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Potential misclassification of causes of death from COPD in a Danish population study.

Henriette H Jensen [1], Nina S Godtfredsen [1], Peter Lange [1,2], Jørgen Vestbo [1,3].

1. Department of Cardiology and Respiratory Medicine, Hvidovre Hospital, Hvidovre, Denmark.
2. The Copenhagen City Heart Study, Bispebjerg Hospital, Copenhagen, Denmark.
3. North West Lung Centre, Wythenshawe Hospital, Manchester, UK.

Correspondence: Professor Jørgen Vestbo
Department of Cardiology and Respiratory Medicine 253
H:S Hvidovre Hospital
Kettegård Alle 30
DK-2650 Hvidovre
Denmark

Phone: +45 3632 6295 or +45 3035 0317
Fax: + 45 3632 3784
E-mail: joergen.vestbo@hh.hosp.dk

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Abstract

Little is known about causes of death in COPD and the validity of mortality statistics in COPD. We examined causes of death in the Copenhagen City Heart Study.

Of the 12,979 subjects with sufficient data from the baseline examination in 1976-78, 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 FEV_1/FVC ratio at baseline. In COPD patients, having COPD on the death certificate was associated with chronic mucus hypersecretion (CMH) at baseline, odds ratio (OR) 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 predicted COPD as underlying cause of death, OR's 2.3 (1.5-3.7) and 2.2 (1.4-3.6), respectively.

We conclude that COPD is underreported on death certificates, that biases in the use of COPD as cause of death can be assessed, and that possible "over-diagnosis" of COPD on death certificates in subjects unlikely to have significant disease should make us cautious when using causes of mortality in COPD epidemiology.

Abstract: 200 words

Introduction

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 is little 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 women with COPD – a reflection of the mature smoking epidemic among Danish women (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. We also examined whether COPD was underestimated as primary or contributory cause of death and whether there were signs of bias in recording COPD as cause of death. We used data from a randomly selected cohort of residents in Copenhagen, The Copenhagen City Heart Study.

Methods

Population

The Copenhagen City Heart Study (CCHS) is a prospective epidemiological study including a random, age-stratified sample 19,327 subjects age 19 years and older. Participants were selected randomly among residents in Copenhagen in 1976-78 and 14,223 subjects took part, response rate at 74%. Details of the study have been published previously (13). Participants were asked to fill out a questionnaire about living habits and to participate in a physical examination done by trained personal. 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 (FVC) measured with an electronic spirometer (Monaghan N 403, Littleton, Colorado) which 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 less than 5 %. The highest measurement of FEV_1 and FVC were used in the analyses as percentage of predicted values using internally derived reference values based on a sub-sample of healthy never smokers (14). We stratified the participants into stages of COPD according to the GOLD and ERS/ATS guidelines (15, 16), modified as we only had pre-bronchodilator values available:

No COPD: $FEV_1/FVC \geq 0.7$.

Stage 0: $FEV_1/FVC \geq 0.7$, presence of productive cough.

Stage 1: $FEV_1/FVC < 0.7$, $FEV_1 > 80\%$pred.

Stage 2: $FEV_1/FVC < 0.7$, $FEV_1 < 80\%$pred., and $FEV_1 \geq 50\%$pred.

Stage 3: $FEV_1/FVC < 0.7$, $FEV_1 < 50\%$pred., and $FEV_1 \geq 30\%$pred.

Stage 4: $FEV_1/FVC < 0.7$, $FEV_1 < 30\%$pred.

Subjects without COPD were split in "Normal" and "Restrictive", the latter 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, we were left with 12,979 subjects.

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

Follow-up

Notification of deaths and causes of deaths was 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 31 December 2000 for causes of death; mean follow-up time 23.8 years. The 8th revision of The International Classification of Diseases (ICD) was used until the end of 1993 in Denmark, followed by the 10th revision. We analysed the following groups of diagnoses listed as underlying cause of death: COPD (ICD-8 code 491–2; ICD-10 code J42-44), asthma (ICD-8 493; ICD-10 J45), all non-malignant respiratory diseases (ICD-8 460–519; ICD-10 J00-99), ischemic 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 we also included deaths where COPD was listed as a contributing cause of death.

Statistical methods

When examining predictors of potential diagnostic bias we used a multivariate logistic regression analysis; a p-value of 0.05 was considered statistically significant. We used SPSS Version 12.0.1 for Windows.

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. We chose to separate subjects with a restrictive lung function pattern from those with both normal FEV_1/FVC and FEV_1, since they differ 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, gender, 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 stage 3 and 4 were and 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, 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), gender but not age was a predictor of having COPD mentioned on the death certificate. Women were more likely to have COPD mentioned, odds ratio (OR) 2.7 (95%

confidence interval 1.3-5.6). Chronic mucus hypersecretion 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, 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 FEV_1/FVC ratio at baseline. Among the 11,127 subjects with normal FEV_1/FVC ratio at baseline, neither age nor gender was associated with likelihood of having COPD. Chronic mucus hypersecretion and smoking at baseline were significant predictors of having COPD registered as underlying cause of death, OR's 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).

Additional information on subjects without COPD at baseline was obtained from the second examination, 5 years after baseline. A total of 7,184 of the 8,804 subjects without COPD had spirometry after 5 years and 5.7% of these had FEV_1/FVC < 0.7. Subjects without COPD at baseline who died with COPD as cause of death after more than 5 years (N = 25) were more likely to have developed airflow obstruction within the first 5 years, 36.7%, than those dying from all other causes (N = 2411), 11.7%.

Discussion

Our 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 FEV_1 at a

survey 2 decades earlier.

Previous studies have also concluded that COPD is under-reported on death certificates. Camilli et al from Tucson (17) found rates of mentioning of COPD or asthma on death certificates quite similar to ours. They also found women more likely to have a label of obstructive lung disease on the death certificate but the authors do not separate asthma and COPD in their paper. In an older study by Mitchell et al using autopsy as the gold standard for the correct diagnosis, 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 (18). Mannino et al, using US National Center for Health Statistics data, found obstructive lung disease underestimated in studies looking only at the underlying cause of death (19) and in our study COPD was indeed a rare feature on death certificates. Mannino et al noted the striking difference in changes over time in COPD mortality in women and men but could only speculate on causes for this. Surprisingly, being female in our study increased the likelihood of having a diagnosis of COPD on the death certificate. Most studies on gender and COPD have shown the opposite trend; that is, men being more likely to be diagnosed with COPD given the same clinical findings. Chapman et al found that primary care physicians were significantly less likely to diagnose COPD in women when presented with hypothetical identical case stories, only varying gender (20). Previous analyses of this cohort have indicated that women may be more susceptible to developing COPD (21). We do not know if the increased likelihood of COPD as cause of death in women 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).

The reliability of diagnoses on death certificates in general is known to be far from perfect and this is also the case for COPD. Farebrother et al (23) used 10 case stories when asking doctors from 8 European countries to state the diagnosis they would write on a hypothetical death certificate. The differences in the use of terms COPD, emphysema and asthma were considerable. In our study we did not separate COPD and emphysema; in our study, including asthma would not have changed the overall picture but it is noteworthy that the likelihood of having asthma as 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 the largest single cause was actually lung cancer (7). In our study death from IHD 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 also found that subjects with a restrictive pattern of spirometry had an increased mortality, independent of smoking (24). Most likely, only few of these subjects have interstitial lung disease. The majority will have poor spirometry performance and/or some degree of heart failure.

We found that almost half of the deaths with COPD as cause of death occurred in subjects with normal spirometry at baseline and this seems both surprising and worrying from a health statistics point of view. 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-year follow-up showing a higher 5-year incidence of COPD in subjects subsequently dying with COPD as cause of death than in subjects subsequently ding from other causes. Nevertheless, dying from

COPD within 20 years of having no airflow obstruction does not fit with our understanding of COPD as a slowly progressive disease, and in addition we found that 2/3 of those without COPD at baseline who died with COPD as cause of death after the 5-year follow-up still had normal lung function at this survey. We therefore suggest that some of the deaths recorded as due to COPD may be misclassified, most likely 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 we thought it 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.

What are the implications of our findings? First, they indicate that under-diagnosis is not merely a phenomenon of the living; COPD is insufficiently reported on death certificates when patients with clinical COPD die. Secondly, this lack of a COPD diagnosis on death certificates, and the possible "over-diagnosis" of COPD on death certificates in subjects unlikely to have significant disease, should make us careful when interpreting epidemiological trends based on mortality statistics alone.

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Figure legend

Figure 1.

Survival for the cohort divided according to GOLD classification at baseline.

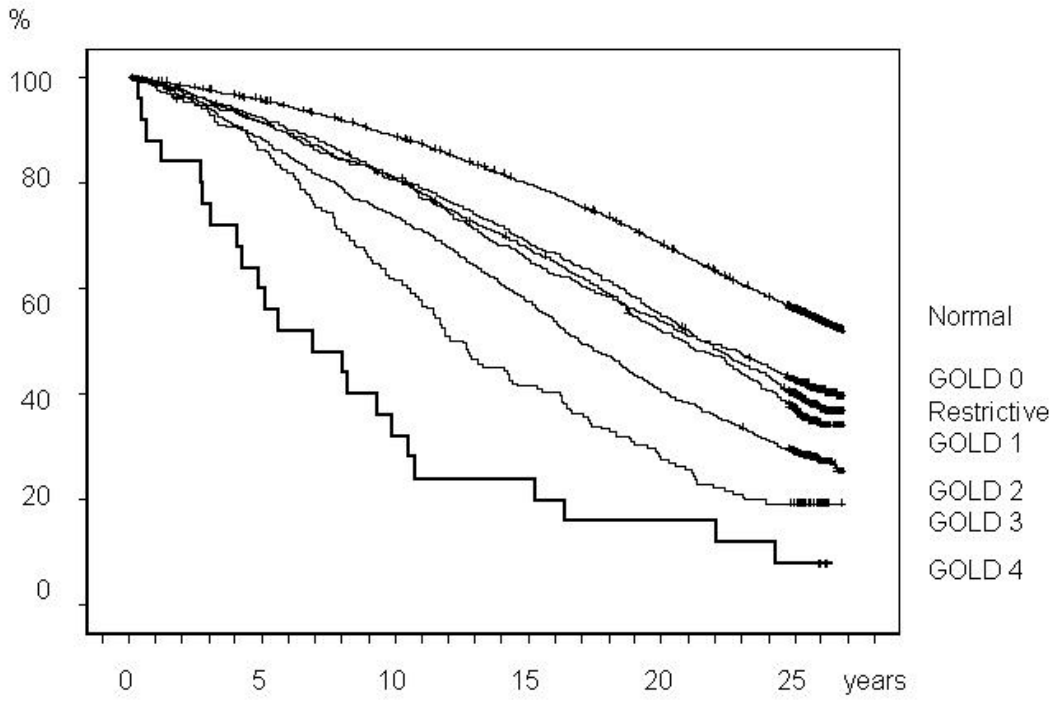

Figure 2.

Proportion of deaths occurring in first or second half of follow-up, divided according to GOLD stage at baseline.

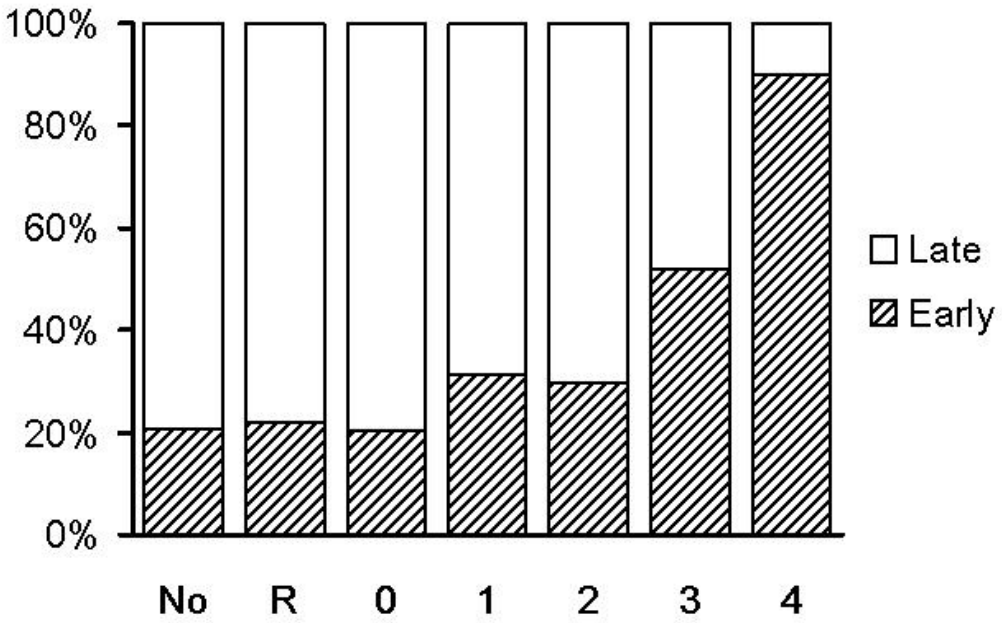
100%
80%
60%
40%
20%
0%
No
R
0
1
2
3
4
Late
Early

Table 1.

Baseline demographics for all participants depending on GOLD Stage.

GOLD Stage	Normal	Restr.*	0	1	2	3	4
N	8,804	1,485	838	664	991	172	25
Mean age (years)	51.4	52.6	52.9	56.5	56.1	57.4	62.0
% men	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 (years)	26.4	28.5	30.6	32.9	33.7	34.4	37.8
Mean FEV_1 in % of predicted	102	71	94	92	67	42	22

* Restrictive lung function patter; i.e., $FEV_1/FVC \geq 0.7$ & $FEV_1 < 80\%$pred.

Table 2.

Mortality and main causes of death depending on baseline GOLD Stage.

GOLD Stage	Normal	Restr.*	0	1	2	3	4
N	8,804	1,485	838	664	991	172	25
Deaths (%)	45.4	61.8	58.6	64.6	72.4	80.2	92.0
Death from (%)							
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
IHD **	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

* Restrictive lung function patter; i.e., $FEV_1/FVC \geq 0.7$ & $FEV_1 < 80\%pred$. ** Ischemic heart disease