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Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study

E. Prescott*, A.M. Bjerg*, P.K. Andersen**+, P. Lange++, J. Vestbo*

Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study. E. Prescott, A.M. Bjerg, P.K. Andersen, P. Lange, J. Vestbo. ©ERS Journals Ltd 1997.

ABSTRACT: Recent findings suggest that females may be more susceptible than males to the deleterious influence of tobacco smoking in developing chronic obstructive pulmonary disease (COPD). This paper studies the interaction of gender and smoking on development of COPD as assessed by lung function and hospital admission.

A total of 13,897 subjects, born after 1920, from two population studies, 9,083 from the Copenhagen City Heart Study (CCHS) and 4,814 from the Glostrup Population Studies (GPS), were followed for 7–16 yrs. Data were linked with information on hospital admissions caused by COPD.

Based on cross-sectional data, in the CCHS the estimated excess loss of forced expiratory volume in one second (FEV_1) per pack-year of smoking was 7.4 mL in female smokers who inhaled and 6.3 mL in male smokers who inhaled. In the GPS, the corresponding excess loss of FEV_1 was 10.5 and 8.4 mL in females and males, respectively. Two hundred and eighteen subjects in the CCHS and 23 in the GPS were hospitalized during follow-up. Risk associated with pack-years was higher in females than in males (relative risks (RRs) for 1–20, 20–40 and >40 pack-years were 7.0 (3.5–14.1), 9.8 (4.9–19.6) and 23.3 (10.7–50.9) in females, and 3.2 (1.1–9.1), 5.7 (2.2–14.3) and 8.4 (3.3–21.6) in males) but the interaction term gender×pack-years did not reach significance (p=0.08). Results were similar in the GPS. After adjusting for smoking in more detail, females in both cohorts had an increased risk of hospitalization for COPD compared to males with a RR of 1.5 (1.2–2.1) in the CCHS and 3.6 (1.4–9.0) in the GPS. This was not likely to be caused by a generally increased rate of hospital admission for females. Results were similar when including deaths from COPD as endpoint.

In two independent population samples, smoking had greater impact on the lung function of females than males, and after adjusting for smoking females subsequently suffered a higher risk of being admitted to hospital for COPD. Results suggest that adverse effects of smoking on lung function may be greater in females than in males.

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*The Copenhagen Center for Prospective Population Studies at the Institute of Preventive Medicine, Copenhagen Hospital Corporation, Copenhagen, Denmark. **Institute of Biostatistics, University of Copenhagen, Denmark. +Danish Epidemiology Science Center, State Serum Institute, Copenhagen, Denmark. ++Dept of Pulmonary Medicine P, Bispebjerg Hospital, Copenhagen, Denmark.

Correspondence: E. Prescott
The Copenhagen Center for Prospective Population Studies
Institute of Preventive Medicine
Kommunehospitalet
DK-1399 Copenhagen K
Denmark

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Mortality from chronic obstructive pulmonary disease (COPD) is increasing in females in Europe and North America, and most noticeably in Denmark [1]. The increase in mortality is generally attributed to increase in tobacco smoking; Danish women are also among the heaviest smokers amongst females in Europe [2].

Although numerous epidemiological studies addressing the effect of tobacco smoking on pulmonary disease include both males and females [3–13], analyses are usually performed for each gender separately, without addressing the issue of possible gender differences in the effects of smoking. Notwithstanding, based on studies of pulmonary function, it has recently been suggested that females may be more susceptible than males to the deleterious effects of smoking with regard to development of COPD [9, 14–16]. There are, however, problems concerning how pulmonary function and loss of pulmonary function should be compared between genders and, because of this, measures of forced expiratory volume in one second (FEV_1) and decline in FEV_1 should not simply be considered "the gold standard". Studies of gender differences focusing on other measures of morbidity are needed. Since COPD is a long-standing, crippling disease with a relatively low mortality rate, hospital admission is an appropriate measure of impact of this disease, and could even be regarded as a form of morbidity *per se* reflecting disease of some severity. In comparison with mortality data, hospitalization is a more sensitive measure of morbidity, with less delay.

The aim of the present study was to determine whether gender modifies the effect of smoking, using both lung function and hospitalization for COPD as outcome.

Methods

The study was based on data from two population studies conducted in the area of Copenhagen: the Copenhagen City Heart Study (CCHS) and the Glostrup Population Studies (GPS), both of which have been described in detail previously [17, 18]. Briefly, the CCHS population comprised a randomly selected, age-stratified sample of 19,698 subjects, aged ≥20 yrs and living in Copenhagen. In 1976/1978, 14,223 subjects were examined (response rate 74%). For this study, subjects born before 1920 were excluded, based on the consideration that smoking habits changed drastically after World War II. This exclusion of subjects who, to a large extent, had already formed their smoking habits before the war would ensure a more homogeneous study population with regard to smoking. Furthermore, by excluding the oldest subjects, hospitalizations caused by general physical frailty rather than the specific disease were also excluded. The CCHS, thus, comprised 9,083 subjects, 5,020 females and 4,063 males.

The GPS have, since 1964, followed different birth cohorts of the population in selected western suburbs of Copenhagen, which, during the study period, has changed from a partly rural to an almost exclusively suburban residential area. For this study, data on 4,814 subjects were used; 2,383 females and 2,431 males, from five birth cohorts (1922, 1932, 1936, 1942, and 1952) examined between 1976 and 1983 (response rates 79–88%).

Because differences in smoking habits between males and females were a key issue, tobacco exposure was studied in as much detail as possible. Current smokers were asked about type of tobacco, daily tobacco consumption (calculated for cheroot and cigar smokers by equating one cheroot to 3 g tobacco and one cigar to 5 g tobacco), years of smoking and whether they inhaled, and ex-smokers were asked how long they had smoked. Age at smoking onset was calculated in current smokers by subtracting years of smoking from age. Pack-years were calculated for all current smokers as (years of smoking×daily consumption in grams/20).

Spirometry was performed in the CCHS and the 1936 birth cohort of the GPS. For each participant, FEV_1 was expressed as a percentage of the predicted value (FEV_1 % pred) based on regression of FEV_1 on age and height among lifelong nonsmokers in the CCHS and the GPS separately.

Since more elderly females than males live alone and cohabitation was expected to affect the risk of hospitalization, this dichotomous variable was included in analyses. Length of education as a proxy for socioeconomic status was also included.

All subjects were followed using the National Hospital Discharge Register. The analyses are based on the first diagnosis registered, which is the main cause of medical action during hospital admission. We focused on COPD-related hospital admissions (International Classification of Diseases (ICD)-8 codes 490-92). To study whether differences in hospital admission rates were merely caused by the threshold for hospital admission being generally lower for females than males, similar analyses of hospital admissions were made for pneumonia (ICD-8 codes 471 and 480-86). CCHS subjects were followed until December 31, 1992 and GPS subjects until December 31, 1990.

Statistical analysis

The effect of smoking on FEV_1 was analysed by multiple linear regression for each gender separately. Accumulated tobacco exposure was summarized into one variable, pack-years, the effect of which could be compared in males and females. The model was as follows:

$$E(Y) = \beta_0 + \beta_1 \text{ pack-yrs}_{\text{inhaler}} + \beta_2 \text{ pack-yrs}_{\text{noninhaler}} + \beta_3 \text{ (age 40 yrs)} + \beta_4 \text{ (height 170 cm)}$$

where $E(Y)$ is expected lung function, β_0 is lung function for lifetime nonsmokers of age 40 yrs and height 170 cm, β_1 is change in FEV_1 per pack-year for smokers who inhale, β_2 is change in FEV_1 per pack-year for smokers who do not inhale, β_3 is dependency of FEV_1 with age, and β_4 is dependency of FEV_1 with height. Inclusion of age-squared or height-squared did not improve this model. Pack-years could not be calculated for ex-smokers, who were excluded from this analysis.

For analysis of morbidity, the Cox proportional hazards model [19] was used, with the outcome of interest being the first hospitalization for the diagnosis in question. Each study subject, thus, contributed with the time from enrolment until first hospitalization for the diagnosis in question or until censoring (death or end of follow-up). Deaths from COPD not preceded by hospitalization for COPD were also censored. The following model was used with age as the underlying time scale:

$$\lambda_i \text{ (age)} = \lambda_0 \text{ (age)} \times \exp (\beta_1 Z_{1i} + \beta_2 Z_{2i} + \ldots + \beta_k Z_{ki})$$

where λ_i is the hazard rate for the i'th subject, λ_0 the basic hazard rate, β_j the parameter estimates for the corresponding covariates, and Z_{ji} the value of the j'th covariate for the i'th subject (j=l,...,k). This model has the advantage that no assumptions regarding effects of age are made, which would otherwise be necessary if time of enrolment was time zero. Regression coefficients were estimated by the maximum partial likelihood method, as suggested by Cox. Covariates on a continuous scale were tested for the assumption of linearity, and the assumption of proportional hazards was checked for all covariates. Analyses were performed using Statistical Analysis System (SAS) software for OS/2 (PHREG procedure, counting process type of input, 1994 [20]).

Results

The study samples consisted of 9,083 subjects from the CCHS followed for 16 yrs, and 4,814 subjects from the GPS followed for 8–14 yrs. Baseline data with emphasis on smoking characteristics are presented in table 1. The table shows that prevalence of smoking was high and that male smokers, in particular in the CCHS, were more heavily exposed than female smokers: they smoked more; more stated that they were inhalers; and they started smoking at a younger age.

Results from the sex-specific multiple linear regression analyses are presented in table 2. Pack-years for inhaling smokers were separated from noninhaling smokers because inhalation differed with gender. In the CCHS, the age- and height-adjusted excess loss of FEV_1 was

Table 1. – Baseline data on study subjects by age and gender

	CCHS			GPS		
	Female (n=5020)	Male (n=4063)	p-value#	Female (n=2383)	Male (n=2431)	p-value#
Age yrs	46 (9)	45 (9)	<0.001	44 (10)	44 (0)	0.16
Lifelong nonsmokers %	24	12	<0.001	34	17	<0.001
Ex-smokers %	13	16	<0.001	14	20	<0.001
Smokers %	63	72	<0.001	52	62	<0.001
Inhalers‡ %	80	87	<0.001	88	88	0.81
Heavy smokers‡$ %	50	69	<0.001	49	64	<0.001
Age at smoking onset‡	22 (7)	18 (6)	<0.001	21 (7)	18 (6)	<0.001
Living alone %	23	21	0.008	9	9	0.93

Values are presented as mean, and SD in parenthesis, or as a percentage of group as appropriate. #: from Chi-square or t-test; ‡: only present smokers included; $: ≥15 g of tobacco·day^{-1}. CCHS: Copenhagen City Heart Study; GPS: Glostrup Population Study.

Table 2. – Estimated effects of smoking on FEV_1 (results from multiple linear regression)

	CCHS		GPS	
	Females (n=4245)	Males (n=3338)	Females (n=484)	Males (n=412)
Pack-years inhalers (mL·pack-yr^{-1})	-7.4 (0.6)***	-6.3 (0.7)***	-10.5 (2.1)***	-8.1 (2.1)***
Pack-years noninhalers (mL·pack-yr^{-1})	-2.6 (1.1)*	-1.0 (1.1)	-12.4 (8.2)	-4.7 (6.4)
Age (mL·yr^{-1})	-24.7 (0.8)***	-37.7 (1.4)***	-	-
Height (mL·cm^{-1})	32.6 (1.1)***	40.7 (1.7)***	31.9 (3.4)***	37.7 (4.4)***
Constant‡	2849 (13)	3401 (20)	2611 (33)	3356 (52)

Values are presented as regression coefficient, and SEM in parenthesis. Ex-smokers were excluded because pack-years could not be calculated; ‡: FEV_1 for person of age 40 yrs and height 170 cm. CCHS: Copenhagen City Heart Study; GPS: Glostrup Population Study, spirometry only performed in the 1936 birth cohort (examined at 40 yrs of age); FEV_1: forced expiratory volume in one second. *,***: $p<0.05$, $p<0.001$, for significance of the regression coefficients. Model: $E(Y) = \beta_0 + \beta_1$ pack-yrs$_{inhaler}$ $+ \beta_2$ pack-yrs$_{noninhaler}$ $+ \beta_3$ (age 40 yrs) $+ \beta_4$ (height 170 cm); see text for explanation.

7.4 mL per pack-year for female smokers who inhaled and 6.3 mL for male smokers who inhaled. In the GPS, the corresponding loss was 10.5 mL for females and 8.1 mL for males. All effects were highly significant. We did not test statistically whether male and female excess loss differed, because females have smaller lungs to begin with so that the same absolute loss would have different impact. With the exception of females in the GPS, excess loss for smokers who were not inhalers was smaller than for smokers who were inhalers, but only reached statistical significance in females in the CCHS.

A total of 218 (2.4%) subjects from the CCHS were admitted to hospital for COPD at least once during follow-up, and 23 (0.5%) from the GPS. Adjusting only for age, the male-female risk ratio was 1.2 (0.9–1.5) in the CCHS and 2.3 (1.0–5.7) in the GPS. For comparison with analyses on prediction of lung function, Cox regression analyses were performed using pack-years to summarize tobacco exposure. The results are presented in figures 1 and 2, and show that both in the CCHS and GPS the risk of being hospitalized was higher in females than males for a given number of pack-years, although differences did not reach statistical significance. There were no hospitalizations among male lifelong nonsmokers, so they could not be used for reference. Instead the reference group consisted of lifelong nonsmokers and noninhaling smokers of the same gender. Difference between the male and female reference group could make the risk seem higher for female smokers but repeating analyses using lifelong nonsmokers and noninhalers of both genders as reference did not change the results. Test of interaction between gender and pack-years was not significant: the female-male linear risk ratio per smoking category presented in figures 1 and 2 was 1.3 (1.0–1.8) in the CCHS and 1.9 (0.5–7.5) in the GPS.

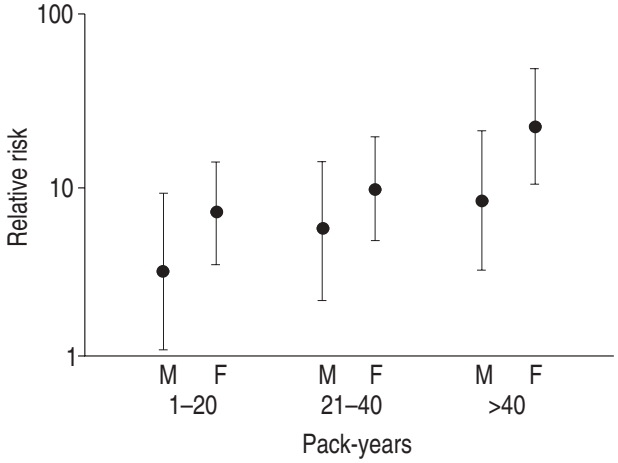

Fig. 1. – Age adjusted relative risk of hospitalization for chronic obstructive pulmonary disease (COPD) by pack years among smokers who inhaled, in the Copenhagen City Heart Study (CCHS). Lifelong nonsmokers and smokers who did not inhale were used as reference (see text). Note the logarithmic scale. M: male; F: female.

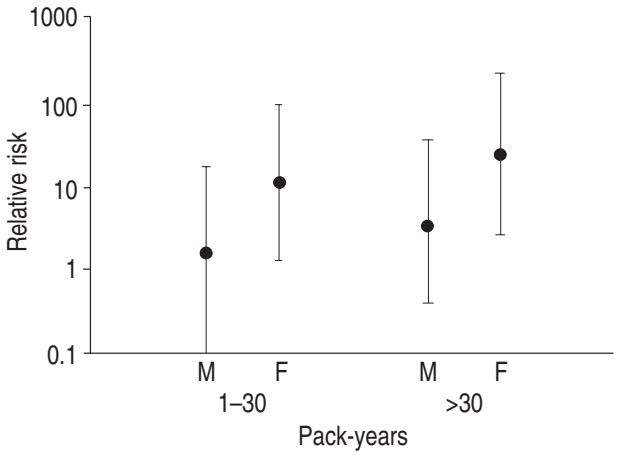

Fig. 2. – Age adjusted relative risk of hospitalization for chronic obstructive pulmonary disease (COPD) by pack years among smokers who inhaled, in the Glostrup Population Studies (GPS). Lifelong nonsmokers and smokers who did not inhale were used as reference (see text). Note the logarithmic scale. M: male; F: female.

Risk of hospitalization was better modelled by including daily tobacco consumption and years of smoking as separate covariates simultaneously. Results from the best model are presented in table 3. In the CCHS, current tobacco consumption for all smokers and years of smoking both for smokers who inhaled and ex-smokers were strong independent predictors of hospitalization, whereas years of smoking for smokers who did not inhale was not associated with hospitalization. Risk estimates were similar in the GPS, although only years of smoking for smokers who inhaled reached statistical significance. In both study populations, females had a higher risk of being hospitalized: in the CCHS the relative risk (RR) for females was 1.5 (1.2–2.1) and in the GPS the RR was 3.6 (1.4–9.0). There were no significant first-order interactions between gender and the tobacco covariates in the model, but at this point the risk associated with smoking was distributed over several risk estimates and power to show interaction with gender was limited.

Table 3. – Relative risk (RR) of hospitalization from COPD (results from Cox regression)

	CCHS (n=9083, 218 events)		GPS (n=4814, 23 events)	
	RR	95% CI	RR	95% CI
Gender				
Male	1		1	
Female	1.5	1.2–2.1	3.6	1.4–9.0
Current tobacco consumption g·day^{-1}				
0	1		1	
<15	2.8	1.2–6.6	1.7	0.2–11.6
15–24	3.9	1.6–9.1	1.7	0.2–12.3
≥25	6.6	2.7–16.2	3.2	0.3–30.4
Years of smoking (per 10 yrs)				
Noninhalers	0.9	0.7–1.3	1.2	0.5–3.2
Inhalers	1.6	1.3–1.8	1.6	1.0–2.7
Ex-smokers	2.0	1.5–2.7	1.6	0.8–3.4

COPD: chronic obstructive pulmonary disease; CCHS: Copenhagen City Heart Study; GPS: Glostrup Population Study; 95% CI: 95% confidence interval. Model: λ_i (age) = λ_0 (age) × exp (β_1 gender + β_2 if light smoker + β_3 if medium smoker + β_4 if heavy smoker + β_5 years of smoking$_{noninhaler}$ + β_6 years of smoking$_{inhaler}$ + β_7 years of smoking$_{ex\text{-}smoker}$).

Seventeen subjects in the CCHS and two in the GPS died, with COPD as the major cause of death, without having been hospitalized for COPD in the observation period. If this was more likely to happen in males than females it could partially explain the gender difference observed. Therefore, analyses were repeated with hospitalization or death from COPD as endpoint. Results regarding female-male risk ratios remained unaffected.

Cohabitation did not predict hospitalization in either of the cohorts. Education was an independent predictor of hospitalization but did not affect parameter estimates for gender or smoking, and was left out of the final models. As expected, FEV1 was a strong predictor of hospitalization for COPD but was not included in the regression models because, as an intermediary variable, it would obscure the association between smoking and hospitalization. Using age as the underlying time scale makes the assumption that hazards, and therefore diagnostic habits, were constant over the follow-up period, and this may not hold true. Therefore, all analyses were repeated with time since entry into the study as time interval and age at entry included as a covariate, and results were the same.

Discussion

In this study of two independent population samples with valid information on follow-up, the main finding was a consistent difference between males and females in effects of smoking on lung function and on subsequent risk of hospitalization for COPD. Excess loss of lung function associated with smoking was greater in females than in males and the adjusted risk of being admitted to hospital for COPD was higher for females than males.

Lung function

The effect of smoking on lung function was analysed using cross-sectional data. Longitudinal data would give a more precise prediction of effects of smoking on lung function but, with the aim of comparing effects of smoking between genders, the use of cross-sectional data is a valid approach. In agreement with previous reports, the study demonstrated a linear association between pack-years and reduced level of FEV1 and the size of the loss per pack-year was also similar [6].

Hospitalization

The use of register-based information on hospital-admissions clearly has the advantage that a large amount of data is available, which would otherwise be very hard to collect. In comparison with mortality data, hospitalization has the advantage that it is more sensitive and there is less delay from onset of disease. The National Hospital Discharge Register is nationwide and there is no loss to follow-up, but as shown in an evaluation of the register [21], it is not without errors regarding validity of the diagnoses. However, for serious morbidity administrative databases tend to be complete and reliable [22]. We know of only one study that has used register-based information on hospitalization in studying COPD morbidity: in a Danish study of 876 randomly selected

males using the National Hospital Discharge Register, the register had high validity in so far as both FEV_1 and respiratory symptoms were strong predictors of hospitalization [23].

For hospitalization to be a suitable marker of gender differences in disease impact, males and females must have equal likelihood of being admitted to hospital, given the same degree of lung disease. Females are generally thought to use health care facilities more than males, but this was not the case for pneumonia. After controlling for smoking, females in the present studies did not have increased risk of being hospitalized for pneumonia. Although this does not preclude the possibility that use of health care facilities differs for other diseases, we have no reason to believe that referral to hospital for COPD is biased in favour of females being admitted more easily than males.

The difference in hospitalization between the two studies (0.5% were hospitalized in the GPS *versus* 2.4% in the CCHS) has several explanations. Subjects in the CCHS were older at study entry and were followed for almost twice as long as subjects from the GPS. Prevalence of smoking was 10% higher in the CCHS (table 1) and, in addition, the CCHS was sampled in the centre of Copenhagen with more socioeconomic problems and higher morbidity and mortality than in the suburbs, where the GPS was sampled.

Smoking

It is well-established that COPD is caused mainly by smoking. In our analyses, tobacco consumption was a strong predictor of hospitalization for COPD. The study demonstrates the importance of adequate controlling for smoking, since this adjustment reversed an increased risk for males to an increased risk for females. In almost all studies based on samples of the general population, males will smoke more, have a longer smoking history, and inhale more often than females. Not controlling thoroughly for this will tend to underestimate the female risk associated with tobacco.

Analyses were based on smoking habits measured at study inclusion. During the 16 yrs of follow-up, one might expect habits to change, but this does not seem to be the case. From 1977 to 1987, smoking habits in Denmark have changed very little, and changes have taken place mainly in the youngest age groups [24]. However, description of changes in smoking habits based on cross-sectional data cannot be conferred to changes within individuals. Most studies show individual smoking habits to be remarkably constant. In the present study, subjects were re-examined after 5 or 10 yrs. The percentage of smokers who gave up smoking between the two examinations was the same for males and females, ranging 5–15%, depending on age and daily tobacco consumption (only 5% of heavy smokers quit). The percentage of nonsmokers who took up smoking between the two examinations was only 2–5%, and also did not differ with gender. Considering the natural history of COPD, a chronic disease which develops after many years of heavy tobacco exposure, these changes in smoking habits after study inclusion are not likely to affect results.

Gender difference

We used two approaches to analyse risk of hospitalization. In the model using pack-years to describe accumulated tobacco exposure, risk associated with pack-years was consistently higher for females than for males in both population studies but the interaction term gender×pack-years did not reach significance ($p=0.08$ in the larger CCHS study). As the number of covariates describing tobacco increased in the second regression model, the interaction term lost further power. However, in the final model, a significant male-female difference was present in both cohorts. Given the gender difference in risk associated with pack-years in the simple model and the fact that COPD is almost exclusively caused by smoking (only 3% of hospital admissions occurred in lifelong nonsmokers), the remaining female excess risk of hospitalization for COPD may be caused by difference in susceptibility to tobacco.

Surprisingly, studies assessing differences in the onset and course of COPD by gender are relatively few. The present findings on gender difference are consistent with several earlier reports [9, 14–16, 25–27] but in contrast to others [6]. In the Beijing Respiratory Health Study of 3,287 subjects, a greater smoking effect both on FEV_1 and forced vital capacity (FVC) was found among females than among males [9]. Similar results were reported on longitudinal data from the Vlagtwedde-Vlaardingen study in The Netherlands [16], in which 4,554 subjects were followed for 6 yrs. In an analysis of 1,149 subjects in Canada, FEV_1 decreased more with increasing pack-years in females than in males [14]. In another study from Canada, which included 1,633 subjects, there was a positive interactive effect of grain-farming exposure and smoking on lung function and prevalence of COPD in females but not in males [15]. In a case-control study of 417 COPD patients, females manifested significant lung disease with less cigarette smoking than males [25]. A recent paper on smoking and lung function in 10,060 adolescents has suggested that girls of this age may be more vulnerable to the effects of smoke [28]. On the other hand, absolute loss of lung function was higher in male smokers than in female smokers in the Six Cities Study [4, 6], and in the Tucson study of 1,705 adults, excess loss of lung function among smokers was also greater in males than in females [29]. In the Lung Health Study [26, 27], airways hyperreactivity among smokers with borderline to moderate airflow limitation was strongly related to gender (85% of females *vs* 59% of males), but this was explained by differences in airway calibre. None of the studies have adjusted for gender differences in inhalation.

Although convincing explanations for these differing results are difficult to construct, difference in study design, data analyses and smoking habits of the study populations may, at least in part, be responsible. In the present study, the same results have been found in two independent population samples that were both random samples of the general population. Analyses are based on a total of 13,897 subjects and smoking prevalence was high both among females and males. Most importantly, however, gender difference in the effect of smoking on lung function was paralleled by gender difference in subsequent risk of hospitalization for COPD.

Previous reports on the mortality rate for COPD in the CCHS have not focused on gender differences. However, COPD-related mortality and ventilatory impairment associated with smoking have been found to be consistently higher among females than among males [10], especially for younger subjects [8]. Moreover, recent results have shown that female heavy smokers have a greater excess decline in lung function than their male counterparts [30]. Future studies will focus on gender differences in mortality rate and loss of lung function.

This study suggests that the adverse effects of smoking on lung function are greater in females than in males. How sex modifies the influence of smoking on lung function is unclear. One obvious possibility is that in females the smoke is distributed into smaller airways, resulting in a larger effective dose per square inch of lung tissue, but genetic or hormonal aetiologies are also possible. Although insight into the mechanisms is insufficient, increased susceptibility may be a contributing factor to the increasing mortality related to chronic obstructive pulmonary disease that is now seen in females.

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