 E. Medical Center Drive, 3916 Taubman Center, University of Michigan Health System, Ann Arbor, MI 48109-0360. E-mail: Fmartine@umich.edu

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Sex differences in chronic obstructive pulmonary disease are increasingly recognized.

What This Study Adds to the Field

In patients with severe COPD, women, relative to men, exhibit anatomically smaller airway lumens with disproportionately thicker airway walls, and emphysema that is less extensive and characterized by smaller hole size and less peripheral involvement.

Keywords: chronic obstructive pulmonary disease; emphysema; computed tomography; pulmonary function; gender

The prevalence and mortality of chronic obstructive pulmonary disease (COPD) in female smokers is rapidly increasing (1). Female smokers are more likely than men to report respiratory symptoms (2–4) and exhibit greater baseline airway responsiveness to methacholine (5). Indirect evidence suggests that women may be more predisposed to develop smoking-induced lung function impairment (4, 6, 7) and experience greater mortality (8). Despite these compelling data, COPD continues to be underdiagnosed in women (9), and research into sex differences in advanced COPD remains limited (4, 10, 11). Using carefully characterized patients from the National Emphysema Treatment Trial (NETT), we hypothesized that differences in disease expression in severe emphysema would be identified between males and females. Specifically, we sought to examine differences in the symptomatic, physiological, radiological, and histological expression of emphysema.

METHODS

Patient Selection

The study group consisted of 1,053 patients randomized at 17 NETT clinics (12) in whom baseline high resolution computed chest tomographs (HRCT) were available for analysis at the Imaging Analysis Center of the University of Iowa (*see below*). The design and methods of the trial have been detailed previously (12, 13); major enrollment criteria are enumerated in the online supplement.

Clinical Assessment

Demographic data and medical history were collected using standardized instruments. Health status was assessed using general and disease-specific instruments. Dyspnea was quantified using the University of California, San Diego Shortness of Breath Questionnaire (UCSD SOBQ) (14). Depression was assessed using the Beck Depression Inventory (15).

Physiological Testing

Patients underwent spirometry before and after albuterol administration, while plethysmographic lung volumes were measured after albuterol administration. Diffusing capacity and arterial blood gases were also measured. The protocol for 6-minute walk testing (6MWT) has been described (16). Maximal exercise capacity was measured using a cycle ergometer. A multidimensional index, the BODE, was modified using previously described methodology (mBODE) (17).

Diagnostic Imaging Studies

Emphysema severity and distribution was determined from chest computed tomography (CT) scans obtained at full inspiration. After segmenting and dividing the lung according to previously described protocols (18), images were analyzed using custom-built software, the Pulmonary Analysis Software Suite (PASS). The density histogram was plotted, with values less than −950 HU corresponding to severe emphysema and regions with values of −910 HU and −850 HU roughly equating to moderate and mild emphysema, respectively. The alpha value (inverse slope) was determined from the log–log relationship of hole size versus number of holes (19). Lungs with greater proportions of small lesions have a steep negative slope and a large alpha.

Histological Assessment

Lung tissue was available for analysis in 101 subjects from five centers (Baylor, Colorado, Michigan, Pittsburgh, and Temple). Previous reports have described the methods used to process the tissue and to estimate airways remodeling and luminal occlusion by inflammatory exudates containing mucus (20). We examined cross sections of airways < 2 mm in diameter. Maximal lumen area was calculated (18, 21). Wall thickness included the area between the epithelial luminal surface and the connective tissue at the outer limit of the adventitia. The fractional areas (Vv) taken up by epithelium, lamina propria, the smooth muscle itself, and the adventitia were also measured. The ratio of tissue area to basement membrane length was used to express the volume to surface (V/S) ratio or thickness of the airway wall and its compartments.

Statistical Analysis

Continuous data were compared using *t* tests. Multivariate linear regression models were used to assess the relationships between sex and dependent variables of FEV_1% predicted, mBODE, dyspnea, depression, health status scores, whole-lung emphysema, and whole-lung alpha. Potential confounders included age, number of pack-years, whole-lung emphysema proportions, and FEV_1% predicted (confounder excluded when it was the dependent variable in the model). mBODE or inspiratory capacity (IC)/TLC were also explored as confounders when appropriate. All sex comparisons of airway wall and its compartments were performed using a mixed hierarchical model, which accounted for the clustering of airway analysis within subjects (Proc Mixed, version 9.1; SAS, Carey, NC).

RESULTS

Patient Demographics and Baseline Physiology

Compared with males, female subjects were slightly younger, had a slightly lower mean Body Mass Index (BMI), and reported significantly shorter smoking histories and an older age at the time of smoking onset (Table 1). Women exhibited slightly less severe airflow obstruction but a similar TLC, slightly lower diffusing capacity (D_{LCO}), IC/TLC, Pa_{O_2}, and higher Pa_{CO_2}. The difference in Pa_{O_2} persisted when adjusted for differences in Pa_{CO_2} (difference −2.21 mm Hg; 95% confidence interval [95% CI], −3.44, −0.98; $P = 0.0004$). The 6MWT and maximal exercise capacity were lower in women. Men exhibited slightly lower α_1-antitrypsin levels than women (Table 1), although the distribution of α_1 genotypes was not different ($P = 0.44$, data not shown). In the cohort there were only 16 patients felt to be α_1-deficient; in this group, only two were females.

After adjusting for age, pack-years of smoking, and whole-lung emphysema proportion, women showed a higher prebronchodilator FEV_1% predicted than men (mean FEV_1% predicted 2.98% greater; 95% CI, 2.19, 3.78; $P < 0.0001$). Although the results were not statistically confirmed when predicted values of Hankinson and coworkers (22) were substituted for those of Crapo and colleagues (23–25), the direction remained suggestive (mean FEV_1% predicted 0.69% greater; 95% CI, −0.14, 1.51; $P = 0.10$). All interactions involving sex and other predictors in the model were investigated; none were found to be significant. Results were similar when postbronchodilator FEV_1 was examined (data not shown). Lower D_{LCO} in females remained significant (−2.79% pred; 95% CI, −3.99, −1.58) after adjustment for whole lung emphysema proportion, age, and pack-years of smoking.

Breathlessness, Depression, and Health Status

Female patients noted greater breathlessness (UCSD SOBQ) and depression (Beck total score), and lower SF-36 mental component score (MCS) (Table 1). Increased breathlessness in women (average adjusted UCSD SOBQ score 5.03 higher; 95% CI, 2.57–7.49) remained significant ($P < 0.0001$) after adjusting for age, FEV_1% predicted, whole-lung emphysema proportion, and pack-years (Table 2). Results were similar when postbronchodilator FEV_1 was used in the models (data not shown), although they were less evident when the IC/TLC was included in the model (*see* Table E1 in the online supplement).

In separate multivariate models predicting total Beck score (Table 2) and SF-36 MCS (Table 2), significant interactions between age and sex were found after adjusting for FEV_1% predicted, whole-lung emphysema proportion, and pack-years. These sex interactions remained when the FEV_1 was replaced by the IC/TLC score or the mBODE (Tables E1 and E2). Based on these interaction analyses, our data suggest that women under the age of 79.2 years tended to have a higher total Beck score than men, but as age increased, the total Beck score tended to decrease more rapidly in women than in men (Figure 1A). Similarly, women under the age of 73.5 years tended to have a lower SF-36 MCS than men of the same age, with the disparity between sexes decreasing with age (Figure 1B). These strong sex interactions remained evident after adjustment for mBODE scores (Figure E1). No other interactions with sex were found to be significant in Table 2.

Few differences were noted between sexes in health status, as assessed by the SF-36 physical component score or the SGRQ, in either univariate or multivariate analyses (Table 2). In univariate analysis, QWB was marginally lower in women than men ($P = 0.05$). In the multivariate setting (Table 2), the statistical significance of the association of QWB with female sex increased after adjusting for confounders (on average females lower by 0.02; 95% CI, −0.003, 0.036 lower; $P = 0.02$). Results were quantitatively similar using both sets of predicted values for FEV_1. When postbronchodilator FEV_1 was used in modeling the association of QWB and sex, it became marginally significant (0.001; 95% CI, −0.00001, 0.0002; $P = 0.05$).

Radiographic Assessment of Emphysema Proportion and Distribution

The proportion of whole-lung emphysema in women was lower using a threshold that identifies moderate emphysema (−910 HU,

TABLE 1. BASELINE CHARACTERISTICS FOR PATIENTS WITH SEVERE EMPHYSEMA

Parameter	Men (n = 644) Mean (SD)	Women (n = 409) Mean (SD)	P Value
Demographics/Laboratory			
Age, yr	67.0 (6.2)	65.4 (6.1)	0.0001
BMI, kg/m^2	25.0 (3.7)	24.4 (4.2)	0.007
Pack-years	71.1 (32.3)	54.8 (24.2)	0.0001
Age at onset of smoking habit, yr	16.0 (3.7)	17.7 (3.9)	< 0.0001
α_1-antitrypsin, mg/dl	152.4 (36.0)	163.0 (37.5)	< 0.0001
Physiology*			
Pre BD FEV_1, ppd	22.7 (6.4)	25.6 (6.2)	0.0001
Post BD FEV_1, ppd	25.9 (7.1)	29.0 (6.6)	< 0.0001
(Post BD FEV_1-Pre BD FEV_1)/Pre BD FEV_1	0.15 (0.13)	0.15 (0.14)	0.50
Post BD FEV_1ppd –Pre BD FEV_1ppd	3.23 (2.80)	3.46 (3.15)	0.22
TLC, ppd	128.3 (13.9)	129.3 (14.8)	0.28
$D_{L_{CO}}$, ppd	29.3 (10.0)	27.2 (9.0)	0.0005
6MWT, ft	1185.5 (322.5)	1076.7 (291.7)	0.0001
Maximum load, watts	43.0 (22.4)	26.2 (14.4)	< 0.0001
Pa_{O_2}, mm Hg	65.8 (10.13)	62.8 (10.30)	< 0.0001
Pa_{CO_2}, mm Hg	42.2 (5.17)	43.3 (5.40)	0.0008
IC/TLC	0.23 (0.06)	0.21 (0.06)	< 0.0001
Symptoms and Health Status			
UCSD SOBQ	64.0 (18.9)	67.4 (18.8)	0.005
SF-36 PCS	28.4 (7.7)	28.5 (7.6)	0.92
SF-36 MCS	53.1 (10.8)	51.6 (10.8)	0.03
QWB	0.542 (0.120)	0.527 (0.127)	0.05
SGRQ overall score	56.4 (13.0)	56.2 (13.2)	0.79
Beck Total Score	8.7 (5.59)	10.4 (6.90)	0.0001
Multidimensional Index			
mBODE	5.27 (1.59)	5.72 (1.59)	< 0.0001
Imaging			
Whole lung emphysema proportion			
−950 HU threshold	0.16 (0.11)	0.15 (0.11)	0.07
−910 HU threshold	0.44 (0.12)	0.41 (0.12)	0.0001
Alpha			
−950 HU threshold	1.02 (0.20)	1.06 (0.24)	0.001
−910 HU threshold	0.71 (0.12)	0.74 (0.14)	0.01
Whole lung peel emphysema proportion at −950 HU	0.123 (0.091)	0.105 (0.086)	0.002
Whole lung core emphysema proportion at −950 HU	0.207 (0.128)	0.207 (0.138)	0.93

Definition of abbreviations: 6MWT = six minute walk test; BD = bronchodilator; BMI = body mass index; $D_{L_{CO}}$ = diffusing capacity for carbon monoxide; HU = Hounsfield Unit; IC = inspiratory capacity; maximum load = maximal exercise capacity measured on cycle ergometry while breathing 30% F_IO_2; mBODE = modified BODE; MCS = mental component scale; Pa_{O_2} = room air resting Pa_{O_2} in mm Hg; Pa_{CO_2} = room air resting Pa_{CO_2} in mm Hg; ppd = percent predicted; PCS = physical component scale; QWB = quality of well-being; SF-36 = Short form 36 health survey; SGRQ = St. George's Respiratory Questionnaire; UCSD SOBQ = University of California, San Diego Shortness of Breath Questionnaire.

*Physiologic predicted values of Crapo and coworkers (23–25).

$P < 0.0001$), and marginally lower using a threshold for severe emphysema (−950 HU, $P = 0.07$) (Table 1). These associations were maintained in multivariate models (Table 3) (on average 3% less moderate emphysema; 95% CI, 1.4–4.6% less; $P = 0.0002$, on average 16.4% less severe emphysema; 95% CI, 0.2–30.5% less; $P = 0.02$). Postbronchodilator FEV_1 was significant when included in the model identifying severe emphysema (−950 HU) (−0.001; 95% CI, −0.002, −0.0002, $P = 0.01$), while other differences were unchanged. These results remained qualitatively similar when the FEV_1 was replaced by the IC/TLC (Table E3) and the mBODE (Table E4). Similarly, women exhibited significantly higher whole-lung alpha value using either emphysema threshold (Tables 1 and 3). No significant interactions of other covariates with sex were found in any of the multivariate models in Table 3. When the analyses were adjusted for IC/TLC (Table E3) and mBODE (Table E4) in place of FEV_1, the direction of these differences was similar.

Emphysema distribution also differed between sexes (Table 1). Women showed a similar proportion of emphysema in the core of the lung ($P = 0.93$) but a lower proportion in the peel ($P = 0.002$). Results were quantitatively similar using both sets of predicted values for FEV_1.

Histological Assessment

The small airways of the female lung had a reduced basement membrane length (PI) compared with male lungs, but only marginally lower total wall area (Table 4). This disparity resulted in clear sex differences ($P < 0.05$) in estimates of thickness obtained from the ratio of wall area/PI for the total wall and its epithelial and adventitial compartments.

DISCUSSION

This retrospective analysis of a large, prospectively studied cohort of patients with severe COPD enrolled in a clinical trial of lung volume reduction surgery documents sex-specific disparities in symptom severity, health status, and distribution of pathologic changes assessed using both radiological and histological techniques. For a given age, FEV_1% predicted, smoking history, and proportion of emphysema, women experienced greater dyspnea,

TABLE 2. MULTIVARIATE LINEAR REGRESSION MODELS PREDICTING THE mBODE, DYSPNEA, BECK DEPRESSION SCORES, AND HEALTH STATUS IN PATIENTS WITH SEVERE EMPHYSEMA (N = 1,053)

	Parameter Estimate	95% Confidence Interval	*P* Value
Modified BODE			
Intercept	5.69	(4.47, 6.90)	< 0.0001
Age	−0.02	(−0.04, −0.003)	0.02
Whole lung emphysema proportion, −910 HU	0.01	(0.005, 0.02)	0.002
Pack-years	0.002	(−0.001, 0.006)	0.19
Female sex	0.42	(0.20, 0.64)	0.0002
UCSD SOBQ			
Intercept	98.22	(84.8, 111.68)	< 0.0001
FEV_1, % predicted	−0.59	(−0.77, −0.41)	< 0.0001
Age, yr	−0.31	(−0.50, −0.13)	0.001
Whole lung emphysema proportion, −910 HU	−5.57	(−14.8, 3.68)	0.24
Pack-years	0.036	(−0.001, 0.07)	0.06
Female sex	5.03	(2.57, 7.49)	< 0.0001
Beck Total score			
Intercept	12.56	(7.18, 17.9)	< 0.0001
FEV_1, % predicted	−0.05	(−0.11, 0.01)	0.09
Age, yr	−0.07	(−0.15, 0.002)	0.06
Whole lung emphysema proportion, −910 HU	0.40	(−2.63, 3.43)	0.80
Pack-years	0.03	(0.02, 0.04)	< 0.0001
Female sex	11.09	(3.02, 19.2)	0.007
Age, yr · female sex	−0.14	(−0.26, −0.01)	0.03
SF-36 Physical component score			
Intercept	12.82	(7.27, 18.4)	< 0.0001
FEV_1, % predicted	0.06	(−0.01, 0.14)	0.11
Age, yr	0.20	(0.12, 0.28)	< 0.0001
Whole lung emphysema proportion, −910 HU	2.49	(−1.33, 6.30)	0.20
Pack-years	−0.004	(−0.02, 0.01)	0.64
Female sex	0.20	(−0.82, 1.21)	0.70
SF-36 Mental component score			
Intercept	52.52	(42.9, 62.1)	< 0.0001
FEV_1, % predicted	0.03	(−0.07, 0.14)	0.56
Age, yr	0.02	(−0.12, 0.15)	0.80
Whole lung emphysema proportion, −910 HU	2.76	(−2.64, 8.16)	0.32
Pack-years	−0.04	(−0.06, −0.01)	0.002
Female sex	−19.1	(−33.50, −4.74)	0.009
Age, yr · female sex	0.26	(0.04, 0.48)	0.02
QWB Score			
Intercept	0.394	(0.304, 0.483)	< 0.0001
FEV_1, % predicted	0.0008	(−0.0004, 0.002)	0.17
Age, yr	0.002	(0.0007, 0.003)	0.002
Whole lung emphysema proportion, −910 HU	0.056	(−0.005, 0.117)	0.07
Pack-years	−0.0004	(−0.0006, −0.001)	0.003
Female sex	-0.02	(−0.036, −0.003)	0.02
SGRQ Total Score			
Intercept	90.61	(81.31, 99.91)	< 0.0001
FEV_1, % predicted	−0.24	(−0.36, −0.11)	0.0002
Age, yr	−0.41	(−0.54, −0.28)	< 0.0001
Whole lung emphysema proportion, −910 HU	−7.69	(−14.09, −1.30)	0.02
Pack-years	0.03	(−0.0005, 0.05)	0.05
Female sex	0.02	(−1.68, 1.72)	0.98

Definition of abbreviations: HU = Hounsfield Unit; QWB = quality of well-being; SF-36 = Short form 36 health survey; UCSD SOBQ University of California, San Diego Shortness of Breath Questionnaire.

higher mBODE scores, higher depression scores, a lower SF-36 MCS, and a lower quality of well-being than men. Women also showed less severe overall emphysema than men, particularly in the lung peel, and smaller emphysema hole size, even with adjustment for FEV_1% predicted, age, and smoking history. The small (< 2 mm diameter) airways of women had relatively thicker walls and disproportionately reduced airway lumens. By simultaneously correlating symptoms with carefully standardized physiological, radiological, and histological data, these results for the first time unite several previously separate lines of investigation in women's health and COPD.

These data showing greater breathlessness in women relative to men at similar degrees of airflow obstruction and emphysema severity are important because they imply that sex-specific anatomic differences must be considered in models of COPD pathogenesis. Interestingly, this difference was less evident after adjustment in IC/TLC, suggesting that part of this difference may relate to differences in lung volume. Our data agree with population-based studies in which women reported greater respiratory symptoms (3, 26–31), with two multinational studies based on physician-reported COPD, in which women were more likely to report severe dyspnea (2, 32), and with two case-control

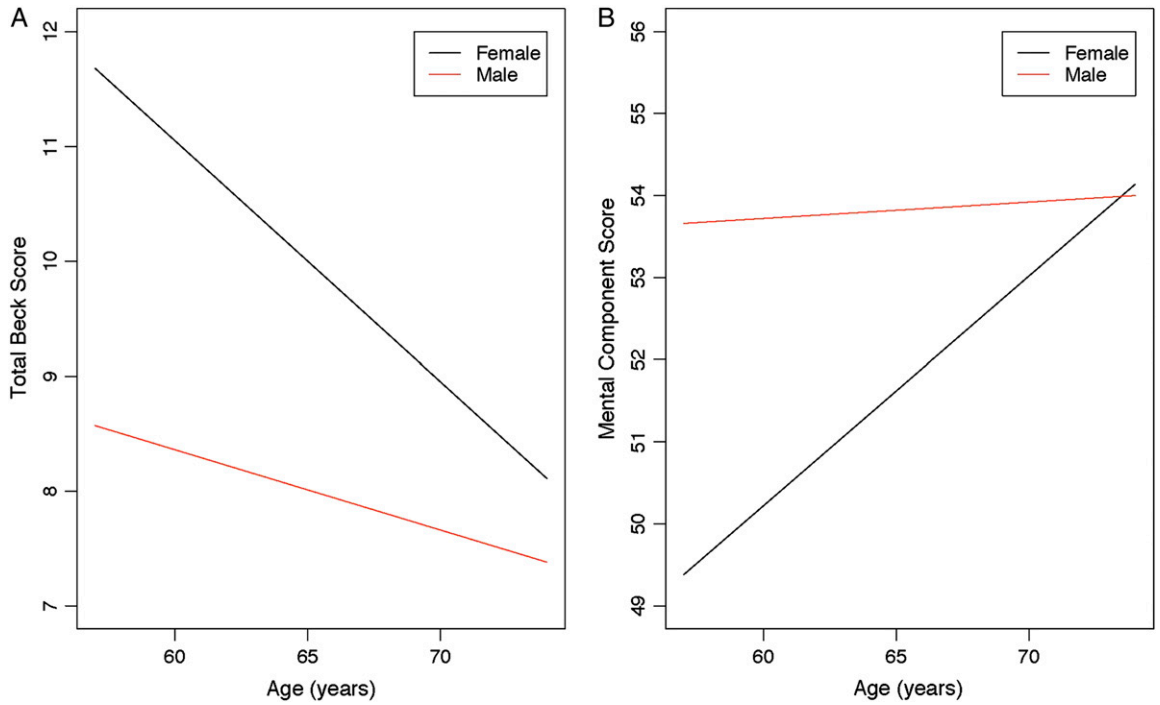

Figure 1. (*A*) Relationship of total Beck score (*y* axis) to age (*x* axis) when FEV_1% predicted, whole-lung % emphysema proportion, and pack-years are held constant. An interaction of age and sex is evident, and is significant ($P = 0.03$). (*B*) Relationship of SF-36 Mental Component Score (*y* axis) to age (*x* axis) when FEV_1% predicted, whole-lung % emphysema proportion, and pack-years are held constant. An interaction of age and sex is evident and is significant ($P = 0.02$).

studies (33, 34). The magnitude of difference in breathlessness in multivariate modeling in our data was above the level felt to be a minimal clinically important difference with this instrument (35). When the dyspnea score was incorporated in a validated multidimensional index (36), the mBODE (17), we also found that women exhibited higher scores than men. Extending these findings using state-of-the-art quantitative CT imaging and histological techniques, our results lay the groundwork to integrate

TABLE 3. MULTIVARIATE MODELS PREDICTING EMPHYSEMA PROPORTION IN PATIENTS WITH SEVERE EMPHYSEMA (N = 1,053)

	Parameter Estimate	95% Confidence Interval	*P* Value
Whole-lung emphysema proportion (−950 HU)			
Intercept	0.270	(0.197, 0.341)	< 0.0001
FEV_1, % predicted	−0.0008	(−0.0018, 0.0003)	0.16
Age, yr	−0.001	(−0.0021, 0.00006)	0.06
Pack-years	−0.0003	(−0.0005, −0.00007)	0.01
Female sex	−0.164	(−0.305, −0.002)	0.02
Whole-lung emphysema proportion (−910 HU)			
Intercept	0.564	(0.483, 0.645)	< 0.0001
FEV_1, % predicted	−0.0025	(−0.004, −0.001)	< 0.0001
Age, yr	−0.0007	(−0.002, 0.0005)	0.28
Pack-years	−0.0004	(−0.0006, −0.0001)	0.004
Female sex	−0.030	(−0.046, −0.014)	0.0002
Whole-lung alpha (−950 HU)			
Intercept	0.87	(0.73, 1.01)	< 0.0001
FEV_1, % predicted	0.0001	(−0.002, 0.002)	0.96
Age, yr	0.002	(−0.0005, 0.004)	0.14
Pack-years	0.0005	(0.0001, 0.001)	0.02
Female sex	0.06	(0.03, 0.08)	< 0.0001
Whole-lung alpha (−910 HU)			
Intercept	0.60	(0.52, 0.69)	< 0.0001
FEV_1, % predicted	0.002	(0.0006, 0.003)	0.004
Age, yr	0.0006	(−0.0007, 0.002)	0.36
Pack-years	0.0003	(0.00007, 0.0006)	0.01
Female sex	0.02	(0.006, 0.04)	0.009

Definition of abbreviation: HU = Hounsfield Unit.

TABLE 4. HISTOLOGICAL FINDINGS IN MEN AND WOMEN WHO UNDERWENT VOLUME REDUCTION SURGERY IN THE NETT (N = 101)

	Males Mean (SD)	Females Mean (SD)	*P* Value
Number	59	42	
Age, yr	65.2 ± 6.4	66.3 ± 5.7	0.458
FEV_1, % predicted	24.5 ± 6.7	29.7 ± 7.0	0.001
Pack-years	71.7 ± 29.9	54.4 ± 19.8	0.003
Pi, mm*	2.63 (1.26)	2.37 (1.33)	0.026
Total wall area, mm^2	0.433 (0.301)	0.379 (0.327)	0.090
Total wall area/Pi*	0.256 (0.066)	0.267 (0.072)	0.040
Epithelium/Pi*	0.119 (0.026)	0.122 (0.031)	0.052
Muscle/Pi*	0.096 (0.029)	0.094 (0.029)	0.530
Lamina propria /Pi*	0.100 (0.034)	0.098 (0.031)	0.929
Adventitia/Pi*	0.175 (0.059)	0.190 (0.064)	0.004

* Expressed as square root of tissue area divided by the length of the basement membrane (Pi).

population-based COPD research with current concepts on the neuropsychological responses to stress and the molecular pathogenesis of inflammation.

Sex-specific Parenchymal and Airway Abnormalities in Relation to Airflow Limitation

The significant differences in the amount and distribution of emphysema in women compared with men are novel findings that encompass both severe (< -950 HU) and less severe (< -910 HU) emphysema. Few studies have examined the severity or distribution of emphysema in women with severe COPD. In a population-based study, patients with clinically defined emphysema were primarily male, whereas patients with chronic asthmatic bronchitis were predominantly female (37). Using state-of-the-art CT imaging, we confirm that emphysema is less severe in women, especially distally, and when present, is characterized by smaller hole size. Although the absolute differences between the sexes were modest, all analyses were remarkably consistent in their direction. Furthermore, in multivariate analysis adjusting for FEV_1, IC/TLC, mBODE, smoking history, and age, the proportion of severe emphysema was significantly lower in women, suggesting distinct differences in emphysema severity and distribution.

Whether comparable degrees of cigarette smoking induce greater reductions in lung function in female smokers is controversial, with data for (6, 26, 38–40) and against (41–43) that premise. Based on the ability to adjust for the proportion of emphysema, we noted a higher FEV_1% predicted in women at a given duration of cigarette smoking, and no significant interaction between sex and smoking history. Women in our cohort initiated smoking at a later age than men. Given their lower mean age at the time of randomization, these changes are consistent with those reported by other investigators (http://www.cdc.gov/tobacco/sgr/sgr_forwomen/pdfs/chp2.pdf), and may explain the lesser total pack-years of cigarette smoke exposure. Because our patients were selected for severe chronic airflow obstruction and an emphysematous phenotype, our data do not exclude the possibility that lung function deteriorates faster in female smokers during earlier stages of COPD (6, 26, 38–40, 44, 45). We noted a lower D_{LCO} in women despite lesser anatomic emphysema. This finding may relate to the complex contributions of lung mechanics and gas exchange which contribute to D_{LCO}. Interestingly, previous studies have identified a differential impact of central relative to distal emphysema on D_{LCO} (46). Thus, differences in emphysema distribution identified in women in the current study may help explain the differences in D_{LCO}.

The similarity between the sexes seen in FEV_1% predicted implies that women should have a greater degree of peripheral airway pathology (20). Indeed, using validated morphometric techniques to analyze airway histology in a subset of our patients with similar airflow obstruction and smoking history to the entire cohort, we confirm that women have smaller airway lumens and disproportionately thicker airway walls than men. This change would be anticipated to alter airway compliance and increase airways resistance. Theoretical analysis of the effect of airway wall thickness on resistance indicates that in proportion to the change in lumen radius even a minor thickening of the airway wall amplifies the effect of muscle shortening on lumen caliber and increases resistance of the airways (47).

Sex Differences in Health Status and Depression in Advanced COPD

Women in our study had worse health status, reflected in a lower QWB, although SF-36 PCS and SGRQ scores were similar in both sexes. These data are congruent with the limited data on sex differences in health status in COPD (48), which found that women expressed greater dissatisfaction with their lives (49), and were more likely to categorize their global self-reported health as "not very well" than as "well" (30). Recently, a small case control study suggested worse SGRQ in women (33), although this finding was not supported by others (34, 50). Women might report greater respiratory symptoms and worse health status because they perceive a given physiological perturbation differently (51).

Women in our study exhibited greater depression and significantly worse SF-36 MCS scores. In addition, age and sex interacted, with younger women exhibiting significantly greater Beck and lower SF-36 MCS scores than older women; this trend was much less evident in males. The magnitude of the difference in multivariate modeling is within the range identified for mild depression (15). Sex differences in depressive symptoms have recently been reported in COPD (34, 52). Furthermore, depression may potentiate the sensation of breathlessness (34, 53). Similar interactions between age and sex on depression have been reported previously in healthy subjects (54). Several explanations have been proposed for age and sex differences in depression, including differences in defensiveness and rumination, respectively (54). Older adults exhibit greater defensiveness (55) and an increased ability to regulate emotions (56). Importantly, women show greater defensiveness than men with increasing age. Rumination is associated with increased depression, is more common in women, and among women is inversely related to age (57). Younger women's tendencies to feel less control over emotions and negative events, and feel a greater responsibility for the emotional tone of relationships, may mediate the relationship between rumination and depression (58). However, in another recent study (59) rumination and depression were positively associated with peripheral blood lymphocyte, leukocyte, and B cell counts, as well as health care utilization, in healthy older adults but not in younger adults. Our data cannot provide a mechanistic explanation for the reported differences, but suggest that additional investigation in this area is required.

Potential Sex-specific Differences in Smaller Airways and Parenchyma

Why cigarette smoking differentially affects the airways and lung parenchyma of men versus women is unclear. Potential explanations include greater baseline airway hyperresponsiveness in women (5, 60–62) and differences in particulate deposition within the airways (2, 4). The magnitude and character of the inflammatory response to cigarette smoke is likely to be

affected by sex hormones, for which several leukocyte subsets have receptors. Progesterone induces cyclical changes in IL-8 production (63) and promotes a Th2 cytokine response (64). Cyclical changes in estradiol concentrations in women have been associated with changes in lung adrenergic receptor density and in concentrations of mucus, acetylcholine, and prostaglandin (4). Estradiol also increases T cell expression of receptors for CC chemokines and alters T cell homing patterns (65). Interestingly, analysis of bronchoalveolar fluid in healthy individuals showed a significantly increased percentage of CD4+ T cells in women over age 43, compared with men and with younger women (66). Idiopathic cough, associated with lymphocytic inflammation manifest as bronchoalveolar lymphocytosis, is seen predominately in older women (67). However, even though human innate and adaptive immune responses show complex degrees of sexual dimorphism that vary with the specific pathogen and over the life of the individual (68), current understandings of this dimorphism do not fully explain sex-based differences in COPD pathogenesis or phenotype, and most importantly, do not yet suggest opportunities for prevention or treatment.

Limitations of this study come from its highly selective sample population. All subjects were enrolled in NETT, a randomized trial of lung volume reduction surgery for patients with a predominantly emphysematous phenotype. As such, selection bias was imposed by requirements for sustained smoking cessation and absence of comorbidities or significant sputum production. Similarly, the requirement for severe emphysema limits generalizability to all patients with COPD, as does the potential of a referral bias varying by sex. On the other hand, no specific sex-related factors were included in the evaluation process or in the inclusion/exclusion criteria, which should minimize bias in the current analyses. The cross-sectional nature of the analyses also limits the ability to define mechanisms and distinct phenotypes. Nevertheless, the results of our study should be considered as hypothesis generating. It is possible that our findings on emphysema characteristics and airway abnormalities result principally from the greater size of the adult male lung. Importantly, sex differences in emphysema distribution and proportion persisted after extensive analyses adjusting for lung volume.

In summary, this study shows that women with severe COPD exhibit distinct disease manifestations than men. Relative to men, advanced COPD in women is characterized anatomically by smaller airway lumens and disproportionately thick airway walls, and by emphysema that is less extensive, manifest by smaller hole size and less peripheral involvement. These anatomic differences are accompanied by distinctive symptomatology. At a given FEV_1% predicted, age, and proportion of emphysema, female patients with COPD report greater breathlessness and depression, despite similar health status. Our data should motivate future studies to determine the complex interactions between biological and sociocultural factors (4) that contribute to these differences, and thus to provide a foundation for novel therapies to reduce the increasingly disproportionate burden of this common disease in women.

Conflict of Interest Statement: F.J.M. is a consultant for Altana Pharma and has received compensation greater than $10K. He has been a member of several Advisory Boards, CME committees and the Speaker's Bureau for Boehringer Ingelheim (BI), Pfizer, and GlaxoSmithKline (GSK). Total compensation per company is greater than $10K. In addition, he is on the advisory board for Novartis and speaker's bureau for Sepracor and Astra, receiving less than $10K per company. He has been an investigator for industry-sponsored studies for GSK, BI, and Actelion. J.L.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. F.S. does not have a financial relationship with a commercial entity that has aninterest in the subject of this manuscript. J.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. N.D.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. G.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. E.K. is a member of the GERRAF board, for which she receives $2,500 annually, and serves on the advisory board for GE, CT, and GE Healthcare, for which she has received less than $3,000 annually. S.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. G.J.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. D.D.S. has received honoraria for speaking engagements from Astra Zeneca (AZ) in 2004 ($3,000) and in 2005 ($11,000), and from GSK in 2004 ($8,000), in 2005 ($6,000), and in 2006 ($12,000). He has also received unrestricted research funding as either the principal investigator or co-principal investigator from GSK in 2004 for $1.5 million and from AZ in 2007 ($100,000). He has also received $1,500 from GSK for consultancy work in 2006. J.H. has acted as an advisor to Altana in February 2006, GSK in September 2006, and Sepicor in October 2006. He has served as a consultant for GSK and Bronchus Technologies in 2006. He has received grants through a peer reviewed Canadian Institutes of Health Research-industry sponsored program in which Merck and GSK have served as the industrial partners. He has received less than Can $20,000 as compensation for this work. A.L.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.P.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. B.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. E.A.H. is a founder and shareholder in VIDA Diagnostics, a company commercializing image analysis software used in this study. Z.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

The members of the National Emphysema Treatment Trial Research Group were as follows: *Office of the Chair of the Steering Committee, University of Pennsylvania, Philadelphia, PA*: Alfred P. Fishman, M.D. (Chair); Betsy Ann Bozzarello; Ameena Al-Amin. Clinical Centers: *Baylor College of Medicine, Houston, TX*: Marcia Katz, M.D. (Principal Investigator); Carolyn Wheeler, R.N., B.S.N. (Principal Clinic Coordinator); Elaine Baker, R.R.T., R.P.F.T.; Peter Barnard, Ph.D., R.P.F.T.; Phil Cagle, M.D.; James Carter, M.D.; Sophia Chatziioannou, M.D.; Karla Conejo-Gonzales; Kimberly Dubose, R.R.T.; John Haddad, M.D.; David Hicks, R.R.T., R.P.F.T.; Neal Kleiman, M.D.; Mary Milburn-Barnes, C.R.T.T.; Chinh Nguyen, R.P.F.T.; Michael Reardon, M.D.; Joseph Reeves-Viets, M.D.; Steven Sax, M.D.; Amir Sharafkhaneh, M.D.; Owen Wilson, Ph.D.; Christine Young, P.T.; Rafael Espada, M.D. (Principal Investigator 1996–2002); Rose Butanda (1999–2001); Minnie Ellisor (2002); Pamela Fox, M.D. (1999–2001); Katherine Hale, M.D. (1998–2000); Everett Hood, R.P.F.T. (1998–2000); Amy Jahn (1998–2000); Satish Jhingran, M.D. (1998–2001); Karen King, R.P.F.T. (1998–1999); Charles Miller III, Ph.D. (1996–1999); Imran Nizami, M.D. (Co-Principal Investigator, 2000–2001); Todd Officer (1998–2000); Jeannie Ricketts (1998–2000); Joe Rodarte, M.D. (Co-Principal Investigator 1996–2000); Robert Teague, M.D. (Co-Principal Investigator 1999–2000); Kedren Williams (1998–1999). *Brigham and Women's Hospital, Boston, MA*: John Reilly, M.D. (Principal Investigator); David Sugarbaker, M.D. (Co-Principal Investigator); Carol Fanning, R.R.T. (Principal Clinic Coordinator); Simon Body, M.D.; Sabine Duffy, M.D.; Vladmir Formanek, M.D.; Anne Fuhlbrigge, M.D.; Philip Hartigan, M.D.; Sarah Hooper, E.P.; Andetta Hunsaker, M.D.; Francine Jacobson, M.D.; Marilyn Moy, M.D.; Susan Peterson, R.R.T.; Roger Russell, M.D.; Diane Saunders; Scott Swanson, M.D. (Co-Principal Investigator, 1996–2001). *Cedars-Sinai Medical Center, Los Angeles, CA*: Rob McKenna, M.D. (Principal Investigator); Zab Mohsenifar, M.D. (Co-Principal Investigator); Carol Geaga, R.N. (Principal Clinic Coordinator); Manmohan Biring, M.D.; Susan Clark, R.N., M.N.; Jennifer Cutler, M.D.; Robert Frantz, M.D.; Peter Julien, M.D.; Michael Lewis, M.D.; Jennifer Minkoff-Rau, M.S.W.; Valentina Yegyan, B.S., C.P.F.T.; Milton Joyner, B.A. (1996–2002). *Cleveland Clinic Foundation, Cleveland, OH*: Malcolm DeCamp, M.D. (Principal Investigator); James Stoller, MD (Co-Principal Investigator); Yvonne Meli, R.N., (Principal Clinic Coordinator); John Apostolakis, M.D.; Darryl Atwell, M.D.; Jeffrey Chapman, M.D.; Pierre DeVilliers, M.D.; Raed Dweik, M.D.; Erik Kraenzler, M.D.; Rosemary Lann, L.I.S.W.; Nancy Kurokawa, R.R.T., C.P.F.T.; Scott Marlow, R.R.T.; Kevin McCarthy, R.C.P.T.; Pricilla McCreight, R.R.T., C.P.F.T.; Atul Mehta, M.D.; Moulay Meziane, M.D.; Omar Minai, M.D.; Mindi Steiger, R.R.T.; Kenneth White, R.P.F.T.; Janet Maurer, M.D. (Principal Investigator, 1996–2001); Terri Durr, RN (2000–2001); Charles Hearn, D.O. (1998–2001); Susan Lubell, P.A.-C. (1999—2000); Peter O'Donovan, M.D. (1998–2003); Robert Schilz, D.O. (1998–2002). *Columbia University, New York, NY in consortium with Long Island Jewish Medical Center, New Hyde Park, NY*: Mark Ginsburg, M.D. (Principal Investigator); Byron Thomashow, M.D. (Co-Principal Investigator); Patricia Jellen, M.S.N., R.N. (Principal Clinic Coordinator); John Austin, M.D.; Matthew Bartels, M.D.; Yahya Berkmen, M.D.; Patricia Berkoski, M.S., R.R.T. (Site coordinator, L.I.J.); Frances Brogan, M.S.N., R.N.; Amy Chong, B.S., C.R.T.; Glenda DeMercado, B.S.N.; Angela DiMango, M.D.; Sandy Do, M.S., P.T.; Bessie Kachulis, M.D.; Arfa Khan, M.D.; Berend Mets, M.D.; Mitchell O'Shea, B.S., R.T., C.P.F.T.; Gregory Pearson, M.D.; Leonard Rossoff, M.D.; Steven Scharf, M.D., Ph.D. (Co-Principal Investigator, 1998–2002); Maria Shiau, M.D.; Paul Simonelli, M.D.; Kim Stavrolakes, M.S., P.T.; Donna Tsang, B.S.; Denise Vilotijevic, M.S., P.T.; Chun Yip, M.D.; Mike Mantinaos, M.D. (1998–2001); Kerri McKeon, B.S., R.R.T., R.N. (1998–1999); Jacqueline Pfeffer, M.P.H., P.T. (1997–2002). *Duke University Medical Center, Durham, NC*: Neil MacIntyre, M.D. (Principal Investigator); R. Duane Davis, M.D. (Co-Principal Investigator); John Howe, R.N. (Principal Clinic Coordinator); R. Edward Coleman, M.D.; Rebecca Crouch, R.P.T.; Dora Greene; Katherine Grichnik, M.D.; David Harpole, Jr., M.D.; Abby Krichman,

R.R.T.; Brian Lawlor, R.R.T.; Holman McAdams, M.D.; John Plankeel, M.D.; Susan Rinaldo-Gallo, M.E.D.; Sheila Shearer, R.R.T.; Jeanne Smith, A.C.S.W.; Mark Stafford-Smith, M.D.; Victor Tapson, M.D.; Mark Steele, M.D. (1998–1999); Jennifer Norten, MD (1998–1999). *Mayo Foundation, Rochester, MN*: James Utz, M.D. (Principal Investigator); Claude Deschamps, M.D. (Co-Principal Investigator); Kathy Mieras, C.C.R.P. (Principal Clinic Coordinator); Martin Abel, M.D.; Mark Allen, M.D.; Deb Andrist, R.N.; Gregory Aughenbaugh, M.D.; Sharon Bendel, R.N.; Eric Edell, M.D.; Marlene Edgar; Bonnie Edwards; Beth Elliot, M.D.; James Garrett, R.R.T.; Delmar Gillespie, M.D.; Judd Gurney, M.D.; Boleyn Hammel; Karen Hanson, R.R.T.; Lori Hanson, R.R.T.; Gordon Harms, M.D.; June Hart; Thomas Hartman, M.D.; Robert Hyatt, M.D.; Eric Jensen, M.D.; Nicole Jenson, R.R.T.; Sanjay Kalra, M.D.; Philip Karsell, M.D.; Jennifer Lamb; David Midthun, M.D.; Carl Mottram, R.R.T.; Stephen Swensen, M.D.; Anne-Marie Sykes, M.D.; Karen Taylor; Norman Torres, M.D.; Rolf Hubmayr, M.D. (1998–2000); Daniel Miller, M.D. (1999–2002); Sara Bartling, R.N. (1998–2000); Kris Bradt (1998–2002). *National Jewish Medical and Research Center, Denver, CO*: Barry Make, M.D. (Principal Investigator); Marvin Pomerantz, M.D. (Co-Principal Investigator); Mary Gilmartin, R.N., R.R.T. (Principal Clinic Coordinator); Joyce Canterbury; Martin Carlos; Phyllis Dibbern, P.T.; Enrique Fernandez, M.D.; Lisa Geyman, M.S.P.T.; Connie Hudson; David Lynch, M.D.; John Newell, M.D.; Robert Quaife, M.D.; Jennifer Propst, R.N.; Cynthia Raymond, M.S.; Jane Whalen-Price, P.T.; Kathy Winner, O.T.R.; Martin Zamora, M.D.; Reuben Cherniack, M.D. (Principal Investigator, 1997–2000). *Ohio State University, Columbus, OH*: Philip Diaz, M.D. (Principal Investigator); Patrick Ross, M.D. (Co-Principal Investigator); Tina Bees (Principal Clinic Coordinator); Jan Drake; Charles Emery, Ph.D.; Mark Gerhardt, M.D., Ph.D.; Mark King, M.D.; David Rittinger; Mahasti Rittinger. *Saint Louis University, Saint Louis, MO*: Keith Naunheim, M.D. (Principal Investigator); Robert Gerber, M.D. (Co-Principal Investigator); Joan Osterloh, R.N., M.S.N. (Principal Clinic Coordinator); Susan Borosh; Willard Chamberlain, D.O.; Sally Frese; Alan Hibbit; Mary Ellen Kleinhenz, M.D.; Gregg Ruppel; Cary Stolar, M.D.; Janice Willey; Francisco Alvarez, M.D. (Co-Principal Investigator, 1999–2002); Cesar Keller, M.D. (Co-Principal Investigator, 1996–2000). *Temple University, Philadelphia, PA*: Gerard Criner, M.D. (Principal Investigator); Satoshi Furukawa, M.D. (Co-Principal Investigator); Anne Marie Kuzma, R.N., M.S.N. (Principal Clinic Coordinator); Roger Barnette, M.D.; Neil Brister, M.D.; Kevin Carney, R.N., C.C.T.C.; Wissam Chatila, M.D.; Francis Cordova, M.D.; Gilbert D'Alonzo, D.O.; Michael Keresztury, M.D.; Karen Kirsch; Chul Kwak, M.D.; Kathy Lautensack, R.N., B.S.N.; Madelina Lorenzon, C.P.F.T.; Ubaldo Martin, M.D.; Peter Rising, M.S.; Scott Schartel, M.D.; John Travaline, M.D.; Gwendolyn Vance, R.N., C.C.T.C.; Phillip Boiselle, M.D. (1997–2000); Gerald O'Brien, M.D. (1997–2000). *University of California, San Diego, San Diego, CA*: Andrew Ries, M.D., M.P.H. (Principal Investigator); Robert Kaplan, Ph.D. (Co-Principal Investigator); Catherine Ramirez, B.S., R.C.P. (Principal Clinic Coordinator); David Frankville, M.D.; Paul Friedman, M.D.; James Harrell, M.D.; Jeffery Johnson; David Kapelanski, M.D.; David Kupferberg, M.D., M.P.H.; Catherine Larsen, M.P.H.; Trina Limberg, R.R.T.; Michael Magliocca, R.N., C.N.P.; Frank J. Papatheofanis, M.D., Ph.D.; Dawn Sassi-Dambron, R.N.; Melissa Weeks. *University of Maryland at Baltimore, Baltimore, MD in consortium with Johns Hopkins Hospital, Baltimore, MD*: Mark Krasna, M.D. (Principal Investigator); Henry Fessler, M.D. (Co-Principal Investigator); Iris Moskowitz (Principal Clinic Coordinator); Timothy Gilbert, M.D.; Jonathan Orens, M.D.; Steven Scharf, M.D., Ph.D.; David Shade; Stanley Siegelman, M.D.; Kenneth Silver, M.D.; Clarence Weir; Charles White, M.D. *University of Michigan, Ann Arbor, MI*: Fernando Martinez, M.D. (Principal Investigator); Mark Iannettoni, M.D. (Co-Principal Investigator); Catherine Meldrum, B.S.N., R.N., C.C.R.N. (Principal Clinic Coordinator); William Bria, M.D.; Kelly Campbell; Paul Christensen, M.D.; Kevin Flaherty, M.D.; Steven Gay, M.D.; Paramjit Gill, R.N.; Paul Kazanjian, M.D.; Ella Kazerooni, M.D.; Vivian Knieper; Tammy Ojo, M.D.; Lewis Poole; Leslie Quint, M.D.; Paul Rysso; Thomas Sisson, M.D.; Mercedes True; Brian Woodcock, M.D.; Lori Zaremba, R.N. *University of Pennsylvania, Philadelphia, PA*: Larry Kaiser, M.D. (Principal Investigator); John Hansen-Flaschen, M.D. (Co-Principal Investigator); Mary Louise Dempsey, B.S.N., R.N. (Principal Clinic Coordinator); Abass Alavi, M.D.; Theresa Alcorn, Selim Arcasoy, M.D.; Judith Aronchick, M.D.; Stanley Aukberg, M.D.; Bryan Benedict, RRT; Susan Craemer, BS, RRT, C.P.F.T.; Ron Daniele, M.D.; Jeffrey Edelman, M.D.; Warren Gefter, M.D.; Laura Kotler-Klein, M.S.S.; Robert Kotloff, M.D.; David Lipson, M.D.; Wallace Miller, Jr., M.D.; Richard O'Connell, R.P.F.T.; Staci Opelman, M.S.W.; Harold Palevsky, M.D.; William Russell, R.P.F.T.; Heather Sheaffer, M.S.W.; Rodney Simcox, B.S.R.T., R.R.T.; Susanne Snedeker, RRT, C.P.F.T.; Jennifer Stone-Wynne, M.S.W.; Gregory Tino, M.D.; Peter Wahl; James Walter, RPFT; Patricia Ward; David Zisman, M.D.; James Mendez, M.S.N., C.R.N.P. (1997–2001); Angela Wurster, MSN, CRNP (1997–1999). *University of Pittsburgh, Pittsburgh, PA*: Frank Sciurba, M.D. (Principal Investigator); James Luketich, M.D. (Co-Principal Investigator); Colleen Witt, M.S. (Principal Clinic Coordinator); Gerald Ayres; Michael Donahoe, M.D.; Carl Fuhrman, M.D.; Robert Hoffman, M.D.; Joan Lacomis, M.D.; Joan Sexton; William Slivka; Diane Strollo, M.D.; Erin Sullivan, M.D.; Tomeka Simon; Catherine Wrona, R.N., B.S.N.; Gerene Bauldoff, R.N., M.S.N. (1997–2000); Manuel Brown, M.D. (1997–2002); Elisabeth George, R.N., M.S.N. (Principal Clinic Coordinator 1997–2001); Robert Keenan, M.D. (Co-Principal Investigator 1997–2000); Theodore Kopp, M.S. (1997–1999); Laurie Silfies (1997–2001). *University of Washington, Seattle, WA*: Joshua Benditt, M.D. (Principal Investigator), Douglas Wood, M.D. (Co-Principal Investigator); Margaret Snyder, M.N. (Principal Clinic Coordinator); Kymberley Anable; Nancy Battaglia; Louie Boitano; Andrew Bowdle, M.D.; Leighton Chan, M.D.; Cindy Chwalik; Bruce Culver, M.D.; Thurman Gillespy, M.D.; David Godwin, M.D.; Jeanne Hoffman; Andra Ibrahim, M.D.; Diane Lockhart; Stephen Marglin, M.D.; Kenneth Martay, M.D.; Patricia McDowell; Donald Oxorn, M.D.; Liz Roessler; Michelle Toshima; Susan Golden (1998–2000). Other Participants: *Agency for Healthcare Research and Quality, Rockville, MD*: Lynn Bosco, M.D., M.P.H.; Yen-Pin Chiang, Ph.D.; Carolyn Clancy, M.D.; Harry Handelsman, D.O. *Centers for Medicare and Medicaid Services, Baltimore, MD*: Steven M. Berkowitz, Ph.D.; Tanisha Carino, Ph.D.; Joe Chin, M.D.; JoAnna Baldwin; Karen McVearry; Anthony Norris; Sarah Shirey; Claudette Sikora; Steven Sheingold, Ph.D. (1997–2004). *Coordinating Center, The Johns Hopkins University, Baltimore, MD*: Steven Piantadosi, M.D., Ph.D. (Principal Investigator); James Tonascia, Ph.D (Co-Principal Investigator); Patricia Belt; Amanda Blackford, Sc.M.; Karen Collins; Betty Collison; Ryan Colvin, M.P.H.; John Dodge; Michele Donithan, M.H.S.; Vera Edmonds; Gregory L. Foster, M.A.; Julie Fuller; Judith Harle; Rosetta Jackson; Shing Lee, Sc.M.; Charlene Levine; Hope Livingston; Jill Meinert; Jennifer Meyers; Deborah Nowakowski; Kapreena Owens; Shangqian Qi, M.D.; Michael Smith; Brett Simon, M.D.; Paul Smith; Alice Sternberg, ScM; Mark Van Natta, M.H.S.; Laura Wilson, Sc.M.; Robert Wise, M.D. *Cost Effectiveness Subcommittee*: Robert M. Kaplan, Ph.D. (Chair); J. Sanford Schwartz, M.D. (Co-Chair); Yen-Pin Chiang, Ph.D.; Marianne C. Fahs, Ph.D.; A. Mark Fendrick, M.D.; Alan J. Moskowitz, M.D.; Dev Pathak, Ph.D.; Scott Ramsey, M.D., Ph.D.; Steven Sheingold, Ph.D.; A. Laurie Shroyer, Ph.D.; Judith Wagner, Ph.D.; Roger Yusen, M.D. *Cost Effectiveness Data Center, Fred Hutchinson Cancer Research Center, Seattle, WA*: Scott Ramsey, M.D., Ph.D. (Principal Investigator); Ruth Etzioni, Ph.D.; Sean Sullivan, Ph.D.; Douglas Wood, M.D.; Thomas Schroeder, M.A.; Karma Kreizenbeck; Kristin Berry, M.S.; Nadia Howlader, M.S. *CT Scan Image Storage and Analysis Center, University of Iowa, Iowa City, IA*: Eric Hoffman, Ph.D. (Principal Investigator); Janice Cook-Granroth, B.S.; Angela Delsing, R.T.; Junfeng Guo, Ph.D.; Geoffrey McLennan, M.D.; Brian Mullan, M.D.; Chris Piker, B.S.; Joseph Reinhardt, Ph.D.; Blake Robinswood; Jered Sieren, R.T.R.; William Stanford, M.D. *Data and Safety Monitoring Board*: John A. Waldhausen, M.D. (Chair); Gordon Bernard, M.D.; David DeMets, Ph.D.; Mark Ferguson, M.D.; Eddie Hoover, M.D.; Robert Levine, M.D.; Donald Mahler, M.D.; A. John McSweeny, Ph.D.; Jeanine Wiener-Kronish, M.D.; O. Dale Williams, Ph.D.; Magdy Younes, M.D. *Marketing Center, Temple University, Philadelphia, PA*: Gerard Criner, M.D. (Principal Investigator); Charles Soltoff, M.B.A. *Project Office, National Heart, Lung, and Blood Institute, Bethesda, MD*: Gail Weinmann, M.D. (Project Officer); Joanne Deshler (Contracting Officer); Dean Follmann, Ph.D.; James Kiley, Ph.D.; Margaret Wu, Ph.D. (1996–2001). Other acknowledgments: Arthur Gelb, M.D., Lakewood Regional Medical Center, Lakewood, CA.

References

1. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance - United States, 1971–2000. *MMWR Surveill Summ* 2002;51:1–16.
2. Watson L, Vestbo J, Postma DS, Decramer M, Rennard S, Kiri VA, Vermeire PA, Soriano JB. Gender differences in the management and experience of Chronic Obstructive Pulmonary Disease. *Respir Med* 2004;98:1207–1213.
3. Langhammer A, Johnsen R, Holmen J, Gulsvik A, Bjermer L. Cigarette smoking gives more respiratory symptoms among women than among men: the Nord-Trøndelag Health Study (HUNT). *J Epidemiol Community Health* 2000;54:917–922.
4. Becklake MR, Kauffmann F. Gender differences in airway behavior over the human life span. *Thorax* 1999;54:1119–1138.
5. Kanner RE, Connett JE, Altose MD, Buist AS, Lee WW, Tashkin DP, Wise RA. Gender difference in airway hyperresponsiveness in smokers with mild COPD: the Lung Health Study. *Am J Respir Crit Care Med* 1994;150:956–961.
6. Prescott E, Bjerg AM, Andersen PK, Lange P, Vestbo J. Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal study. *Eur Respir J* 1997;10:822–827.
7. Birring SS, Brightling CE, Bradding P, Entwisle JJ, Vara DD, Grigg J, Wardlaw AJ, Pavord ID. Clinical, radiologic, and induced sputum features of chronic obstructive pulmonary disease in nonsmokers: a descriptive study. *Am J Respir Crit Care Med* 2002;166:1078–1083.
8. Machado MC, Krishnan JA, Buist SA, Bilderback AL, Fazolo GP, Santarosa MG, Queiroga F Jr, Vollmer WM. Sex differences in survival of oxygen-dependent patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;174:524–529.
9. Chapman KR, Tashkin DP, Pye DJ. Gender bias in the diagnosis of COPD. *Chest* 2001;119:1691–1695.
10. Chapman KR. Chronic obstructive pulmonary disease: are women more susceptible than men? *Clin Chest Med* 2004;25:331–341.
11. Legato MJ. Beyond women's health: the new discipline of gender-specific medicine. *Med Clin North Am* 2003;87:917–937.
12. National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003;348:2059–2073.
13. National Emphysema Treatment Trial Research Group. Rationale and design of the National Emphysema Treatment Trial: a prospective randomized trial of lung volume reduction surgery. *Chest* 1999;116:1750–1761.

14. Eakin EG, Resnikoff PM, Prewitt LM, Ries AL, Kaplan RM. Validation of a new dyspnea measure: the UCSD Shortness of Breath Questionnaire. University of California, San Diego. *Chest* 1998;113:619–624.
15. Goldberg RT, Hillberg R, Reinecker L, Goldstein R. Evaluation of patients with severe pulmonary disease before and after pulmonary rehabilitation. *Disabil Rehabil* 2004;26:641–648.
16. Sciurba F, Criner GJ, Lee SM, Mohsenifar Z, Shade D, Slivka W, Wise RA, for the National Emphysema Treatment Trial Research Group. Six-minute walk distance in chronic obstructive pulmonary disease. Reproducibility and effect of walking course layout and length. *Am J Respir Crit Care Med* 2003;167:1522–1527.
17. Martinez FJ, Foster G, Curtis JL, Criner G, Weinmann G, Fishman A, DeCamp MM, Benditt J, Sciurba F, Make B, *et al.* Predictors of mortality in patients with emphysema and severe airflow obstruction. *Am J Respir Crit Care Med* 2006;173:1326–1334.
18. Hoffman EA, Reinhardt JM, Sonka M, Simon BA, Guo J, Saba O, Chon D, Samrah S, Shikata H, Tschirren J, *et al.* Characterization of the interstitial lung diseases via density-based and texture-based analysis of computed tomography images of lung structure and function. *Acad Radiol* 2003;10:1104–1118.
19. Mishima M, Oku Y, Kawakami K, Sakai N, Fukui M, Hirai T, Chin K, Ohi M, Nishimura K, Itoh H, *et al.* Quantitative assessment of the spatial distribution of low attenuation areas on X-ray CT using texture analysis in patients with chronic pulmonary emphysema. *Front Med Biol Eng* 1997;8:19–34.
20. Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, Cherniack RM, Rogers RM, Sciurba FC, Coxson HO, *et al.* The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:2645–2653.
21. James AL, Hogg JC, Dunn LA, Pare PD. The use of the internal perimeter to compare airway size and to calculate smooth muscle shortening. *Am Rev Respir Dis* 1988;138:136–139.
22. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179–187.
23. Crapo R, Morris A, Gardner R. Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis* 1981;123:659–664.
24. Crapo R, Morris AH, Clayton PD, Nixon CR. Lung volumes in healthy nonsmoking adults. *Bull Eur Physiopathol Respir* 1982;18:419–425.
25. Crapo R, Morris A. Standardized single breath normal values for carbon monoxide diffusing capacity. *Am Rev Respir Dis* 1981;123:185–189.
26. Guslvik A. Prevalence of respiratory symptoms in the city of Oslo. *Scand J Respir Dis* 1979;60:275–285.
27. Krzyzanowski M, Lebowitz MD. Changes in chronic respiratory symptoms in two populations of adults studied longitudinally over 13 years. *Eur Respir J* 1992;5:12–20.
28. Krzyzanowski M, Jedrychowski W, Wysocki M. Factors associated with the change in ventilatory function and the development of chronic obstructive pulmonary disease in a 13-year follow-up of the Cracow study. *Am Rev Respir Dis* 1986;134:1011–1019.
29. Viegi G, Prediletto R, Paoletti P, Carrozzi L, Di Pede F, Vellutini M, Di Pede C, Giuntini C, Lebowitz MD. Respiratory effects of occupational exposure in a general population sample in north Italy. *Am Rev Respir Dis* 1991;143:510–515.
30. Langhammer A, Johnsen R, Gulsvik A, Holmen TL, Bjermer L. Sex differences in lung vulnerability to tobacco smoking. *Eur Respir J* 2003;21:1017–1023.
31. Lindberg A, Eriksson E, Larsson LG, Ronmark E, Sandstrom T, Lundback B. Seven-year cumulative incidence of COPD in an age-stratified general population sample. *Chest* 2006;129:879–885.
32. Rennard S, Decramer M, Calverley PMA, Pride NB, Soriano JB, Vermeire PA, Vestbo J. Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey. *Eur Respir J* 2002;20:799–805.
33. de Torres JP, Casanova C, Hernandez C, Abreu J, Aguirre-Jaime A, Celli BR. Gender and COPD in patients attending a pulmonary clinic. *Chest* 2005;128:2012–2016.
34. Di Marco F, Verga M, Reggente M, Maria Casanova F, Santus P, Blasi F, Allegra L, Centanni S. Anxiety and depression in COPD patients: The roles of gender and disease severity. *Respir Med* 2006;100:1767–1774.
35. Kupferberg DH, Kaplan RM, Slymen DJ, Ries AL. Minimal clinically important difference for the UCSD Shortness of Breath Questionnaire. *J Cardiopulm Rehabil* 2005;25:370–377.
36. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto-Plata V, Cabral HJ. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:1005–1012.
37. Burrows B, Bloom JW, Traver GA, Cline MG. The course and prognosis of different forms of chronic airways obstruction in a sample from the general population. *N Engl J Med* 1987;317:1309–1314.
38. Chen Y, Horne SL, Dosman JA. Increased susceptibility to lung dysfunction in female smokers. *Am Rev Respir Dis* 1991;143:1224–1230.
39. Xu X, Weiss ST, Rijcken B, Schouten JP. Smoking, changes in smoking habits, and rate of decline in FEV1: new insight into gender differences. *Eur Respir J* 1994;7:1056–1061.
40. Connett JE, Murray RP, Buist AS, Wise RA, Bailey WC, Lindgren PG, Owens GR, for the Lung Health Study Research Group. Changes in smoking status affect women more than men: results of the Lung Health Study. *Am J Epidemiol* 2003;152:973–979.
41. Camilli AE, Burrows B, Knudson RJ, Lyle SK, Lebowitz MD. Longitudinal changes in forced expiratory volume in one second in adults: effects of smoking and smoking cessation. *Am Rev Respir Dis* 1987;135:794–799.
42. Peat JK, Woolcock AJ, Cullen K. Decline of lung function and development of chronic airflow limitation: a longitudinal study of smokers and non-smokers in Busselton, Western Australia. *Thorax* 1990;45:32–37.
43. Anthonisen NR, Connett JE, Murray RP, for the Lung Health Study Research Group. Smoking and lung function of lung health study participants after 11 years. *Am J Respir Crit Care Med* 2002;166:675–679.
44. Silverman EK, Chapman HA, Drazen JM, Weiss ST, Rosner B, Campbell EJ, O'Donnell WJ, Reilly JJ, Ginns L, Mentzer S, *et al.* Genetic epidemiology of severe, early-onset chronic obstructive pulmonary disease. Risk to relatives for airflow obstruction and chronic bronchitis. *Am J Respir Crit Care Med* 1998;157:1770–1778.
45. Silverman EK, Weiss ST, Drazen JM, Chapman HA, Carey V, Campbell EJ, Denish P, Silverman RA, Celedon JC, Reilly JJ, *et al.* Gender-related differences in severe, early-onset chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;162:2152–2158.
46. Nakano Y, Sakai H, Muro S, Hirai T, Oku Y, Nishimura K, Mishima M. Comparison of low attenuation areas on computed tomographic scans between inner and outer segments of the lung in patients with chronic obstructive pulmonary disease: incidence and contribution to lung function. *Thorax* 1999;54:384–389.
47. James AL, Pare PD, Hogg JC. The mechanics of airway narrowing in asthma. *Am Rev Respir Dis* 1989;139:242–246.
48. Ferrer M, Villasante C, Alonso J, Sobradillo V, Gabriel R, Vilagut G, Masa JF, Viejo JL, Jimenez-Ruiz CA, Miravitlles M. Interpretation of quality of life scores from the St. George's Respiratory Questionnaire. *Eur Respir J* 2002;19:405–413.
49. Isoaho R, Keistinen T, Laippala P, Kivela SL. Chronic obstructive pulmonary disease and symptoms related to depression in elderly persons. *Psychol Rep* 1995;76:287–297.
50. Stahl E, Lindberg A, Jansson SA, Ronmark E, Svensson K, Andersson F, Lofdahl CG, Lundback B. Health-related quality of life is related to COPD disease severity. *Health Qual Life Outcomes* 2005;3:56.
51. Kastelik JA, Thompson RH, Aziz I, Ojoo JC, Redington AE, Morice AH. Sex-related differences in cough reflex sensitivity in patients with chronic cough. *Am J Respir Crit Care Med* 2002;166:961–964.
52. Chavannes NH, Huibers MJ, Schermer TR, Hendriks A, van Weel C, Wouters EF, van Schayck CP. Associations of depressive symptoms with gender, body mass index and dyspnea in primary care COPD patients. *Fam Pract* 2005;22:604–607.
53. Neuman A, Gunnbjornsdottir M, Tunsater A, Nystrom L, Franklin KA, Norrman E, Janson C. Dyspnea in relation to symptoms of anxiety and depression: A prospective population study. *Respir Med* 2006;100:1843–1849.
54. Thomsen DK, Mehlsen MY, Viidik A. Age and gender differences in negative affect--Is there a role for emotion regulation? *Personality Individ Diff* 2005;38:1935–1946.
55. Ray JJ. Lie scales and the elderly. *Personality Individ Diff* 1988;9:417–418.
56. Cartensen LL, Isaacowitz DM, Charles ST. Taking time seriously--a theory of socioemotional selectivity. *Am Psychol* 1999;54:165–181.
57. Nolen-Hoeksema S, Larson J, Grayson C. Explaining the gender difference in depressive symptoms. *J Personal Soc Psychol* 1999;77:1061–1072.
58. Nolen-Hoeksema S, Jackson B. Mediators of the gender differences in rumination. *Psychol Women Q* 2001;25:37–47.
59. Thomsen DK, Mehlsen MY, Hokland M, Viidik A, Olesen F, Avlund K, Munk K, Zachariae R. Negative thoughts and health associations among rumination, immunity, and health care utilization in a young and elderly sample. *Psychosom Med* 2004;66:363–371.

60. Paoletti P, Carrozzi L, Viegi G, Modena P, Ballerin L, Di Pede F, Gado L, Baldacci S, Pedreschi M, Vellutini M, *et al.* Distribution of bronchial responsiveness in a general population: effect of sex, age, smoking, and level of pulmonary function. *Am J Respir Crit Care Med* 1995; 151:1770–1777.
61. Scichilone N, Messina M, Battaglia S, Catalano F, Bellia V. Airway hyperresponsiveness in the elderly: prevalance and clinical implications. *Eur Respir J* 2005;25:364–375.
62. Manfreda J, Sears MR, Becklake MR, Chan-Yeung M, Dimich-Ward H, Siersted HC, Ernst P, Sweet L, Van Til L, Bowie DM, *et al.* Geographic and gender variability in the prevalance of bronchial responsiveness in Canada. *Chest* 2004;125:1657–1664.
63. Kelly RW, Illingworth P, Baldie G, Leask R, Brouwer S, Calder AA. Progesterone control of interleukin-8 production in endometrium and choriodecidual cells underlies the role of the neutrophil in menstruation and parturition. *Hum Reprod* 1994;9:253–258.
64. Piccinni MP, Giudizi MG, Biagiotti R, Beloni L, Giannarini L, Sampognaro S, Parronchi P, Manetti R, Annunziato F, Livi C. Progesterone favors the development of human T helper cells producing Th2-type cytokines and promotes both IL-4 production and membrane CD30 expression in established Th1 cell clones. *J Immunol* 1995;155: 128–133.
65. Mo R, Chen J, Grolleau-Julius A, Murphy HS, Richardson BC, Yung RL. Estrogen regulates CCR gene expression and function in T lymphocytes. *J Immunol* 2005;174:6023–6029.
66. Mund E, Christensson B, Larsson K, Gronneberg R. Sex dependent differences in physiological ageing in the immune system of lower airways in healthy non-smoking volunteers: study of lymphocyte subsets in bronchoalveolar lavage fluid and blood. *Thorax* 2001;56:450–455.
67. Mund E, Christensson B, Gronneberg R, Larsson K. Noneosinophilic CD4 lymphocytic airway inflammation in menopausal women with chronic dry cough. *Chest* 2005;127:1714–1721.
68. Shames RS. Gender differences in the development and function of the immune system. *J Adolesc Health* 2002;30:59–70.