Eur Respir J 2006; 28: 781–785
DOI: 10.1183/09031936.06.00152205

Potential misclassification of causes of death from COPD

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ABSTRACT: Little is known about causes of death in chronic obstructive pulmonary disease (COPD) and the validity of mortality statistics in COPD. The present authors examined causes of death using data from the Copenhagen City Heart Study.

Of the 12,979 subjects with sufficient data from the baseline examination during 1976–1978, 6,709 died before 2001. Of these, 242 died with COPD as cause of death. Among subjects with at least severe COPD at baseline, only 24.9% had COPD as cause of death and, in almost half of the cases where COPD was listed as cause of death, the subject had a normal forced expiratory volume in one second /forced vital capacity ratio at baseline.

In COPD patients, having COPD on the death certificate was associated with chronic mucus hypersecretion (CMH) at baseline, an odds ratio (OR) of 3.6 (95% confidence interval 1.7–7.7), and being female (OR 2.7 (1.3–5.6)). In subjects without COPD, CMH and smoking were predictors of COPD as underlying cause of death, ORs 2.3 (1.5–3.7) and 2.2 (1.4–3.6), respectively.

It was concluded that chronic obstructive pulmonary disease is underreported on death certificates, that biases in the use of chronic obstructive pulmonary disease as cause of death can be assessed, and that possible ''over-diagnosis'' of chronic obstructive pulmonary disease on death certificates in subjects unlikely to have significant disease should initiate caution when using causes of mortality in chronic obstructive pulmonary disease epidemiology.

KEYWORDS: Chronic obstructive pulmonary disease, epidemiology, health statistics, mortality

Chronic obstructive pulmonary disease (COPD) is a leading cause of both mortality and morbidity globally [1, 2]. COPD is often diagnosed late and surveys indicate that diagnosed patients with COPD only reflect part of the burden of the disease. From the American National Health and Nutrition Examination Survey (NHANES), it seems that not only mild but also moderate and severe stages of COPD are underdiagnosed [3]. There are few data available concerning underestimation of COPD as cause of death; in fact, only relatively few studies have focused on causes of death in COPD [4–8] and several of them have selected populations. Very little is known about the validity of mortality statistics in COPD.

It has been estimated that at least 200,000 subjects in Denmark suffer from COPD [9] and Denmark is characterised by having a high number of females with COPD, a reflection of the mature smoking epidemic among Danish females [10–12]. Despite this, the acknowledgement of the disease is poor among the general population and COPD is not regarded as one of ''the big killers''.

The aim of the present study was to examine causes of death in subjects with COPD. Whether COPD was underestimated as a primary or contributory cause of death and whether there were signs of bias in recording COPD as cause of death were also investigated. Data were used from a randomly selected cohort of residents in Copenhagen who had taken part in the Copenhagen City Heart Study (CCHS).

METHODS

Population

The CCHS is a prospective epidemiological study including a random, age-stratified sample of 19,327 subjects aged $\geqslant$19 yrs. Participants were selected randomly among residents in Copenhagen during 1976–1978 and 14,223 subjects took part, with a response rate of 74%. Details of the study have been published previously [13]. Participants were asked to fill in a questionnaire about living habits and to participate in a physical examination carried out by trained personnel. In the questionnaire, subjects reported whether they were current smokers, ex-smokers or never-smokers, their present amount and type of tobacco smoked, smoking history and if they inhaled at present. The examination included values of forced expiratory volume in one second (FEV_1) and forced vital capacity

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Received:
December 27 2005
Accepted after revision:
June 08 2006

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

(FVC) measured with an electronic spirometer (Monaghan N403; Monaghan, Littleton, CO, USA) that was calibrated daily. Three sets of values were obtained, and as a criterion for correct performance of the procedure, at least two values had to differ by <5%. The highest measurements of FEV_1 and FVC were used in the analyses as a percentage of predicted values using internally derived reference values based on a subsample of healthy never-smokers [14]. The participants were stratified into stages of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the European Respiratory Society/American Thoracic Society guidelines [15, 16], modified as only pre-bronchodilator values were available as follows. No COPD: $FEV_1/FVC \geqslant 0.7$; stage 0: $FEV_1/FVC \geqslant 0.7$, presence of productive cough; stage 1: $FEV_1/FVC < 0.7$, $FEV_1 > 80\%$ predicted (% pred); stage 2: $FEV_1/FVC < 0.7$, $FEV_1 < 80\%$ pred, and $FEV_1 \geqslant 50\%$ pred; stage 3: $FEV_1/FVC < 0.7$, $FEV_1 < 50\%$ pred, and $FEV_1 \geqslant 30\%$ pred; and stage 4: $FEV_1/FVC < 0.7$, $FEV_1 < 30\%$ pred.

Subjects without COPD were split into ''normal'' and ''restrictive'', the latter being characterised by an FEV_1 <80% pred. Patients with self-reported asthma were excluded from the analyses and, after additionally excluding individuals with insufficient information on other variables, 12,979 subjects remained.

A total of 12,698 subjects attended a second examination during 1981–1983 (response rate 70%), and underwent the same examinations as described previously.

Follow-up

Notification of deaths and causes of deaths were obtained from The Danish Register of Causes of Deaths. This register includes dates and causes for all deaths in Denmark. Follow-up covers the period until December 31, 2000 for causes of death; this gave a mean follow-up time of 23.8 yrs. The eighth revision of The International Classification of Diseases (ICD) was used until the end of 1993 in Denmark, followed by the 10th revision. The following groups of diagnoses listed were analysed as underlying cause of death: COPD (ICD-8 code 491–492; ICD-10 code J42–44), asthma (ICD-8 493; ICD-10 J45), all nonmalignant respiratory diseases (ICD-8 460–519; ICD-10 J00–99), ischaemic heart disease (ICD-8 410–414; ICD-10 I20–25), pulmonary embolism (ICD-8 450; ICD-10 I26), and malignant diseases of trachea, bronchus and lung (ICD-8 160–163; ICD-10 C33–34). When looking at underdiagnosis of COPD, deaths where COPD was listed as a contributing cause of death were also included.

Statistical methods

When examining predictors of potential diagnostic bias, a multivariate logistic regression analysis was used; a p-value of 0.05 was considered statistically significant.

RESULTS

Baseline characteristics for the 12,979 subjects are shown in table 1. There was an increase in age and duration of smoking with increasing severity of COPD. The present authors chose to separate subjects with a restrictive lung function pattern from those with both normal FEV_1/FVC and FEV_1, since they differed by proportion of smokers.

Over the follow-up period 6,709 subjects died (51%). Survival curves are shown in figure 1; the graph is not adjusted for differences between groups in age, sex or other predictors of mortality. There was a clear pattern of decreasing survival with increasing severity of COPD; all COPD stages had significantly worse survival than subjects with normal lung function. Five-year mortality rates in stages 3 and 4 were 14 and 40%, respectively. Subjects with a restrictive lung function pattern had decreased survival, roughly comparable to that of GOLD stage 1. Table 2 shows selected causes of death for all subjects according to GOLD stage at baseline. In subjects with very severe COPD (GOLD stage 4), only one in five had COPD coded as the underlying cause of death and more than half did not have COPD mentioned at all on the death certificate. The likelihood of having COPD registered as cause of death or registered at all varied with time from baseline for the different categories, as shown in figure 2. As expected, most of the 242 deaths with a label of COPD occurred early in patients with severe COPD, whereas subjects without COPD at baseline mainly had a label of COPD on their death certificate if they died late during the follow-up period.

When looking at patients with severe and very severe COPD, GOLD stages 3 and 4 (n=197), and sex, but not age, were predictors of having COPD mentioned on the death certificate. Females were more likely to have COPD mentioned (odds ratio (OR) 2.7 (95% confidence interval 1.3–5.6)). Chronic mucus hypersecretion (CMH) at baseline was also significantly associated with COPD on the death certificate (OR 3.6 (1.7–7.7)), whereas the predictive value of smoking at baseline was not statistically significant (p=0.52). Patients with stage 4 tended to be more likely to have COPD mentioned than stage 3

TABLE 1 Baseline demographics for all participants depending on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage

	Normal	Restrictive#	GOLD				
			0	1	2	3	4
Subjects n	8804	1485	838	664	991	172	25
Mean age yrs	51.4	52.6	52.9	56.5	56.1	57.4	62.0
Males %	43	40	53	60	53	55	76
Current smokers %	58	72	79	68	77	73	68
Former smokers %	18	13	11	17	11	17	24
Productive cough %	0	5	100	10	18	32	28
Duration of smoking yrs	26.4	28.5	30.6	32.9	33.7	34.4	37.8
Mean FEV_1 % pred	102	71	94	92	67	42	22

FEV1: forced expiratory volume in one second; % pred: % of the predicted. #: restrictive lung function pattern, *i.e.* FEV_1/forced vital capacity $\geqslant 0.7$ and FEV_1 <80% pred.

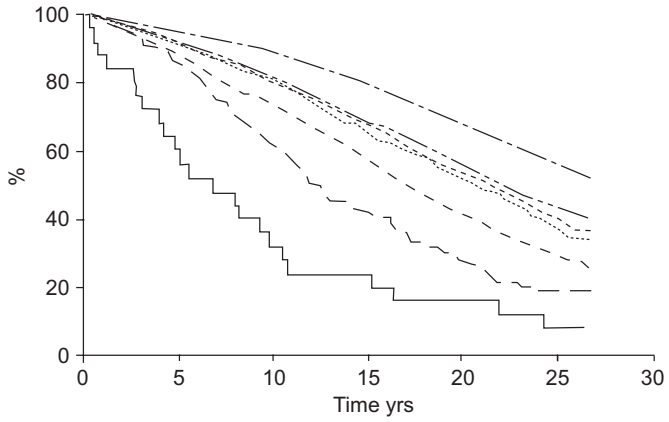

FIGURE 1. Survival for the cohort divided according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification at baseline. — - — - : normal; ----: restrictive; — -- — : GOLD 0; ·····: GOLD 1; – – – –: GOLD 2; — — — — : GOLD 3; ———: GOLD 4.

(OR 2.0 (0.7–5.4)) but this difference was not statistically significant (p=0.18).

Of the 242 deaths with COPD coded as the underlying cause of death, 114 (47%) had a normal FEV1/FVC ratio at baseline. Among the 11,127 subjects with normal FEV1/FVC ratio at baseline, neither age nor sex was associated with likelihood of having COPD. CMH and smoking at baseline were significant predictors of having COPD registered as underlying cause of death (OR 2.3 (1.5–3.7) and 2.2 (1.4–3.6), respectively). Having a restrictive lung function pattern was associated with COPD as cause of death (OR 2.5 (1.7–3.7)).

TABLE 2 Mortality and main causes of death depending on baseline the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage

	Normal	Restrictive#	GOLD				
			0	1	2	3	4
Subjects n	8804	1485	838	664	991	172	25
Deaths %	45.4	61.8	58.6	64.6	72.4	80.2	92.0
Cause of death %							
COPD	1.4	4.1	3.9	4.2	9.8	25.4	21.7
Asthma	0.2	0.2	0.2	0.5	0.8	1.4	4.3
All respiratory	3.2	5.8	5.9	7.7	12.9	28.2	26.0
Ischaemic heart disease	18.1	15.0	19.6	18.2	15.2	17.4	13.0
Respiratory cancer	6.0	8.1	11.0	8.2	11.6	9.4	13.0
COPD mentioned on certificate %	3.0	9.8	8.9	9.5	17.5	37.0	45.5

COPD: chronic obstructive pulmonary disease. #: restrictive lung function pattern, *i.e.* forced expiratory volume in one second (FEV1)/forced vital capacity ⩾0.7 and FEV1 <80% pred.

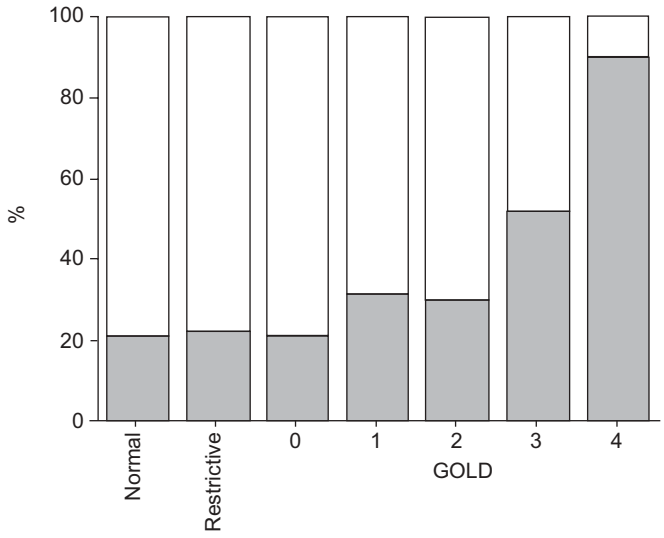

FIGURE 2. Proportion of deaths occurring in the first (■) or second (□) half of follow-up, divided according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage at baseline.

Additional information on subjects without COPD at baseline was obtained from the second examination, 5 yrs after baseline. A total of 7,184 of the 8,804 subjects without COPD had spirometry after 5 yrs, and 5.7% of these had FEV1/FVC <0.7. Subjects without COPD at baseline who died with COPD as cause of death after >5 yrs (n=25) were more likely to have developed airflow obstruction within the first 5 yrs (36.7%) than those dying from all other causes (n=2,411; 11.7%).

DISCUSSION

The present study has shown that causes of death may not necessarily reflect burden of disease in studies of the impact of COPD. Patients with severe and even very severe COPD may not have COPD listed on their death certificate, and a substantial proportion of COPD deaths occurred in subjects without airflow obstruction or abnormal FEV1 in a survey two decades earlier.

Previous studies have also concluded that COPD is underreported on death certificates. From a study carried out in Tucson, AZ, USA, CAMILLI *et al.* [17] found rates of mentioning of COPD or asthma on death certificates quite similar to those of the present study. They also found that females were more likely to have a label of obstructive lung disease on the death certificate; however, the authors do not separate asthma and COPD in their paper. In an older study by MITCHELL *et al.* [18], using autopsy as the gold standard for the correct diagnosis, a lack of mentioning of chronic bronchitis or emphysema on the death certificate occurred in 18–33% of cases in patients dying at Veterans Administration hospitals. Using the US National Center for Health Statistics data, MANNINO *et al.* [19] found obstructive lung disease underestimated in studies looking only at the underlying cause of death and, in the present study, COPD was indeed a rare feature on death certificates. MANNINO *et al.* [19] noted the striking difference in changes

over time in COPD mortality in females and males, but could only speculate on causes for this. Surprisingly, being female in the present study increased the likelihood of having a diagnosis of COPD on the death certificate. Most studies on sex and COPD have shown the opposite trend, *i.e.* males were more likely to be diagnosed with COPD, given the same clinical findings. CHAPMAN *et al.* [20] found that primary care physicians were significantly less likely to diagnose COPD in females when presented with hypothetically identical case stories, varying only by sex. Previous analyses of this cohort have indicated that females may be more susceptible to developing COPD [21]. It is not known if the increased likelihood of COPD as cause of death in females is the result of an increased awareness of COPD within the last decade. The fact that awareness plays a role for registration of causes of death is reflected in the overall mortality statistics; in Copenhagen, the proportion of deaths registered as ''chronic bronchitis, emphysema and asthma'' increased from 3.4% in 1977 to 6.1% in 2001 [22].

In general, the reliability of diagnoses on death certificates is known to be far from perfect and this is also the case for COPD. FAREBROTHER *et al.* [23] used 10 case reports when asking doctors from eight European countries to state the diagnosis they would write on a hypothetical death certificate. The differences in the use of the terms COPD, emphysema and asthma were considerable. In the present study, COPD and emphysema were not separated; including asthma would not have changed the overall picture, but it is noteworthy that the likelihood of having asthma as a cause of death increased with increasing COPD stage. It is well known that most COPD patients die from causes other than COPD. In mild COPD in the Lung Health Study [7], the largest single cause was actually lung cancer. In the present study, death from ischaemic heart disease was more frequent; however, among subjects with COPD, death from lung cancer made up 10% of all deaths. Subjects with a restrictive lung function constitute an interesting group receiving little attention in respiratory epidemiology. MANNINO *et al.* [24] also found that subjects with a restrictive pattern of spirometry had an increased mortality, independent of smoking. It is most probable that only few of these subjects have interstitial lung disease; the majority will have poor spirometry performance and/or some degree of heart failure.

It was found that almost half of the deaths listed with COPD as cause of death occurred in subjects with normal spirometry at baseline, and this seems both surprising and worrying from the point of view of health statistics. Most of these deaths occurred late in the follow-up period and it is therefore possible that some of these subjects had indeed developed COPD before their death. This is supported by data from the 5-yr follow-up study, showing a higher 5-yr incidence of COPD in subjects subsequently dying with COPD as cause of death than in subjects subsequently dying from other causes. Nevertheless, dying from COPD within 20 yrs of having no airflow obstruction does not fit with the authors' present understanding of COPD as a slowly progressive disease and, in addition, it was found that two out of three of those without COPD at baseline who died with COPD as cause of death after the 5-yr follow-up study still had normal lung function at this survey. The present authors therefore suggest that some of the deaths recorded as due to COPD may have been misclassified, most probably in subjects with cardiac disease causing breathlessness. This seems to be supported by the higher risk of COPD as cause of death in subjects with a restrictive spirometry pattern.

Finally, it can, to some extent, be seen as unfair to evaluate previous ways of registering deaths from COPD using today's tools. When using ICD-8, the term COPD was not an option for coding and most COPD deaths were likely to be coded as due to ''chronic bronchitis'' or ''emphysema''. It is possible to have chronic bronchitis without COPD, but it was thought unlikely that anybody could have chronic bronchitis as the underlying cause of death without having airflow obstruction. Conversely, patients with even severe COPD can of course die from other diseases unrelated to COPD. However, clinicians are asked to also enter other significant diseases on the death certificate present at the time of death.

The implications of the present findings are as follows. First, they indicate that underdiagnosis is not merely a phenomenon of the living; chronic obstructive pulmonary disease is insufficiently reported on death certificates when patients with clinical chronic obstructive pulmonary disease die. Secondly, this lack of a chronic obstructive pulmonary disease diagnosis on death certificates, and the possible over-diagnosis of chronic obstructive pulmonary disease on death certificates in subjects unlikely to have significant disease, should initiate care when interpreting epidemiological trends based on mortality statistics alone.

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