



Original Research

Large underreporting of COPD as cause of death-results from a population-based cohort study

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ABSTRACT

Background: In 2019, WHO estimated COPD to be the third leading cause of death in the world. However, COPD is probably underestimated as cause of death due to the well-known under-diagnosis.

Aim: To evaluate the proportion of and factors associated with COPD recorded as cause of death in a long-term follow-up of a population-based COPD cohort.

Methods: The study population includes all individuals ($n = 551$) with COPD defined as chronic airway obstruction (post-bronchodilator $FEV_1/FVC < 0.70$) + respiratory symptoms identified after re-examinations of four population-based cohorts. Mortality and underlying or contributing cause of death following ICD-10 classification were collected from the Swedish National Board of Health and Welfares register from date of examination in 2002–04 until 2016.

Results: The study sample consisted of 32.3% GOLD 1, 55.9% GOLD 2, and 11.8% GOLD 3–4. The mean follow-up time was 10.3 (SD3.77) years and the cumulative mortality 45.0%. COPD (ICD-10 J43-J44) was recorded on 28.2% ($n = 70$) of the death certificates (11.1%, 25.7% and 57.1% by GOLD stage), whereof $n = 35$ had COPD recorded as underlying and $n = 35$ as contributing cause of death. To have COPD recorded as cause of death was independently associated with ex- and current smoking and a self-reported physician diagnosis of COPD, while male sex, overweight/obesity and higher $FEV_1\%$ of predicted associated with the absence.

Conclusions: COPD was largely underreported cause of death. Even among those with severe/very severe disease, COPD was only mentioned on 57.1% of the death certificates.

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major health problem and in 2019 the World Health Organization, WHO, estimated COPD to be the third leading cause of death, surpassed only by ischemic heart disease and stroke [1]. Within the European Union, respiratory disease has been reported to be the third main cause of deaths, and COPD accounted for 40% of all deaths due to respiratory diseases [2].

Individuals with COPD have a significantly higher mortality rate than those without obstructive lung function impairment [3–7] and all-cause mortality increases with disease severity [3,4,8]. However, COPD is largely under-diagnosed, and only around a third of all individuals with COPD are recognized [9–13]. This substantial under-recognition implies that also official statistics regarding COPD as

cause of death is underestimated, supported by data from the large-scale population-based Copenhagen City Heart Study (CCHS). In a 25-year follow-up conducted in 2001, merely around every other individual with very severe pre-bronchodilator airway obstruction had COPD listed on their death certificates [14].

Prospective population-based studies evaluating respiratory causes of death among individuals with COPD are rare [14], and hardly anyone includes post-bronchodilator spirometry. Furthermore, there is truly a difference between mortality among individuals with COPD and death due to COPD. Thus, when investigating to what extent respiratory conditions are acknowledged on the death certificates among deceased with COPD, both underlying and contributing causes of death are important to consider.

Hence, the aim of this study was to evaluate the proportion with

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COPD recorded as either underlying or contributing cause of death among deceased in a long-term follow up of a population-based COPD cohort, and to identify clinically relevant factors associated with having COPD on the death certificates.

2. Materials and methods

2.1. Study population

During 2002–2004, four adult population-based cohorts within the epidemiological research program the Obstructive Lung disease In Northern Sweden (OLIN) studies were invited to re-examination including spirometry and a structured interview following a validated questionnaire [15]. All individuals with airway obstruction, pre-bronchodilator FEV₁/VC < 0.70 (n = 993), were identified whereof n = 736 had post-bronchodilator, i.e. chronic airway obstruction (CAO). The study sample for the present study include those with CAO and at least one of the following respiratory symptoms during the last 12 months (n = 551): longstanding cough, cough with phlegm most days during at least three months, recurrent wheeze or dyspnea (mMRC-dyspnea [16] score ≥2). Cross-sectional data from the clinical examinations was linked to data on mortality and causes of death from the Swedish National Board of Health and Welfares registry, from the date of examination at recruitment until April 2016. The study was approved by the Regional Ethics Committee at Umeå University (Dnr 04–045 M and supplementary application for mortality including cause of death 2015/446-31Ö).

2.2. Definitions based on data collected by structured interview

Smoking habits were classified into non-smokers, ex-smokers (since at least one year), and current smokers.

Self-reported physician-diagnosis of COPD: affirmative answer to the question ‘has a physician told you that you have COPD, chronic bronchitis or emphysema’.

Exacerbation: affirmative answer to the question ‘have you contacted health care due to respiratory complaints during the last 12 months.

Frequent exacerbations: two or more such events during the last 12 months.

2.3. Spirometry and spirometric classification

Lung function testing was performed in accordance with the American Thoracic Society’s (ATS) guidelines [17]. The Mijnhardt Vicatest 5 dry volume spirometer was used. Vital capacity (VC) was defined as the best value of slow and forced vital capacity (SVC and FVC). Reversibility testing was performed using 0.8 mg salbutamol (4 × 0.2 mg Ventoline discus®) if FEV₁/VC < 0.70 or FEV₁<90% of predicted. CAO was defined as FEV₁/VC < 0.70 based on the highest values pre- or post-bronchodilation. Airflow limitation was classified according to GOLD into 1–4 based on FEV₁% of predicted [18]. The Swedish OLIN reference values were used [19].

2.4. Causes of death

In accordance with WHO, the medical certificate on cause of death (hereafter labelled death certificate) in Sweden is divided into part I, underlying causes of death, and part II, contributing causes of death. Causes of death were classified according to the 10th version of International Statistical Classification of Diseases (ICD-10) [20]. COPD was defined as ICD-code J43 Emphysema or J44 COPD, with/without acute exacerbation.

2.5. Statistical analyses

The Statistical Package for the Social Sciences (SPSS) software

version 25 was used. P-values < 0.05 from two-sided tests were considered statistically significant. Logistic regression models were constructed to estimate odds ratios (OR) with 95% confidence intervals (CI) for age, sex, smoking habits (non-smoker, ex-smoker and current smoker), BMI categories (underweight (<18.5), normal (18.5–25), and overweight/obesity (>25)), FEV₁% of predicted, dyspnea, frequent exacerbations, CVD and a self-reported physician diagnosis of COPD in association to having COPD recorded on the death certificate. These analyses were performed both unadjusted, and by including age and all significantly associated covariates in the same adjusted models.

2.6. Sensitivity analyses

To further evaluate potential impact of under-diagnosis and misclassification of COPD, analyses were also performed for having *any respiratory diseases* (ICD-codes J00–J99) recorded on the death certificates, and by conducting separate analyses among those with a self-reported physician diagnosis of COPD at recruitment.

3. Results

3.1. Clinical characteristics and cumulative mortality

The study population (Table 1) included n = 551 with COPD, with a distribution by GOLD stage of n = 178 (32.3%) GOLD 1, n = 308 (55.9%) GOLD 2, and n = 65 (11.8%) GOLD 3–4. The all-cause cumulative mortality was 45.0% (n = 248) over a mean follow-up time of 10.3 (SD3.77) years, increasing by GOLD-stage: 35.4%, 44.2% and 75.4% in GOLD 1, GOLD 2 and GOLD 3–4 (Table 2). All cause-specific mortality by underlying causes of death among deceased is presented in online Table 1 following the systematic structure of the ICD-10 code chapters. The most common underlying causes of death were diseases of the circulatory system (n = 102, 41.1%), followed by neoplasms (n = 61, 24.6%) and diseases of the respiratory system (n = 42, 16.9%).

Table 1

Clinical characteristics of the study population, all individuals with COPD at recruitment. Presented as n (%) unless otherwise stated.

Characteristics	n = 551
Age, mean (SD)	65.6 (11.2)
Sex, female	249 (45.2)
BMI categories	
underweight (<18.5)	7 (1.3)
normal weight (18.5–25)	233 (42.3)
overweight/obese (>25)	311 (56.4)
Smoking habits	
non-smoker	119 (20.0)
ex-smoker	212 (38.5)
current smoker	229 (41.6)
Pack years, mean (SD)	17.8 (16.8)
FEV ₁ % pred ^a , mean (SD)	70.9 (17.6)
Longstanding cough	250 (45.4)
Productive cough ^b	338 (61.3)
Recurrent wheeze ^c	367 (66.6)
Dyspnea ^d	209 (37.9)
Frequent exacerbations	65 (11.8)
CVD ^e	149 (27.0)
Self-reported physician diagnosis of COPD	151 (27.4)

^a Post-bronchodilation.

^b Cough with phlegm most days during at least three months the last 12 months.

^c Recurrent wheeze during the last 12 months.

^d mMRC ≥ 2.

^e Cardiovascular disease (heart disease, claudication or cerebrovascular disease).

Table 2

Number of deceased in the total study population and by GOLD stage presenting the proportion, n (%), with COPD (J43-J44) recorded on the death certificate, and also any respiratory diseases (J00-J99, i.e. including J43-J44), further divided into underlying and contributing cause of death, respectively.

	COPD, all	GOLD 1	GOLD 2	GOLD 3-4
Number of deceased, total	n = 248	n = 63	n = 136	n = 49
COPD (J43-J44)	70 (28.2)	7 (11.1)	35 (25.7)	28 (57.1)
Underlying cause of death	35 ^a	2	14	19
Contributing cause of death	35 ^b	5	21	9
Any respiratory diseases (J00-J99)	96 (38.7)	15 (23.8)	50 (36.8)	31 (63.2)
Underlying cause of death	42	2	19	20
Contributing cause of death	54	13	31	11

^a J43 n = 4, J44 n = 31.

^b J44 n = 35.

3.2. COPD recorded as cause of death

COPD (J43-J44) was recorded as either underlying or contributing cause of death on 28.2% (n = 70) of the death certificates (Fig. 1), with increasing proportions by GOLD stage 1, 2 and 3–4 accordingly: 11.1%, 25.7% and 57.1%. Among the deceased with COPD on their death certificates, it was recorded as underlying cause of death in 50% (n = 35) and this proportion increased by GOLD-stage, 28.6%, 40.0% and 67.9% (Table 2).

3.3. Factors associated with COPD on the death certificates

In unadjusted analyses among the deceased, ex- and current smoking, dyspnea, frequent exacerbations and a self-reported physician diagnosis of COPD at recruitment were associated with COPD on the death certificates, while male sex, overweight/obesity and higher FEV₁% of predicted rather were associated with the absence (Table 3). In the adjusted model including age, sex, BMI-categories, smoking habits, FEV₁% predicted, dyspnea, frequent exacerbations and self-reported physician diagnosis of COPD, the associations with dyspnea and frequent exacerbations were lost, but otherwise the pattern was similar to the unadjusted results (Fig. 2).

3.4. Sensitivity analyses

Any respiratory diseases (J00-J99) were recorded on 38.7% (n = 96) of the death certificates and the proportion increased by GOLD stage, 23.8%, 36.8% and 63.2% in GOLD 1, GOLD 2 and GOLD 3–4, respectively. Among deceased with any respiratory diseases recorded on the death certificates it was the underlying cause in 43.8%, a proportion that mainly was driven by COPD and that increased by GOLD stage (13.3%,

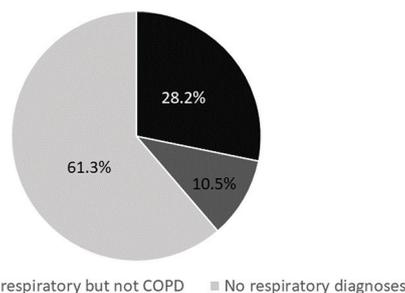


Fig. 1. The distribution of COPD (ICD-code J43 Emphysema or J44 COPD), any respiratory but not COPD and no respiratory diagnoses on the death certificates in the study population.

Table 3

Unadjusted analyses of factors associated with COPD (J43-J44) recorded on the death certificates among deceased, expressed as Odds Ratios (OR) and 95% Confidence Intervals (CI). Significant values in bold.

	OR	95% CI
Age ^a	1.00	0.97–1.03
Male sex	0.56	0.32–0.98
BMI-categories		
normal weight	1	
underweight	1.09	0.18–6.80
overweight/obesity	0.41	0.23–0.73
Smoking habits		
non-smoker	1	
ex-smoker	4.81	1.38–16.76
current smoker	7.68	2.21–26.67
FEV ₁ % pred ^{a,b}	0.95	0.93–0.97
Dyspnea ^c	2.87	1.61–5.14
Frequent exacerbations	3.20	1.62–6.35
CVD ^d	1.01	0.58–1.76
Self-reported physician diagnosis COPD	4.33	2.41–7.79

^a Continuous variable.

^b Post-bronchodilation.

^c mMRC ≥ 2.

^d Cardiovascular disease (heart disease, claudication or cerebrovascular disease).

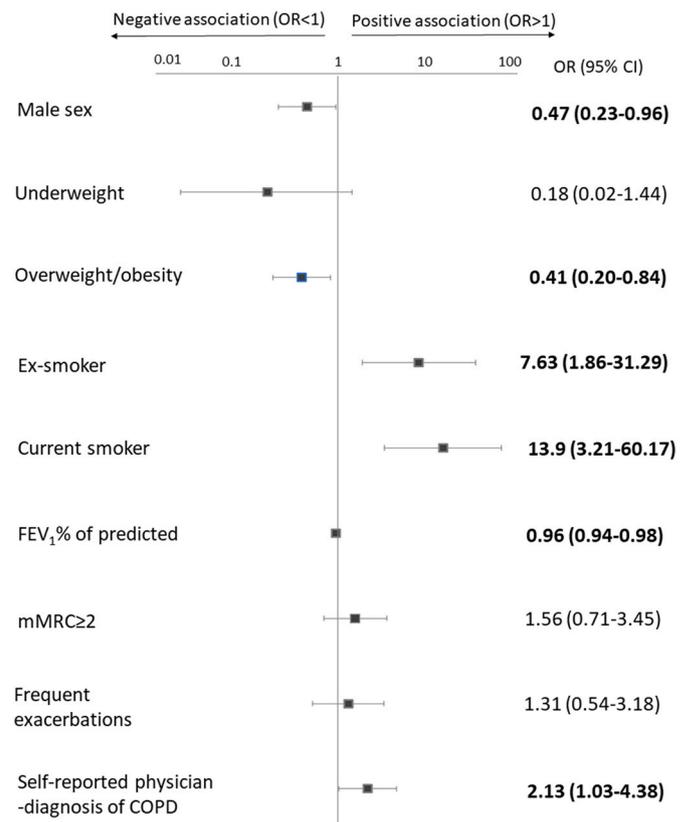


Fig. 2. Adjusted analyses of factors associated with COPD (ICD-code J43 Emphysema or J44 COPD) on the death certificates, expressed as Odds Ratios (OR) and 95% Confidence Intervals (CI). Besides the presented factors also adjusted for age. Results are presented on a log scale.

38.0% and 64.5%) (Table 2). Correspondingly, a similar pattern as for COPD was observed regarding factors associating with any respiratory diseases on the death certificates (online Table 2).

In total, there were 151 individuals (27.4%) with a self-reported physician diagnosis of COPD at recruitment, n = 26 in GOLD 1, n = 82 in GOLD 2, and n = 43 in GOLD 3–4 (online Table 3). Among them,

the cumulative mortality was 57.6% ($n = 87$). COPD was recorded on 48.3% ($n = 42$) of the death certificates (23.1%, 41.0% and 65.7% by GOLD stage), and among them it was the underlying cause of death in 50% (online Table 4).

4. Discussion

Over the ten years of follow up, 45% of this population-based COPD cohort died, yet COPD was recorded on merely 28.2% of the death certificates as either underlying or contributing cause of death. Among the deceased with COPD on their death certificates, it was recorded as the underlying cause of death in 50%. As expected, the cumulative mortality and likewise the proportion with COPD on the death certificates increased by GOLD stage. Still, among those with severe/very severe disease, COPD was not mentioned even as contributing cause of death on 43% of the death certificates. Male sex and overweight/obesity were associated with the absence of COPD on the death certificates, and so was under-diagnosis of COPD at inclusion to the study.

A majority of individuals with COPD in the society have mild-to moderate disease, and the substantial under-diagnosis [9–13] is related to disease severity [10,12,21,22]. The pattern of causes of death differs across disease severity, as mild/moderate disease seems to be burdened by death due to cardiovascular disease and cancer, while death due to respiratory conditions is more common among those with severe disease [4,14,23]. There is indeed a considerable difference between death among individuals with COPD and death due to COPD, and it has been shown that merely underlying cause of death will not capture the extent of awareness of COPD on death certificates [24–26]. Yet, both aspects were covered in the current study, in that both contributing and underlying causes of death were included. Our results indicate that both under-diagnosis of COPD and under-recognition of COPD as cause of death, underlying as well as contributing, seems to infer a considerable underestimation of COPD associated mortality.

In the previously referred large-scale population-based Copenhagen City Heart study (CCHS) 24.9% of deceased with at least severe pre-bronchodilator airway obstruction at baseline had COPD on their death certificate [14]. The results from the CCHS were on a similar level as an older publication from the early nineties [27]. Also in the 22-year follow-up of the large NHANES I in the U.S. pre-bronchodilator spirometry was used for classification of airway obstruction [4]. Among those with severe airway obstruction, 47.7% had COPD or related respiratory conditions (asthma, bronchiectasis) recorded on their death certificates, while 17.8% among those with moderate and 3.8% among those with mild COPD [4]. Our use of stricter criteria for COPD, i.e. post-bronchodilator spirometry with requirement of respiratory symptoms, may contribute to the higher proportion with COPD recorded as cause of death. Still, the above referred studies were population based which means that the effect of the COPD under-diagnosis was taken into account and further, both studies included data on underlying as well as contributing causes of death.

For comparison, among patients with very severe COPD on long term oxygen treatment included in the Swedish National Oxygen register, COPD was recorded as underlying cause of death in 71% [23]. Data on causes of death have also been published from clinical pharmaceutical trials where the study populations also include highly selected groups of COPD patients. In studies with 3–4 years of follow up, for example the TORCH study, COPD was listed on the death certificates in 58% [28], while non-malignant respiratory death contributed to 22% in the ISOLDE and 25% in the UPLIFT study [29,30]. In a 14.5 year follow-up of the Lung Health Study, including smokers with mild-moderate COPD, the primary cause of death was lung cancer in 33% and respiratory disease other than cancer in 7.8% of the deceased [31]. Besides highly selected study populations also differences in follow-up time may contribute to the above reported high proportions of respiratory causes of death among deceased.

As expected, current smoking was associated with COPD recorded on

the death certificates in the current study, and so was a self-reported physician diagnosis of COPD, while higher FEV₁% of predicted associated with the absence. Also male sex was associated with absence of COPD on the death certificates, in line with the previously referred publication from the CCHS, where women were more likely to have COPD recorded on their death certificates [14]. However, the known U-shaped pattern for the association between BMI and increased mortality [32] was apparently the reverse among the deceased in the current study with regard to recorded COPD on the death certificates. A possible contributing factor is that overweight and obesity may be associated with under-diagnosis of airflow limitation which in turn may lead to under-diagnosis of COPD [33]. The sex-dependent changes in smoking-habits observed since the second half of the 20th century most probably contributes to recent data indicating that the difference in prevalence of COPD between men and women has decreased or disappeared [34,35]. Still, in the large multinational study following the BOLD-protocol (Burden of Obstructive Lung Disease) male sex was independently associated with under-diagnosis of COPD, even though some sites showed an inverted pattern with larger under-diagnosis among women [13]. Accordingly, BMI and sex may at least in part interact with the under-diagnosis of COPD, thereby affecting the presence of COPD diagnosis on death certificates.

Due to the large and well-known under-diagnosis [10,13,21,22] but also misclassification [36–38] of COPD we conducted sensitivity analyses with regard to “any respiratory diagnoses” recorded on the death certificates. The pattern was similar as for COPD and was clearly driven by the fact that mainly COPD was recorded on the death certificates. Additional sensitivity analyses conducted among those with a self-reported physician diagnosis of COPD further strengthened the insight that the under-diagnosis/misclassification is a key factor of importance to understand the true burden of COPD mortality in the society [37,38].

Strengths of the current study include that recurrent or chronic respiratory symptoms were required in addition to post-bronchodilator airway obstruction to identify clinically relevant COPD, in line with the criteria of the GOLD strategy document [18]. Other strengths are the population-based recruitment procedure, the long follow-up time and the large cohort comparable to the size of the COPD-population in the NHANES I [4]. Furthermore, mortality data was obtained from the Swedish National Board of Health and Welfare, and since registration of cause of death is compulsory in Sweden, there was no missing data.

Regarding weaknesses, the methodological approach did not allow for identification of causes of death beyond what was listed on the death certificate. There are likely situations where COPD did not contribute to death or where other competing diagnoses were more proximal to be recorded as cause of death. Autopsy rates have declined in most countries and was in 2015 around 11% in Sweden [39], and thus, the diagnoses on death certificates are most often based on clinical observations. Both under-diagnosis and misclassification of COPD in clinical practice [13,36] will thereby undoubtedly interfere with the recorded diagnoses on death certificates. A previous Swedish study indicate that COPD actually may be underreported or misclassified on death certificates even among hospitalized patients despite a diagnosis of COPD in the medical records [40]. Unfortunately, we lack data regarding in hospital vs. out of hospital deaths, and the self-reported physician diagnoses of COPD were not confirmed by medical records. Nevertheless, death certificates are today the best data available for studies on causes of death among individuals with COPD.

To conclude, COPD was largely underreported even as contributing cause of death in this long-term follow up of a population-based COPD cohort. Even among those with severe/very severe disease, COPD was only mentioned on 57.1% of the death certificates. Among the deceased with COPD on their death certificates, it was recorded as the underlying cause of death in 50%. The study highlights the discrepancy between registry-based, i.e. official statistics, and population-based estimates of COPD associated mortality. Improved recognition and diagnosis of

COPD is indeed essential to gain a true estimate of the burden of mortality among those with COPD. Awareness of potential bias due to sex and BMI may further improve the recognition of COPD as cause of death.

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CRediT authorship contribution statement

Anne Lindberg: Formal analysis, Data curation, Writing – original draft, study design, collection of data, analyzes of data, interpretation of results, drafting the manuscript and also guarantor of the manuscript. **Lina Lindberg:** Data curation, data management, interpretation of results and revising the manuscript critically for important intellectual content. **Sami Sawalha:** data management, interpretation of results and revising the manuscript critically for important intellectual content. **Ulf Nilsson:** interpretation of results and revising the manuscript critically for important intellectual content. **Caroline Stridsman:** interpretation of results and revising the manuscript critically for important intellectual content. **Bo Lundbäck:** study design, interpretation of results and critically revising the manuscript for important intellectual content. **Helena Backman:** Formal analysis, Writing – original draft, critically revised the analysis plan, interpretation of results and drafting the manuscript. All authors approved the final version of the manuscript to be submitted.

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Appendix A. Supplementary data

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