Sex Differences in Mortality of People Who Visited Emergency Rooms for Asthma and Chronic Obstructive Pulmonary Disease

JORDI SUNYER, JOSEP M. ANTÓ, DAVE MCFARLANE, ANTONIA DOMINGO, AURELIO TOBÍAS, MARIA-ANTONIA BARCELÓ, and ALVARO MÚÑOZ

Units of Respiratory and Environmental Research, and Health Services Research, Institut Municipal d'Investigació Mèdica (IMIM), Barcelona, Catalonia, Spain; and Department of Epidemiology, The Johns Hopkins School of Public Health, Baltimore, Maryland

We assess the sex differences in mortality in a population-based cohort of those Barcelona residents older than 14 yr of age who received emergency room services (ERS) for either chronic obstructive pulmonary disease (COPD) or asthma, during the period from 1985 to 1989. Vital status was followed to the end of 1995. A total of 15,517 individuals, 9,918 males and 5,599 females were included in the study. Asthma was diagnosed in 16% of males and 53% of females. Overall, 50% of males and 30% of females died during the follow-up period. The mortality rates in both males and females who visited emergency rooms for COPD or asthma were significantly higher than the expected rates in the general population. These relative increases in the mortality rates were significantly higher in females than in males for both causes of death, COPD (age-adjusted female/male ratio = 2.39), and asthma (ratio = 3.95). However, survival was better in females than males among individuals in the study. The higher fatality in males than females was observed for all causes of death, all respiratory causes, and COPD (risk ratio among patients with COPD = 0.42, 0.29–0.59, and among patients with asthma = 0.11, 0.02–0.60), but not for asthma. Mortality for asthma was higher in females with a diagnosis of COPD (2.79, 1.52–5.13), but it was not different among individuals in whom asthma was diagnosed (1.02, 0.56–1.87). Greater severity of COPD in males than in females could explain a higher risk of dying for all respiratory causes and COPD in males. The increased risk of asthma death in females may be due to problems of coding the term "asthma" in death certificates. The higher rates in females than in males when comparing with the general population, may be an expression of a greater similarity in risk factors, such as smoking, in our population than in males and females of the general population. Sunyer J, Antó JM, Mcfarlane D, Domingo A, Tobías A, Barceló M-A, Múñoz A. Sex differences in mortality of people who visited emergency rooms for asthma and chronic obstructive pulmonary disease. AM J RESPIR CRIT CARE MED 1998;158:851–856.

Obstructive lung diseases, including asthma and chronic obstructive pulmonary disease (COPD), are a leading cause of death in developed countries (1). Few studies have addressed the sex differences in mortality due to COPD or asthma, although recent descriptive studies have reported a decrease in the male/female ratio of mortality for COPD (1–3), attributable to the increase of smoking in females (2), and also to an increase of deaths due to asthma in females in comparison to males (4, 5). Obstructive lung diseases have been seen as a paradigm of the complexity of the health differences between males and females (2). Before age 40, death is very rare and most of the medical visits and hospitalization are associated with a diagnosis of asthma with a certain female predominance (1–7). After that age, males have higher risk of hospitalization and death and in most of the subjects COPD is diagnosed (1–7). Differences in susceptibility factors, smoking, perception of the disease, and access to health services, and also the influence of sex on the differential diagnosis of asthma versus COPD (8, 9), have been related with sex differences in prevalence, hospitalization, and mortality (2).

We assess the sex differences in mortality, and specific mortality for COPD and asthma, in a population-based cohort of individuals who visited emergency rooms in Barcelona for COPD or asthma, including a high number of deaths due to COPD and a relatively high number of deaths due to asthma in comparison with previous follow-up studies (10–16). The study of mortality resulting from obstructive airway disease faces the difficulty of imprecision in the underlying cause expressed in death certificates, in part owing to the link between sex and the coding of COPD or asthma (17).

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Correspondence and requests for reprints should be addressed to Dr. Jordi Sunyer, Unitat de Recerca Respiratòria i Ambiental, Institut Municipal d'Investigació Mèdica (IMIM), Doctor Aiguader 80, E-08003 Barcelona, Catalonia, Spain.

METHODS

Recruitment of the Cohort

We followed the vital status, up to the end of 1995, of Barcelona residents older than 14 yr of age who received emergency room services (ERS) for either COPD or asthma during the period from 1985 to 1989. Data were collected from the clinical records of the four largest urban hospitals, which covered around 80% of all Barcelona COPD and asthma emergency room visits (18). Visits recorded at other hospitals in the city did not differ in terms of social or demographic characteristics (18). Physicians reviewed the clinical records of all daily visits and selected those with labels in the diagnostics section of the clinical record, which matched a list drawn up by a panel of chest physicians. Using this information and, if necessary, other data in the clinical record, they classified the emergency visit as due to asthma, COPD, or other respiratory causes as explained elsewhere (18, 19). Briefly, asthma referred to an attack of asthma, shortness of breath, or bronchospasm, whereas COPD referred to an exacerbation of chronic bronchitis or emphysema. Subjects with bronchospasms or an attack of shortness of breath and a concomitant diagnosis of COPD were classified as COPD. A validity study showed that identification of asthma emergencies was highly reliable (kappa value, $\kappa = 0.81$), as was the agreement after restriction to only individuals with asthma or COPD ($\kappa = 0.91$) (18). Data on name and both surnames, age, sex, address, and details of their referral or discharge (as a surrogate of severity) were recorded.

Entry to the cohort was episode-based (i.e., an emergency room visit for either COPD or asthma). In order to group together episodes referring to the same individual we employed a "flexible deterministic record linkage," using software developed in-house. Data on a given name, both surnames, age, sex, and address were used as clues for the linkage. Age was converted to year of birth. Prior to clustering episodes into individuals, names and addresses were subjected to a standardization procedure which included removal of punctuation, changing multiple spaces to one, suppression of articles from names, expansion of abbreviated forms of surnames, and substitution of some special Spanish and Catalan characters. The process of creating possible pairwise combinations and grouping of the similar records together in clusters began by comparing each record with all those following it in the standardized input file, and assigning a similarity score to each pair formed. Pairs achieving an established cutoff were retained and grouped together. The groups were inspected visually and corrections made in the assignment of episodes to groups if necessary. A total of 16,911 individuals were identified corresponding to 31,002 episodes (99.8% of all episodes).

Follow-up

Follow-up started at the first visit to to the emergency room during the period 1985–1989. Vital status was ascertained using a procedure similar to that outlined previously through record linkage of the cohort individuals with the Catatonia Mortality Registry for the years 1985 to 1995. Fields used for linkage were full name, sex, and year of birth. A total of 15,517 individuals (91.7% of the initial cohort) were included. Exclusions were due to ambiguous linkage with more than one death record after automated comparison followed by intense manual review of groups generated. People not detected as dead in the Mortality Registry were considered alive at the end of the study period (31 December 1995). Causes of death were based on the underlying cause in the death register and classified according to the ninth revision of the International Classification of Diseases (ICD-9) (20). Respiratory mortality refers to codes 460 to 519, COPD to codes 490 to 492, and asthma to 493. A validity study of the goodness of the linkage was carried out in 326 asthmatics whom we had contacted via telephone during 1996. Linkage classified death correctly in 98% of cases. The linkage was able to classify as deaths 93% (39 from 42) of those who actually died, and vice versa classified as alive 99% (282 from 284) of those who actually were alive.

Analysis

Comparison with external population. Mortality rate ratios for the entire period 1985–1995 were obtained using Poisson regression methods, standardized by age (in four groups) and time period (in two periods) for subjects given the same diagnosis at all emergency room visits. Expected mortality was based on mortality for Barcelona City in 1990, at the middle of the follow-up period. The person-year method was used for calculating mortality rates.

Internal comparisons. Assessment of the mortality hazard by sex was carried out using survival methods, with age as the time scale (21), and using the STATA statistical package. Using age as the time scales allows comparisons of the hazard of death in groups of comparable ages but in different calendar periods. Because individuals entered into observation at different ages, survival methods used here are those for cohort studies with staggered entries. An individual only contributes to the risk sets at ages when the individual could have been observed. In accordance with the study design we did two distinct analyses for the periods 1985–1989 and 1990–1995. During 1985–1989 we updated information on diagnosis and severity of each visit and thus the units of analysis were the person-time units corresponding to the age spans after an individual had attended with a given diagnosis and severity until the following visit or the end of the study. An individual contributed in as many individual periods as visits to the emergency services. Estimates of survival curves by sex were done using the Kaplan-Meier method for deaths occurring between 1985–1995. The relative hazard by sex, taking into account diagnosis in emergency services, severity, and age, was estimated with Cox regression (21) both for the period 1985–1989 and for 1990–1995.

The second analysis carried out in the period 1990–1995 allowed us to determine the effect of the individual history during the period 1985–1989 (consisting of the number of visits, and the proportion of asthma and COPD visits discharged home or admitted into the hospital) on the risk of death between 1990 and 1995, after restriction to individuals alive on 31 December 1989. In this analysis, the unit of analysis was the individual, with adjustment for discordant diagnoses of asthma or COPD made on different visits, as it was used in other

TABLE 1

DESCRIPTION OF THE COHORT BY SEX: EMERGENCY ROOM VISITS FOR COPD OR ASTHMA BETWEEN 1985 AND 1989, MORTALITY FOLLOWED TO 1995, IN BARCELONA CITY

	Male	Female
n	9,918	5,599
No. deaths	4,968	1,791
Person-years	55,306	38,362
Rate* 1,000 yr†	89.8	46.2
% deaths < 1990	53.1%	50.2%
Mean age*	62.8	59.0
Diagnosis		
Asthma	1,588 (16.0%)	2,967 (53.0%)
COPD	7,793 (78.6%)	2,194 (39.2%)
Both	537 (5.4%)	438 (7.8%)
% Hospital admission	49.0%	49.0%

* At entrance in the cohort.
† Per 1,000 persons per year.

TABLE 2

PROPORTIONAL MORTALITY BY DIAGNOSIS IN ERS AND BY SEX, BARCELONA CITY, 1985–1995

	COPD*				Asthma*			
	Male		Female		Male		Female	
Cause of Death	n	(%)	n	(%)	n	(%)	n	(%)
All	4,495	100	1,173	100	219	100	424	100
Respiratory	1,794	39.9	390	33.2	62	28.3	126	29.7
COPD	1,427	31.7	262	22.3	26	11.9	44	10.3
Asthma	36	0.8	25	2.1	22	10.0	66	15.6

Definition of abbreviation: n = number of deaths.
* Deaths from individuals who always have been diagnosed with COPD or asthma in ERS. Deaths from individuals with different diagnosis at different admissions (254 male and 194 female) are not included in the table.

TABLE 3

AGE-ADJUSTED RATE RATIO OF DYING IN COMPARISON WITH GENERAL POPULATION OF BARCELONA CITY, BY DIAGNOSIS IN ERS AND BY SEX, BARCELONA CITY, 1985–1995

Diagnosis in ERS	Cause of Death	Male	Female	Female/Male Ratio
		Rate Ratio (95% CI)	Rate Ratio (95% CI)	
COPD*	All	2.55 (2.47–2.62)	2.85 (2.69–3.09)	1.12†
	Respiratory	7.69 (7.29–8.10)	13.1 (11.5–14.6)	1.70†
	COPD	10.6 (9.80–11.5)	25.3 (22.5–28.1)	2.39†
	Asthma	5.69 (3.30–8.08)	21.2 (14.4–27.0)	3.73†
Asthma*	All	1.21 (1.05–1.37)	1.39 (1.32–1.46)	1.15†
	Respiratory	3.07 (1.23–4.11)	5.48 (4.70–6.26)	1.78†
	COPD	2.86 (2.44–3.28)	6.37 (2.86–9.87)	2.23
	Asthma	15.1 (9.99–20.1)	59.7 (18.5–90.0)	3.95†

* Individuals who always have been diagnosed with COPD or asthma in ERS. Individuals with different diagnosis at different admisssions (537 male and 438 female) are not included in the table. Rates for all causes of death per 1,000 persons per year were 109.4 and 99.0 among subjects with COPD, and 17.6 and 18.1 among subjects with asthma, respectively for males and females.
† $p < 0.05$.

fields (22). A p value < 0.05 was considered as the criterion of statistical significance.

RESULTS

A total of 15,517 individuals (9,918 males and 5,599 females) were included in the study (Table 1). Among these, 50.1% of males and 30.2% of females died during the follow-up period and the mortality rate was significantly higher in males. Fifty-two percent of the deaths occurred during the years 1985 to 1989. Males were older than females ($p < 0.01$) and the diagnosis of asthma or COPD was strongly associated with age and sex ($p < 0.01$). Thus, asthma was diagnosed in 16% of males and 53% of females. Before age 45, 70% of males (921 of 1,312) and 94% of females (1,268 of 1,384) were diagnosed with asthma, whereas after age 45 this happened in 8% of males (667 of 8,606) and 40% of females (1,699 of 4,215). Around 32% of subjects had more than one emergency room admission. Among these, 22% had received different diagnoses of COPD or asthma at different visits. Subjects with asthma were more likely to be discharged home than admitted to the hospital in comparison with the other diagnostic groups ($p < 0.05$), with no differences between sexes.

Most of the deaths occurred among individuals who visited for COPD (Table 2). Around 32% of males and 22% of females who always visited during the study period for COPD died of this cause. Death due to asthma was rare in our males and females, although in our asthmatics around 10% of all deaths in males and 16% in females were coded as being due to asthma. The proportion of deaths due to all respiratory causes was higher in males and females diagnosed with COPD than asthma.

The mortality rates in both males and females who visited for COPD or asthma were significantly higher than the expected rates in the general population (Table 3). The ratio of mortality rates for all causes of death, all respiratory causes, and COPD in comparison to the mortality in the general population was larger in subjects who visited for COPD than for asthma, and higher in females than in males.

When mortality was directly compared between both sexes among the individuals receiving emergency services for an obstructive lung disease, survival was poorer in males than females both among individuals attending for COPD and for asthma (Figure 1). The higher risk of dying in males than females was found after adjusting for severity of the emergency visit and age (Table 4). The higher mortality in males than fe-

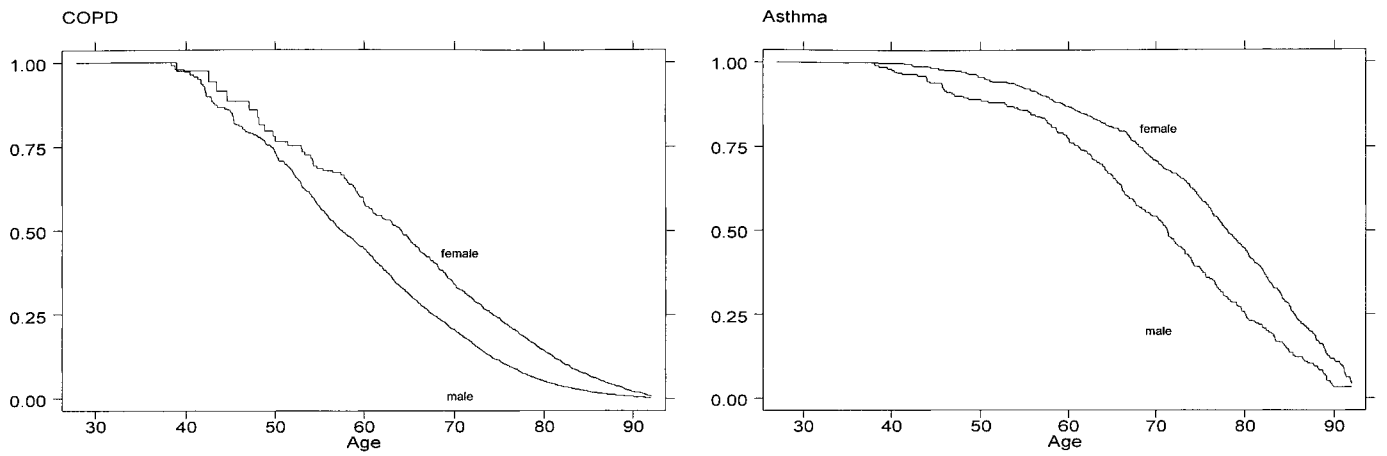

Figure 1. Survival by sex among individuals diagnosed with COPD and asthma in emergency room services. Twenty-eight males and 11 females died before age 30.

TABLE 4

AGE-ADJUSTED FEMALE/MALE RATIO OF THE MORTALITY HAZARD AMONG INDIVIDUALS ATTENDED IN ERS FOR COPD OR ASTHMA

Period	Diagnosis in ERS	Causes of Death			
		All	Respiratory	COPD	Asthma
1985–1989*	COPD	0.76 (0.69–0.82)‡	0.66 (0.57–0.76)‡	0.42 (0.29–0.59)‡	2.79 (1.52–5.13)‡
	Asthma	0.59 (0.46–0.74)‡	0.56 (0.38–0.81)‡	0.11 (0.02–0.60)‡	1.02 (0.56–1.87)‡
	Both	0.73 (0.67–0.80)‡	0.64 (0.56–0.74)‡	0.40 (0.28–0.56)‡	1.67 (1.06–2.64)‡
1990–1995†	All	0.65 (0.60–0.71)‡	0.52 (0.45–0.60)‡	0.31 (0.21–0.48)‡	1.99 (1.26–3.16)‡

* Episode-based analysis: death after an episode between 1985 and 1989, adjusted for diagnosis in ERS and severity.

† Person-based analysis: death for those who survived December 31, 1989 through 1995, adjusted for number of visits, percentage of asthma, or COPD visits, and severity of each visit.

‡ $p < 0.05$.

males was observed for all causes of death, all respiratory causes, and COPD. The sex difference was larger among individuals with asthma than among individuals with COPD or with both conditions. Mortality for asthma was higher in females diagnosed in emergency services as having COPD or receiving both diagnoses. However, mortality for asthma was not different between males and females who visited emergency services for asthma. In the analysis of all individuals who survived 1989, mortality for asthma was also higher in females than in males. But mortality for both causes of death, COPD and asthma together, was higher among males who visited for asthma than among females, although in a nonstatistically significant way (female/male ratio = 0.78, 0.45–1.35).

DISCUSSION

Males who visited ERS for either COPD or asthma had a higher risk of dying due to any cause, due to any respiratory cause, and due to COPD than females. However, when comparing with the expected mortality based on the general population, females had a higher rate ratio than males. Mortality for asthma was higher in females than males in the internal comparisons among individuals seen in emergency services as well as in the external comparisons with the expected mortality in the general population.

Internal Comparison: Fatality was Higher in Males

The higher mortality for all causes in males than females in the internal analysis of the cohort was expected in advance because only a third of deaths were due to respiratory diseases, and males have a higher mortality rate than females for most of the causes of death (2). The fact that sex-related differences in mortality were more important in individuals who had visited for asthma than in individuals who visited for COPD was probably due to the lower proportion of deaths due to respiratory diseases in males with asthma than in males with COPD, thereby increasing the number of persons dying from competing causes of death in asthmatics. However, it is difficult to understand why males attending ERS for obstructive lung diseases showed a higher risk of dying for respiratory causes, and particularly for COPD, than females attending the same services for the same cause. The fact that our analysis adjusted for referral or discharge reduces the possibility that differences in perception of the disease or access to health services were major reasons. Sex differences in severity of COPD (23), or in a poorer compliance of the treatment and secondary preventive measures in males than females (24, 25) are possible reasons that should be further investigated. Although there are few reports on COPD in females, previous investigators had also observed that females with COPD had a more favorable prognosis than males (26, 27). This finding contrasts with the observation that females are more vulnerable than males to the effect of smoking (28–30). The possibility of a differential female underdiagnosis of COPD related with severity of the disease in relation to males was not an explanation because the analysis for all subjects with obstructive lung diseases, controlling for interindividual differences, resulted also in a higher risk for males.

External Comparison: A Higher Relative Increase in Females

A second, and different finding, is that when comparing with a reference population, the relative increase of the mortality rate was higher in females attending the emergency room for COPD and/or asthma than males, and this occurred for all of the death causes assessed. Although our males had a higher fatality than our females, the sex differences in mortality were lower in our individuals than in the general population. Thus, attending emergency services for obstructive lung disease was associated with an increased risk of dying (in comparison with the risk in the general population), which was larger in females than in males. This could be due to the reduction of sex differences in key socioeconomic factors related to death, such as smoking, between our males and females in comparison with males and females of the general population. Coinciding with the smoking explanation, our females with COPD showed a higher relative increase of lung cancer and cardiovascular deaths than males in comparison with the general population (data not shown). A major limitation of our study is the lack of individual data on smoking, and further studies are required to confirm these findings and to assess the role of smoking.

The Peculiarity of Asthma Death

A third finding was that mortality due to asthma was higher in females than males, except in subjects in whom asthma was diagnosed. One explanation is that asthma was more severe in females than in males. In fact, most of the studies of asthmatic patients treated by mechanical ventilation included more females than males (31), and females with asthma are at higher risk of hospitalization than males (32). However, the main problem in the analysis of asthma mortality is misclassification of the asthma diagnosis in the death certificate. Although some patients exhibit features of both conditions, studies using panels of experts assessing death certificates (17, 33) observed an undercoding of asthma deaths more frequently in males than females (17), due to a transfer from asthma to COPD and cardiovascular death. This misclassification increased with age (33). A transfer from COPD to asthma, larger in females than in males, has also been reported (34). We also observed a higher undercoding in males than females

after 45 yr of age (68% of males and 29% of females who visited for asthma and were dying of an obstructive lung disease had a death code of COPD, whereas 2% of males and 9% of females who visited for COPD and were dying of an obstructive lung disease had a death code of asthma). The fact that we observed a larger female/male risk of dying from asthma among patients who attended for COPD than for asthma, and that the risk of dying for all respiratory causes, or the sum of COPD plus asthma, among individuals diagnosed with asthma was higher in males than females, suggests that a differential misclassification of asthma death in the certificates was the cause of the increased risk of asthma death in females.

Validity of the Study

The strengths of the present study are that this is one of the largest cohort studies, including a substantial number of females with COPD and of deaths due to asthma; and that the use of information in repeated visits allowed controlling for misclassification between asthma and COPD. The main limitation was migration out of the region at the time of death, although the migration rate was low during the study period (7% in a sample of our asthmatics). However, the fact that the analysis of the internal comparisons during the period 1985–1989, when migration was less likely since an emergency visit had just occurred, was similar to that in the subsequent period suggests this was a minor problem. The exclusion of subjects due to incomplete linkage did not limit the quality of the study, though it could decrease the external validity. Subjects with the commonest surnames were more likely to be excluded during the linkage process.

The external validity of these findings is limited to the most severe populations with asthma and COPD: patients needing emergency room attendance. According to the European Community Respiratory Health Survey (ECRHS), a general population respiratory survey in individuals younger than 45 yr, in Barcelona 35% of the asthmatics had been attended in emergency room services, probably those with more severe attacks (data not published). Similarly, asthma deaths in our cohort covered 36% of all asthma deaths in the city. To what extent the sex differences observed in this report are limited to the severe populations and cannot be extended to mild asthmatics is debatable. However, we found some similarities between our findings and those of other mortality studies based on general population cohorts (10–16) that included a broader range of severity. The important differences in mortality risk between asthma and COPD support the findings made by Burrows and coworkers (11) based on the Tucson cohort data. Less obvious is the extrapolation of a higher mortality in asthmatics that we found in comparison with the general population. Inclusion of asthmatics with different degrees of severity in the different studies has been attributed as the cause of conflicting results of poorer survival in asthmatics (15). In the cohort of all asthma patients of Rochester (14), an increase in mortality was not found; however, subjects with severe obstructive airflow were excluded. By contrast, the study of a general population cohort in Denmark (15) did find a mortality increase in asthmatics of a magnitude similar to that which we found. Another finding of our study was that most of the asthma deaths occurred at older ages (data not shown), which coincides with a similar result in Rochester (14).

From this large cohort including a high proportion of inhabitants of Barcelona City who visited emergency services for a COPD exacerbation and/or an asthma attack, we conclude that males had a higher risk of dying for all causes, all respiratory causes, and COPD than females. The reasons for a possible higher severity of COPD in males than females should be further investigated. Second, we conclude that death from asthma was more frequent in females than males, but this was due in part to the misclassification of asthma in death certificates. Third, we conclude that attending emergency services for COPD and/or asthma increased the risk of dying disproportionately more in females than males when comparing with mortality rates in the general population, which may be an expression of a greater similarity in risk factors, such as smoking, in our population than in males and females of the general population. Understanding the causes of the sex differences in obstructive airway diseases is relevant in the face of a future increase of obstructive airway diseases in females owing to their increasing prevalence of smoking.

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