Respiratory Medicine (2006) **100**, 1110–1116

ELSEVIER

respiratoryMEDICINE

Racial and gender differences in susceptibility to tobacco smoke among patients with chronic obstructive pulmonary disease ☆

Mark T. Dransfield[a,b,*], Jennifer J. Davis[a], Lynn B. Gerald[a], William C. Bailey[a]

[a]*Division of Pulmonary, Allergy and Critical Care Medicine, The University of Alabama at Birmingham, Birmingham AL 35294, USA*
[b]*Pulmonary Section, The Birmingham VA Medical Center, Birmingham AL 35233, USA*

Received 29 March 2005; accepted 11 September 2005

KEYWORDS
Chronic obstructive pulmonary disease;
Smoking;
Race

Summary
Background: Although chronic obstructive pulmonary disease (COPD) has been considered a disease of Caucasian men, recent data show mortality rising faster among women and African-Americans. Some have suggested these groups are more susceptible to tobacco smoke. We examined this issue in our own population of COPD patients.
Methods: Beginning in March 2003 we prospectively developed a COPD research database to facilitate recruitment for clinical trials. Enrollees are recruited from clinics and paid advertising and their demographics, medical/smoking histories, and spirometric data are recorded. We examined the smoking histories and pulmonary function of enrollees over 45, with $\geqslant$20 pack-years of smoking, FEV_1/FVC (forced expiratory volume forced vital capacity) <0.70, and a race-adjusted post-bronchodilator $FEV_1<80\%$. The primary outcome was the loss of lung function per pack-year smoked, or Susceptibility Index (SI), calculated using the formula: (% predicted FEV_1-100)/pack-years.
Results: A total of 585 patients enrolled during the study period and 330 met our inclusion criteria. Caucasians were older than African-Americans (63 vs. 58, $P=0.0003$) and had more pack-years of smoking (57 vs. 43, $P=0.0003$). There were no differences in lung function or bronchodilator reversibility among the racial or gender subgroups. Caucasians had less loss of lung function per pack-year smoked

Abbreviations: COPD, Chronic obstructive pulmonary disease; FEV_1, Forced expiratory volume; FVC, Forced vital capacity; SI, Susceptibility Index; WHO, World Health Organization; GOLD, Global Initiative for Chronic Obstructive Lung Disease; TNF, Tumor necrosis factor; IL, Interleukin; Ig, Immunoglobulin

☆The authors have no financial interests to declare.

*Corresponding author. 215 THT, 1900 University Blvd, Birmingham, AL 35294, USA. Tel.: +1 205 934 7557; fax: +1 205 934 6229.
E-mail address: mdransfield99@msn.com (M.T. Dransfield).

0954-6111/$ - see front matter
doi:10.1016/j.rmed.2005.09.019

than African-Americans (SI = −1.02% vs. −1.34%, $P = 0.007$) and men less than women (SI = −0.98% vs. −1.21%, $P = 0.001$). Caucasian males appeared relatively protected from tobacco smoke (SI = −0.93%), while African-American women appeared most susceptible (SI = −1.42%).
Conclusions: There are important differences in racial and gender susceptibility to tobacco smoke among patients with COPD. African-American females appear to be at highest risk and may benefit most from smoking cessation.

Introduction

Chronic obstructive pulmonary disease (COPD) is currently the 4th leading cause of death in the United States and mortality continues to increase.[1] Although COPD has long been considered a disease of the white male, data from the last 25 years show that US death rates have risen more rapidly among Caucasian and African-American women and in the year 2000, more women than men died of the disease.[2]

The changing demographics of COPD have been attributed in part to temporal changes in smoking habits and certainly the popularity of cigarette smoking rose later among women than among men.[3] However, some authors have suggested that women and African-Americans may also be more susceptible to the damaging effects of tobacco smoke.[4–7] This possibility is of critical importance as the prevalence of cigarette smoking is rising fastest in young women and in the developing world.[8] Although the World Health Organization (WHO) has already estimated that by the year 2020 COPD will be the 3rd leading cause of death worldwide, its impact may be underestimated if women and non-Caucasians are truly at higher risk for the disease.[9]

This concept of differential susceptibility to tobacco smoke has been controversial and studies have shown mixed results.[4–7,10] In 2000, Vollmer published an analysis of eight previously performed National Heart, Lung, and Blood Institute studies that gathered data on gender, pulmonary function, smoking status, and race.[10] The authors developed two models to address the relationship between smoking and lung function. Although a consistent, dose-related decline in forced expiratory volume (FEV_1) was observed across all subgroups, there were no significant differences in the effects of cigarette smoking between Caucasians and African-Americans or between men and women. The study did suggest that among African-Americans, men may be more susceptible than women and that Asian/Pacific Islanders may be relatively protected. One limitation to this and other population-based studies is that they have included all smokers despite the fact that only 15–20% of regular smokers develop significant COPD. In their retrospective review of end-stage COPD patients, Chatila et al. attempted to address this limitation by examining smoking habits in a group of susceptible smokers.[4] They examined smoking histories in 80 Caucasian and 80 African-American patients who presented for lung transplantation or lung volume reduction surgery at their institution. Despite similarly poor lung function, African-Americans and women presented at an earlier age and with fewer pack-years of smoking than did Caucasians and males.

The results of these two studies are not mutually exclusive as it could be hypothesized that genetic, biologic, or behavioral differences between racial or gender groups not only determine their initial susceptibility to tobacco smoke but also place some at risk for more progressive disease.

We aimed to examine our own population of susceptible smokers to determine the relationships between gender, race, and lung function.

Materials and methods

Patient population

Beginning in March 2003, our group has prospectively developed a database of smokers to facilitate the recruitment of patients for clinical trials of COPD. Current or former smokers are recruited from paid advertising and clinics. Volunteers complete a database-specific study visit during which baseline demographics as well as medical and smoking histories are obtained. Pre- and post-bronchodilator spirometry is also performed and subjects are reimbursed for their time. To be eligible for database entry, patients must have at least a 15 pack-year history of smoking (calculated as lifetime mean pack-years) and an FEV_1/FVC (FVC: forced vital capacity) ratio $<75\%$. As of January 2005, we have enrolled almost 600 patients.

Patients for the current study were selected from the database if they fulfilled the following inclusion criteria: Age >45 years, $\geqslant 20$ pack-years of smoking, FEV_1/FVC ratio <0.70, and a race-adjusted post-bronchodilator $FEV_1<80\%$ of the predicted value. A race-adjusted $FEV_1<80\%$ was chosen to select patients with a minimum Stage IIa disease according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[16]

Pulmonary function tests

All patients underwent pulmonary function testing according to American Thoracic Society (ATS) guidelines.[11] Post-bronchodilator results are reported as percent predicted according to the published estimates of Crapo for Caucasians.[12] We adjusted the predicted values for African-Americans by multiplying by 0.88 as was done in the National Emphysema Treatment Trial and by others.[4,13,14] Bronchodilator reversibility was defined according to ATS standards as an increase in FEV_1 of $\geqslant 200$ mL and $\geqslant 12\%$.[11]

Outcomes and statistics

The primary outcome for the study was the Susceptibility Index (SI) which we defined as the loss of lung function (measured in race-adjusted % predicted FEV_1) per pack-year smoked. The race and gender specific SIs were calculated according to the formula:

$$SI = \frac{[\%\text{Predicted post-bronchodilator } FEV_1 - 100].}{\text{Pack-years smoked}}$$

This analysis presumes that each subject's baseline FEV_1 would be normal (100% predicted) without the damaging effects of cigarette smoke. The SI is therefore designed to quantify the lung damage that has occurred in each subject as a result of cigarette smoking. Importantly, this study is cross-sectional in design and although the SI is reported as loss of lung function per pack-year smoked it cannot be interpreted as an annual rate of decline in lung function.

Differences between African-Americans and Caucasians and between men and women were compared using the chi square test for categorical variables and the Student *t*-test for continuous variables. For comparisons between the four race–gender subgroups one-way analysis of variance (ANOVA) testing with the Tukey HSD test was used. A *P* value <0.05 was considered significant.

Results

Patient demographics and lung function

A total of 330 patients met our inclusion criteria. Of these, there were 172 Caucasian males, 106 Caucasian females, 28 African-American males, and 22 African-American females. There were also 2 Hispanic patients but they were excluded from the analysis due to the small number.

Table 1 shows the demographics, lung function, and baseline medication use for the study population. Caucasians were older than African-Americans (5 years) and had heavier smoking histories (14 pack-years). There were no differences between the two groups in terms of FEV_1, the number of current smokers, or in the frequency of self-reported asthma or COPD. The FEV_1/FVC ratio was statistically lower among Caucasians though the clinical difference was small (0.49 vs. 0.53).

Table 1 Patient characteristics.

Characteristics	African-Americans ($n=50$)	Caucasians ($n=278$)	*P* value
Age, years	58 ± 9	63 ± 9	0.0003
Male gender, number (%)	28 (56)	172 (62)	0.57
Pack-years smoked	43 ± 18	57 ± 26	0.0003
Current smoker, number (%)	17 (34)	108 (39)	0.62
FEV_1/FVC	0.53 ± 0.1	0.49 ± 0.1	0.02
FEV_1 (% predicted)	51 ± 17	51 ± 17	0.95
Self-reported COPD, number (%)	22 (44)	118 (43)	1.0
Self-reported asthma, number (%)	7 (14)	26 (9)	0.45
Taking short acting beta agonists, number (%)	32 (64)	163 (59)	0.58
Short acting anticholinergics, number (%)	14 (28)	83 (30)	0.92
Long acting beta agonists, number (%)	9 (18)	75 (27)	0.24
Long acting anticholinergics, number (%)	1 (2)	2 (1)	0.77
Inhaled corticosteroids, number (%)	10 (20)	77 (28)	0.34

Mean values are followed by standard deviation.

There were also no differences in the use of respiratory medications between the racial groups.

Figure 1 shows the age, smoking history, and FEV_1 for each of the race–gender subgroups. There was no difference in age between Caucasian men and Caucasian women (64 vs. 60, $P > 0.05$); however, Caucasian males were older than African-American males (64 vs. 57, $P < 0.01$) and African-American females (64 vs. 58, $P < 0.01$). Caucasian males also had more pack-years of smoking than any of the other subgroups (16–22 pack-years, $P < 0.05$). There were no differences in pack-years smoked among the other subgroups. There were also no differences in lung function among any of the subgroups with all meeting criteria for moderately severe to severe obstruction based on ATS criteria.

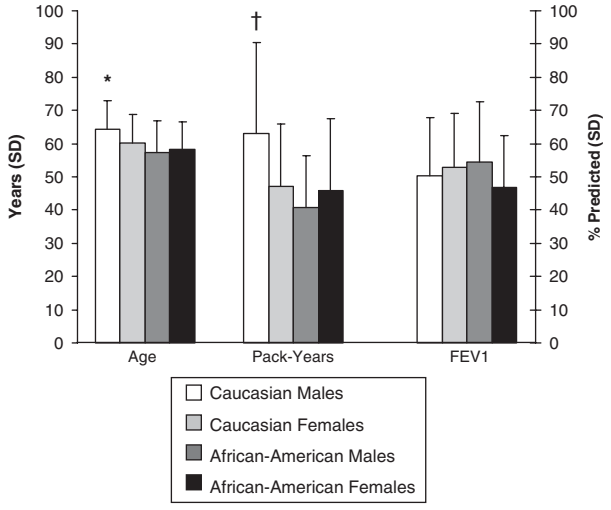

Figure 1 Age, smoking histories, and lung function (FEV_1) for each of the racial and gender subgroups. *Caucasian males were older than African-American men ($P < 0.01$) and African-American women ($P < 0.01$). There was no difference in age between Caucasian males and females ($P > 0.05$). †Caucasian males smoked more than Caucasian females ($P < 0.05$), African-American males ($P < 0.01$), and African-American females ($P < 0.01$). There were no differences in lung function among the subgroups [ANOVA, Tukey HSD test].

Bronchodilator reversibility

Table 2 shows the mean bronchodilator response for each racial and gender subgroup. Overall, 31% of the patients in our study had a greater than 12% and 200 mL increase in their FEV_1 after the administration of bronchodilator. There were no statistically significant differences in the fraction of patients exhibiting bronchodilator reversibility or in the mean bronchodilator response among the subgroups.

Susceptibility indices

Figure 2 shows the SIs for Caucasians vs. African-Americans and for men vs. women. Caucasians had less loss of lung function per pack-year smoked than African-Americans (−1.02%/pack-year vs. −1.34%/pack-year, $P = 0.007$). Similarly, the loss of lung function among men was less than that among women (−0.98%/pack-year vs. −1.21%/pack-year, $P = 0.001$).

Figure 3 shows the SI for each of the race-gender subgroups. Caucasian men had the smallest loss of lung function per pack-year smoked (−0.93%/pack-year) though this was not statistically different than Caucasian women (−1.17%/pack-year). African-American men lost lung function at a 38% faster rate than Caucasian males though African-American women exhibited the largest change, losing lung function 55% faster than Caucasian men (−1.42%/pack-year). There were no statistically significant differences in the calculated SI when the non-Caucasian/male subgroups were compared to one another.

Discussion

Our data argue that there are important differences in susceptibility to tobacco smoke among racial and gender subgroups with obstructive lung disease. Caucasian men appear relatively pro-

Table 2 Bronchodilator responsiveness.

	Fraction Reversible #/Total (%)	Mean bronchodilator response (%)
Caucasian males	60/172 (35)	12.9
Caucasian females	27/106 (25)	14.0
African-American males	6/28 (21)	11.5
African-American females	9/22 (41)	15.5

There were no statistically significant differences among the groups in the fraction of patients exhibiting bronchodilator reversibility or in the mean bronchodilator response.

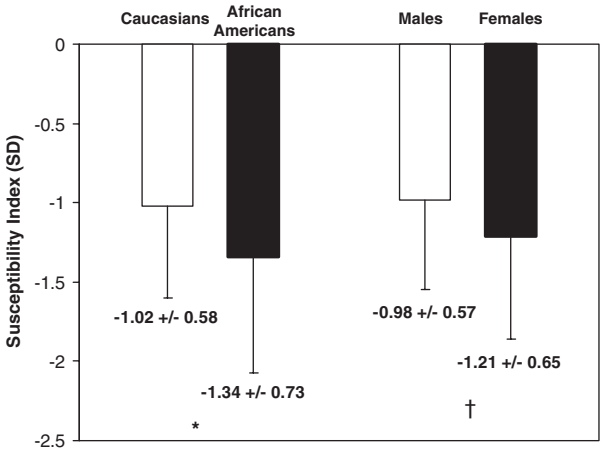

Figure 2 Susceptibility Indices (SI). The SI represents the change in lung function (race-adjusted % predicted FEV_1) per pack-year smoked as calculated by the formula (%FEV_1-100%)/pack-years. *Caucasians lost lung function at a slower rate than did African-Americans ($P = 0.007$) as did †men compared to women ($P = 0.001$) [Student's *t*-test].

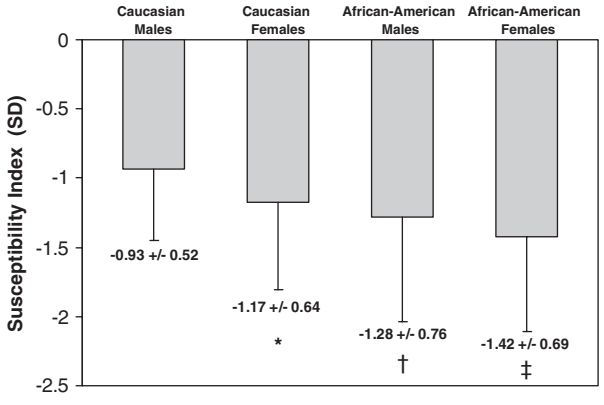

Figure 3 Susceptibility Indices (SI) for each of the racial and gender subgroups. For the entire study population, Caucasian males appeared least susceptible to the effects of tobacco smoke while African-American women were most vulnerable, losing lung function at a 55% faster rate. Comparisons are with Caucasian males and all other comparisons are non-significant (*>0.05, †<0.05, ‡<0.01) [ANOVA, Tukey HSD test].

tected while African-American women are particularly vulnerable to the deleterious effects of smoking on lung function. These results are concerning as the popularity of cigarettes among women and non-Caucasian populations across the globe continues to increase.[8] Although the COPD epidemic is well established, projections for its future impact may be grossly underestimated if these disparities prove correct.

Our results are similar to those observed by Chatila who examined racial and gender differences in smoking history among patients with end-stage COPD.[4] Although no differences in lung function were observed, women and African-Americans were younger and had smoked less than Caucasian men. Individual data for these patients are not available; however, an estimate of the SI for each of Chatila's racial and gender subgroups can be made using their average lung function (FEV_1) and pack-years smoked. For Caucasian males who smoked an average of 74 pack-years and whose mean FEV_1 was 29%, the calculated SI is −0.96%/pack-year (vs. −0.93%/pack-year in our study). When these calculations are made for the other subgroups, a remarkably similar step-up in apparent susceptibility is observed: Caucasian women (−1.24%/pack-year in the Chatila paper vs. −1.17 in ours), African-American men (−1.53% vs. −1.28%), and African-American women (−1.71% vs. −1.42%). It is important to note that both these studies were done in patients who were clearly susceptible to the effects of cigarette smoking and who met the current GOLD definition of COPD.[16] We are aware of no other studies that have attempted to quantify tobacco smoke susceptibility among patients with established obstructive lung disease.

In contrast to these data, population-based studies have demonstrated conflicting results. As mentioned, Vollmer found no difference in the excess decline in FEV_1 attributed to smoking between Caucasians and African-Americans (−10 vs. −7 mL/year, $P > 0.05$) or between men and women (−10 vs. −8 mL year, $P > 0.05$).[10] In a study of 1149 Caucasian smokers, Chen found that the FEV_1 among women smokers declined at a rate 4.1 mL/pack-year faster than among male smokers.[5] Those results were dramatically different from data from the Six Cities study which suggested a 5.4 mL/pack-year greater decline in FEV_1 among men.[6] These inconsistencies are difficult to reconcile though all population-based studies may be problematic as they have included all smokers in their analyses despite the fact that only a fraction of them develop significant COPD.

We believe it would be naïve to assume that tobacco susceptibility for all racial and gender subgroups is the same, and when combined with Chatila's observations, our data argue strongly that this is not the case. The incidence of the only currently known genetic risk factor for COPD, alpha-1 antitrypsin deficiency, is higher among Caucasians than African-Americans.[17] There are numerous other proteins including other proteases (metalloproteinases), anti-oxidants (glutathione-s-transferase), detoxifying enzymes (microsomal epoxide hydrolase), and cytokines (TNF-α, IL-8) that may play a role in the pathogenesis of COPD.[18] It is

unlikely that genetic polymorphisms of these proteins that predispose to COPD will be evenly distributed among racial groups. In fact, a recent study found that certain haplotypes of the COPD candidate gene *CLCA1,* which codes for a protein regulating airway mucous production, were common among Japanese COPD patients but not among Egyptians with the disease.[19]

There also appear to be racial and gender differences in airway reactivity which has long been considered a risk factor for the development of COPD.[20] Joseph and colleagues have shown that African-American children with asthma have higher IgE levels and greater methacholine reactivity than do Caucasian children.[21] Similarly, women enrolled in the Lung Health Study had increased bronchial hyperresponsiveness as compared to male participants.[22] This heightened airway reactivity may disproportionately increase the risk of COPD among African-Americans and women who smoke. Other early life factors such as lower respiratory tract infections, exposure to pollution, and nutritional status may also have unequal effects on the lung function of racial or gender subgroups.[23]

It could be argued that our results and Vollmer's population-based data are not mutually exclusive.[10] If there are unique genetic, biologic, or behavioral factors that determine the initial risk for the development of obstructive airways disease, there may separate factors that then affect the rate of decline of FEV_1. Therefore, while all smokers may be at comparable risk for the development of obstructive lung disease, African-Americans and women who develop COPD may be particularly susceptible to progressive disease.

Our study has several limitations. First, although the data were prospectively obtained, referral and survivor bias may have influenced the population enrolled in the database. African-Americans represented 15% of the entire study population which is somewhat less than the 25% in our metropolitan area and the state of Alabama.[24] It is possible that database patients may have more severe disease than other African-Americans in the community. Although this is a possible explanation for our results, the same bias should have affected the Caucasian male population as well. Similarly, if a population of Caucasian men with early and severe airways disease existed, and these men had died at a young age, then our database would misrepresent the overall susceptibility of the group.

A second potential limitation is that we did not attempt to control for baseline medication usage and no wash-out period was required prior to spirometry. Prior studies of asthmatics suggest that inhaled steroids and other controller medications are used less often in African-Americans than they are in Caucasians.[25] In our study, the frequency of inhaled corticosteroid and long-acting bronchodilator usage was similar between the racial groups and thus this potential bias likely had little effect. The effects of no washout period were minimized by the use of the post-bronchodilator FEV_1.

A third limitation is that we could not correct the SI for potential confounding variables that may affect lung function including occupational or environmental exposure to dusts and other noxious particles as this data was not available. We do not believe, however, that a study of this size would allow for a meaningful multivariate analysis. Chatila and his colleagues attempted to examine the influence of urban vs. suburban living (as a measure of environmental dust exposure) on the severity of COPD in their population.[4] Although they were unable to document an effect in their small study, the possibility that dust exposure or even socioeconomic status may underlie the apparent racial differences in susceptibility to tobacco smoke cannot be ignored. Only larger studies, which we would strongly favor, would allow definitive conclusions about the validity of our observations.

We did not specifically eliminate patients with self-reported asthma from our study. This was based on the potential inaccuracy of self-reported diagnoses and a significant bias against physician diagnosis of COPD among women smokers.[26] Several facts argue against the possibility that our study results were affected by differences in asthma prevalence and severity amongst the subgroups. First, the mean bronchodilator responsiveness and fraction of patients with a significant response is comparable to that reported in other studies of COPD.[15,27,28] Second, although a single test of bronchodilator reversibility is not a reliable way to differentiate asthma and COPD, our results did not change when non-reversible patients were examined alone. In that analysis, Caucasian males again exhibited the smallest loss of lung function per pack-year smoked while African-American women exhibited the largest decline ($SI = -0.97\%$ vs. -1.62%, $P < 0.01$). Lastly, there were no differences in the fraction of patients who reported a history of asthma among any of the subgroups.

More research is needed to determine the basis of our findings. The observed racial and gender differences may be due to multiple factors including genetic determinants, other exposures, or behavior. It is also possible that there are differences in the biology of COPD among subpopulations that may not only affect their susceptibility to the disease but provide unique opportunities to intervene. Although no pharmacologic agent has been

shown to alter the natural history of COPD, it is possible that such a benefit could have been missed in African-Americans and women as these groups have been underrepresented in clinical trials. Our data do argue for more aggressive efforts at smoking cessation among African-American women.

Acknoledgments

The authors acknowledge Dr. Wenquan Wang for his statistical support.

References

1. National Center for Health Statistics. *Deaths: final data for 2001*. Hyattsville, MD: US Department of Health and Human Services, CDC; 2003. Available at http://www.cdc.gov/nchs/pressroom/03facts/mortalitytrends.htm.
2. Mannino DM, Homa DM, Akinbami LJ, et al. Chronic obstructive pulmonary disease surveillance—United States, 1971–2000. *MMWR Surveill Summ* 2002;**51**:S5–6.
3. Shopland DR. Tobacco use and its contribution to early cancer mortality with a special emphasis on cigarette smoking. *Environ Health Perspect* 1995;**103**(Suppl 8): 131–42.
4. Chatila WM, Wynkoop WA, Vance G, Criner GJ. Smoking patterns in African Americans and whites with advanced COPD. *Chest* 2004;**125**:15–21.
5. Chen Y, Horne SL, Dosman JA. Increased susceptibility to lung dysfunction in female smokers. *Am Rev Respir Dis* 1991;**143**:1224–30.
6. Xu X, Dockery DW, Ware JH, et al. Effects of cigarette smoking on rate of loss of pulmonary function in adults: a longitudinal assessment. *Am Rev Respir Dis* 1992;**146**: 1345–8.
7. Massaro D, Cusick A, Katz S. Racial differences in incidence of chronic bronchitis. *Am Rev Respir Dis* 1965;**92**:94–101.
8. Molarius A, Parsons RW, Dobson AJ, et al. Trends in cigarette smoking in 36 populations from the early 1980s to the mid-1990s: findings from the WHO MONICA Project. *Am J Public Health* 2001;**91**:206–12.
9. Murray CJ, Lopez AD. Alternative projection of mortality by cause 1990–2020: global burden of disease study. *Lancet* 1997;**349**:1498–504.
10. Vollmer WM, Enright PL, Pedula KL, et al. Race and gender differences in the effects of smoking on lung function. *Chest* 2000;**117**:764–72.
11. American Thoracic Society. Lung function testing: selection of reference values and interpretive strategies. *Am Rev Respir Dis* 1991;**144**:1202–18.
12. Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis* 1981;**123**:659–64.
13. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. *Am J Respir Crit Care Med* 1999;**159**:179–87.
14. Geddes D, Davies M, Koyama H, et al. Effect of lung volume reduction surgery in patients with severe emphysema. *N Engl J Med* 2000;**343**:239–45.
15. Donohue JF. Therapeutic responses in asthma and COPD: bronchodilators. *Chest* 2004;**126**(Suppl 2):125S–37S.
16. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001;**163**:1256–76.
17. de Serres FJ. Worldwide racial and ethnic distribution of α_1-antitrypsin deficiency. *Summary of an analysis of published genetic epidemiological surveys. Chest* 2002;**122**:1818–29.
18. Barnes PJ. Molecular genetics of chronic obstructive pulmonary disease. *Thorax* 1999;**54**:245–52.
19. Hegab AE, Sakamoto T, Uchida Y, et al. *CLCA1* gene polymorphisms in chronic obstructive pulmonary disease. *J Med Genet* 2004;**41**:e27.
20. Postma DS, Boezen HM. Rationale for the Dutch Hypothesis: allergy and airway hyperresponsiveness as genetic factors and their interaction with environment in the development of asthma and COPD. *Chest* 2004;**126**(Suppl 2):96S–104S.
21. Joseph CLM, Ownby DR, Peterson EL, Johnson CC. Racial differences in physiologic parameters related to asthma among middle-class children. *Chest* 2000;**117**:1336–44.
22. Kanner RE, Connett JE, Altose MD, et al. Gender difference in airway hyperresponsiveness in smokers with mild COPD: The Lung Health Study. *Am J Respir Crit Care Med* 1994;**150**: 956–61.
23. Apostol GG, Jacobs DR, Tsai AW, et al. Early life factors contribute to the decrease in lung function between ages 18 and 40: The Coronary Artery Risk Development In Young Adults study. *Am J Respir Crit Care Med* 2002;**166**: 166–72.
24. Available at http://www.census.gov/popest/states/asrh/SC-EST2003-03.html. Accessed December 7, 2004.
25. Zoratti EM, Havstad S, Rodriguez J, Robens-Paradise Y, Lafata JE, McCarthy B. Health service use by African Americans and Caucasians with asthma in a managed care setting. *Am J Respir Crit Care Med* 1998;**158**:371–7.
26. Chapman KR, Tashkin DP, Pye DJ. Gender bias in the diagnosis of COPD. *Chest* 2001;**119**:1691–5.
27. Donohue JF, Kalberg C, Emmett A, Merchant K, Knobil K. A short-term comparison of fluticasone propionate/salmeterol with ipratropium bromide/albuterol for the treatment of COPD. *Treat Respir Med* 2004;**3**:173–81.
28. Calverley PM, Burge PS, Spencer S, et al. Bronchodilator reversibility testing in chronic obstructive pulmonary disease. *Thorax* 2003;**58**:659–64.