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# The concurrent COPD mortality doubles the mortality estimate from COPD as underlying cause in Lazio, Italy

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## KEYWORDS

Multiple cause-of-death;  
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## Summary

**Background:** In Lazio region (Italy), mortality data are currently available from the death cause registry (DCR), which reports only underlying causes. Mortality due to other causes, defined concurrent mortality, are need to appropriately estimate the health impact from chronic diseases.

The aims of the study were to estimate concurrent mortality from chronic obstructive pulmonary disease (COPD), using hospital discharge registry (HDR), to discuss the validity and limits of this method, and to compare underlying and concurrent mortality from COPD in the Lazio region.

**Methods:** A mortality study was carried out for residents who died in 1996–2000 with COPD listed as the underlying cause of death and those who died in the hospital with a different underlying cause of death listed but with a discharge diagnosis of COPD. Age-standardized mortality rates were obtained for males and females separately, using the direct method. A random sample of death certificates was used to validate concurrent causes of death as defined from discharge diagnoses.

**Results:** Age-standardised mortality for COPD as underlying cause of death was 3.68/10,000 in male and 2.29/10,000 in female residents. Mortality increased slightly in the study period for women, but no trend was evident. Age-standardised mortality for COPD as concurrent cause of death was 2.39/10,000 in male and 1.31/10,000 in female residents. The positive predictive value for concurrent COPD mortality was 54.3%.

**Conclusions:** Concurrent COPD mortality contributed 62.3% to the whole mortality. The estimates of concurrent COPD mortality were comparable to those reported in other countries, though using hospital data may overestimate the real concurrent mortality as estimated from death certificates.

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## Introduction

Describing cause-specific mortality from chronic disease in terms of a single underlying cause of death, was determined to be inappropriate in 1986. Therefore, it was suggested that analyses of mortality based on underlying causes of death be complemented with multiple cause-of-death statistics, where the other causes of death listed on the death certificate could be considered.<sup>1</sup>

The need for indicators of impact and quality of care for chronic diseases adds relevance to this approach. The World Health Organisation (WHO) classified chronic obstructive pulmonary disease (COPD) as the fifth cause of death worldwide in 1999 and predicted it would rise to third by 2020.<sup>2</sup> It has been estimated that COPD as concurrent cause of death contributes 56.7% to the whole burden of mortality in the United States of America (USA)<sup>3</sup> and contributes 43.8% to the whole burden of mortality in the United Kingdom.<sup>4</sup> To monitor COPD rates in the European Union, indicators for COPD mortality include both underlying and contributing causes of death.<sup>5</sup>

Multiple cause-of-death data have been produced routinely in the USA since 1978, based on all causes reported in death certificates,<sup>1</sup> and in the UK all causes of death have been listed electronically since 1993.<sup>4</sup> In countries where these data are not available, like in Italy, identifying multiple causes of death requires carrying out specific surveys or combining different data sources.

The aims of this paper are to estimate the number of deaths to which COPD was a concurrent cause in the Lazio region of Italy between 1996 and 2000, using an indirect method based on hospital discharge diagnoses, to discuss the validity and limits of this method; to compare COPD mortality as underlying cause with COPD mortality as concurrent cause of death.

## Study population and methods

Data to estimate COPD mortality as underlying cause of death were obtained from the regional death cause registry (DCR) that lists underlying causes of death for residents of Lazio, regardless of place of death. Data to estimate COPD mortality as a concurrent cause were obtained from hospital discharge registry (HDR) of the Lazio region (Italy) that reports the patient's vital status at discharge and lists up to four discharge diagnoses. The codes of the International Classification of Diseases 9th version (ICD-9) such as 490.X, 491.X, 492.X, 494.X and 496.X were used to define COPD as cause of death or discharge diagnosis, according to the European protocol.<sup>5</sup>

Residents of the region, who died between 1996 and 2000 were included in the study if COPD was reported in the DCR as the underlying cause of death, coding according to ICD-9; we considered COPD as a concurrent cause of death for subjects who died in the hospital, who had a different cause of death registered in the DCR and an ICD-9 code for COPD listed in the HDR as at least one of the four discharge diagnoses. Information about residence was obtained in both cases, from the DCR. Data of concurrent causes were obtained through a record-linkage between the DCR and HDR using SAS programme version 8; we only included

hospitalised patients for which death and discharge dates in DCR and in HDR, respectively, corresponded.

The Lazio resident population in the period 1996–2000 taken from the National Institute of Vital Statistics was used as the denominator. Specific rates for sex and age were analysed for both underlying and concurrent causes of death. Age-standardized mortality rates were obtained for males and females separately, using the direct method and the mean Italian population in 1996–2000 as the referent population. Trends of both underlying and concurrent mortality were compared; the test for trend was done by linear regression with STATA (version 8).

The ratio of concurrent rate over underlying cause-of-death rate per 100<sup>1</sup> was used to analyse the relationship between the two cause-of-death definitions of COPD mortality as well as the frequencies with which leading causes of death occur when COPD has not been listed as underlying cause.<sup>4</sup>

A random sample of death certificates was used to validate concurrent causes of death as defined from discharge diagnoses. Death certificates were manually searched for 12% of deaths with concurrent COPD and for persons who had resided in Rome; the sample was stratified for sex and age. The positive predicted value of hospital registries with respect to death certificates was calculated as the proportion of patients with a COPD reported in the death certificate over all the concurrent causes of death estimated from the diagnoses listed on HDR. Moreover, the distributions of sex, age, and residence (city of Rome versus towns and villages), were compared between all patients who died from COPD as underlying cause, and the subgroup of those who died in the hospital, to verify possible systematic differences in using only hospitalised patients to estimate concurrent mortality.

## Results

### Mortality for COPD as underlying cause of death

There were 7005 deaths due to COPD as underlying cause or 5.6% of all deaths in the Lazio region in the period 1996–2000. Mortality was 2.68/10,000 inhabitants; rates were higher for men (3.40/10,000) than for women (2.00/10,000) with a gender ratio of 1.7. Notably, the rates increased five or six times by each 10-year age group starting from 35–44 to 65–74 years, both in males and in females; above age 74 the rates were only three times higher in men and four times higher in women compared to the preceding age group (Table 1A). Mortality rates for COPD as underlying cause of death in the period 1996–2000 did not show any statistically significant trend for males (test for trend,  $p$ -value = 0.9) or for females (test for trend,  $p$ -value = 0.3).

Age-standardized mortality rates were higher than crude rates for both men (3.68/10,000) and women (2.29/10,000), as the Italian population is older and presents higher proportions of people 70-year old and older, compared with the regional population. The sex ratio favoured men (1.6), and no trend was appreciable ( $p$ -value = 0.8 for males and  $p$ -value = 0.3 for females) though the age-adjusted rates

slightly increased for females from 0.9/10,000 in 1996 to 1.33/10,000 in 2000 (Fig. 1).

**Mortality for COPD as concurrent cause of death**

There were 4358 people who died with COPD defined as a concurrent cause of death in the period 1996–2000 and mortality was 1.67/10,000. The rates were higher for men (2.22/10,000) than for women (1.15/10,000) with a gender ratio of 1.9. Concurrent COPD mortality rates increased with age (Table 1B) but did not show a trend (test for trend, *p*-value = 0.4 in males and *p*-value = 0.3 in females).

The age-standardized rates for concurrent mortality were 2.39/10,000 for men and 1.31/10,000 for women, higher estimates than the crude rates and a gender ratio in favour of men (1.8). The rates increased slightly from 1996 to 2000 in both sexes but no trend was observed (test for trend, *p*-value = 0.5 in males and *p*-value = 0.4 in females) (Fig. 1) as for underlying COPD mortality. The leading causes of death that reported COPD as concurrent were heart diseases (40.3%), tumours (18.5%), cerebro-vascular diseases (10.6%) and diseases of respiratory system excluding COPD (6.9%) (Table 2).

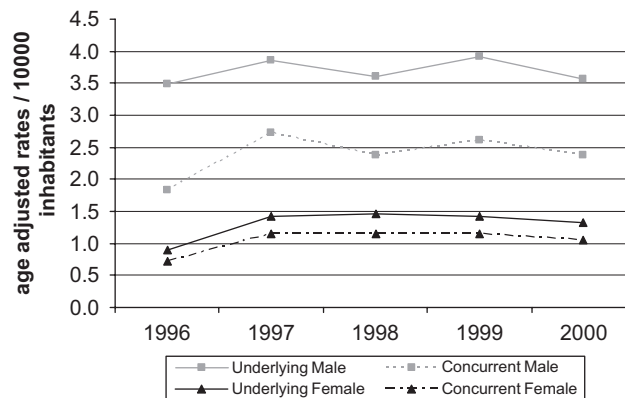
**Relationship between underlying and concurrent causes of death for COPD**

The concurrent/underlying mortality ratio of age-adjusted rates was 62.3%. It was higher among males (65.3%) than

among females (57.5%), and presented the highest value in young-adult from 45 to 74 years of age. The concurrent/underlying mortality ratio increased from 1996 to 2000 in both sexes (Fig. 2).

**Validation of COPD hospital diagnosis as concurrent cause of death**

A sample of 280 death certificates was used to validate our estimates among the 2426 deaths defined as concurrent COPD causes of death that occurred in residents of Rome. The positive predictive value (PPV) of concurrent COPD



**Figure 1** Mortality due to COPD as underlying and concurrent cause, by sex and year. Lazio, 1996–2000.

**Table 1** Mortality rates for COPD as underlying and concurrent cause. Lazio, 1996–2000.

Age groups	Male deaths				Female deaths					
	N	Population	Rate/10,000	95% CI	N	Population	Rate/10,000	95% CI		
<b>(A) Underlying cause</b>										
<15	0	1935352	0		0	1833475	0			
15–24	2	1655134	0.01	0.001	0.04	1	1587749	0.01	0.0002	0.04
25–34	2	2123710	0.01	0.001	0.03	2	2137607	0.01	0.001	0.03
35–44	9	1920883	0.05	0.021	0.09	3	1965900	0.02	0.003	0.04
45–54	41	1706341	0.24	0.17	0.33	16	1798668	0.09	0.05	0.14
55–64	217	1532839	1.42	1.23	1.62	75	1689323	0.44	0.35	0.56
65–74	1024	1144702	8.95	8.41	9.51	404	1436226	2.81	2.55	3.10
75–84	1708	490835	34.80	33.17	36.49	938	808045	11.61	10.88	12.38
85+	1289	123684	104.22	98.63	110.03	1274	290607	43.84	41.47	46.31
Total	4292	12633480	3.40	3.30	3.50	2713	13547600	2.00	1.93	2.08
<b>(B) Concurrent cause</b>										
<15	2	1935352	0.01	0.001	0.04	2	1833475	0.01	0.001	0.04
15–24	1	1655134	0.01	0.0002	0.03	0	1587749	0		
25–34	2	2123710	0.01	0.001	0.03	1	2137607	0.005	0.0001	0.03
35–44	3	1920883	0.02	0.003	0.05	3	1965900	0.02	0.003	0.05
45–54	21	1706341	0.12	0.08	0.19	12	1798668	0.07	0.03	0.12
55–64	161	1532839	1.05	0.89	1.23	48	1689323	0.28	0.21	0.38
65–74	748	1144702	6.53	6.08	7.02	258	1436226	1.80	1.58	2.03
75–84	1168	490835	23.80	22.45	25.20	559	808045	6.92	6.36	7.52
85+	694	123684	56.11	52.02	60.43	675	290607	23.23	21.51	25.05
Total	2800	12633480	2.22	2.14	2.30	1558	13547600	1.15	1.09	1.21

**Table 2** Underlying causes of death in patients who died in hospital with COPD reported as discharge diagnosis but not as underlying cause of death. Lazio, 1996–2000.

Death cause	Deaths	
	N	%
<b>All</b>	<b>4358</b>	<b>100</b>
<b>Respiratory diseases</b>	<b>301</b>	<b>6.91</b>
TB	28	0.64
Asthma	17	0.39
Respiratory failure	47	1.08
Bronchopneumonia	85	1.95
Pneumoconiosis	9	0.21
Others		2.64
<b>Tumors</b>	<b>807</b>	<b>18.52</b>
Trachea, bronchus, lungs	287	6.59
Others	520	11.93
<b>Diabetes</b>	<b>116</b>	<b>2.66</b>
<b>Heart diseases</b>	<b>1754</b>	<b>40.25</b>
Ami	213	4.89
Other forms of ischemic heart diseases	524	12.02
Heart failure	176	4.04
Pulmonary embolism and cor pulmonale	63	1.45
Hypertension	231	5.30
Arrhythmias	100	2.29
Other heart diseases	447	10.26
<b>Cerebral-vascular diseases*</b>	<b>463</b>	<b>10.62</b>
<b>Digestive system disease</b>	<b>248</b>	<b>5.69</b>
<b>Genital-urinary system</b>	<b>92</b>	<b>2.11</b>
Renal failure	74	1.70
Others	18	0.41
<b>Not well defined</b>	<b>73</b>	<b>1.68</b>
<b>Fractures and concussions</b>	<b>135</b>	<b>3.10</b>
<b>Poisoning†</b>	<b>16</b>	<b>0.37</b>
<b>Other diseases</b>	<b>350</b>	<b>8.03</b>
Infectious disease aftermaths	2	0.05
Bacterial or viral infections	18	0.41
Metabolic disorders other than diabetes	28	0.64
Anaemia and other blood diseases	20	0.46
Psychiatric diseases	55	1.26
CNS diseases	59	1.35
PNS diseases	5	0.11
Other vascular diseases	137	3.14
Decubitus ulcers	4	0.09
Bone and joint diseases	18	0.41
Congenital diseases	4	0.09
<b>Not reported</b>	<b>3</b>	<b>0.07</b>

TB = tuberculosis, CNS = central nervous system, PNS = peripheral nervous system.

\*Including arteriosclerosis, aneurysms, thrombo-embolisms.

†Including side effects of drugs or therapeutic procedures' effects.

mortality as estimated from hospital diagnoses compared with that estimated from death certificates was 54.3%. The value was 76.4% when respiratory failures reported on death certificates were analysed as proxy diagnoses of COPD.

When all underlying cause COPDs were compared with the subgroup who died in the hospital, differences were observed in age, sex and residence distributions. There were fewer males and patients over 85 (−4% and −9%, respectively) among those who died in the hospital than among all those who died from COPD. Finally, patients who resided in Rome were more likely to die in the hospital (+4%) than those who resided outside Rome.

## Discussion

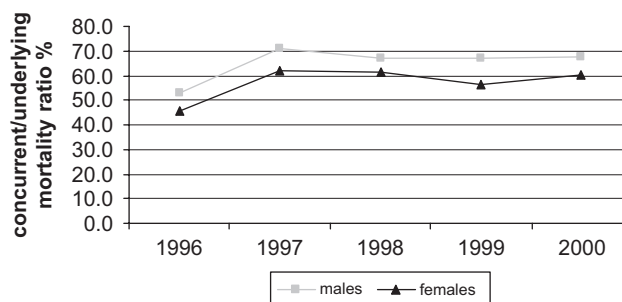
### Mortality for COPD as underlying cause of death

Mortality due to COPD is lower in the Lazio region for males (3.68/10,000) than in Italy (4.02/10,000),<sup>6</sup> while it is higher (2.29 versus 2.00 per 10,000) for females.<sup>6</sup> Mortality rates observed in our region are lower than those reported in the USA, where estimates range between 7.9 and 8.3 per 10,000 males and between 4.7 and 5.7 per 10,000 females in the period 1996–2000<sup>7</sup>; they are also lower than those reported in England and Wales, where estimates range between 12.3 and 11.7 for males and 5.7 and 6.1 for females in 1996–1999.

Mortality rates did not present an increasing trend in our region from 1996 to 2000, following what was observed in rest of Italy.<sup>6</sup> Nevertheless, the rate at which mortality increased from 1996 to 2000 was higher in females (13.2%) than in males (2.0%).

The increase in mortality for COPD at 35+ years of age was observed as reported in other studies<sup>3,4</sup>; however in some European countries<sup>8</sup> mortality increased only in patients 54+ year old. Differences in coding COPD prevent us from comparing age specific mortality rates in the Lazio region with those in Italy; the national mortality<sup>6</sup> in fact, includes asthma (ICD-9 code 493.0), a disease that causes the highest rates in patients under 35, while COPD show the highest rates in patients over 34.<sup>3,4</sup>

The regional and national gender ratio (1.6 and 2.0, respectively) that favours males suggests that work-related exposures and smoking are still prevalent among males in the Lazio region as well as in Italy. Nevertheless, the regional mortality rates for females were higher than national rates, suggesting that the impact of smoking on men and women has been inverted at the regional level. These results have to be confirmed by observations longer than the 5 years studied here, but the inversion of smoking exposure has been previously described in the USA.<sup>7</sup>



**Figure 2** Ratio of concurrent over underlying COPD adjusted mortality in males and females by year. Lazio, 1996–2000.

## The contribution of concurrent mortality to the whole burden of mortality

The rate at which the mortality for COPD increased from 1996 to 2000 was much higher for concurrent causes (29.9% in males, 47.8% in females) than for underlying causes (2.0% in males and 13.2% in females) suggesting that the propensity to code COPD as a concurrent cause became more frequent during the study period. On the other hand, both the underlying and the concurrent mortality increased allowing to conclude that the increase in mortality for COPD is real although no trend was observed, and it cannot be ascribed to codifying modifications of death causes.<sup>3</sup>

A different propensity in coding COPD as underlying cause of death could help explain the differences in mortality rates between different countries and different periods. Mortality rates for underlying COPD in our region were lower than those reported in the USA and also lower than those reported in England and Wales. At the same time, concurrent/underlying COPD ratio is 62.3% in our study, much higher in USA (130%) and much lower (42.0% in males and 37.5% in females) in England.<sup>4</sup> Therefore, it is possible that in USA COPD is codified more often as concurrent cause and in England as underlying cause of death than in Lazio. Both national comparisons and trend analyses would benefit from using a multiple cause-of-death approach, as it allows mortality estimates to be compared apart from geographical differences and time modifications in codifying the underlying causes of death.

Cardiovascular diseases, tumours, cerebro-vascular diseases and other respiratory diseases were the major underlying causes of death where COPD was reported as discharge diagnosis but not as underlying cause of death. The findings are broadly in agreement with those from a UK study<sup>4</sup> and a study from Tucson, Arizona,<sup>9</sup> but we found a higher frequency of cerebro-vascular disease than found in Britain (1.7%). Another study including seven European countries<sup>10</sup> reported the same general groups of diseases, but the highest frequency was found for other respiratory diseases, especially chronic respiratory failure (38%), and heart failure (13%) while malignancy was third. The observation that the most frequent causes of death other than COPD are so similar in different countries allows us to hypothesise that very similar clinical criteria justify attributing a death cause other than COPD in patients ill with COPD.

## Limits of the study

Based on the sex and age distribution of the concurrent/underlying COPD ratio, we could conclude that in our region there is a higher propensity to codify COPD as concurrent in young-adult patients (45–74 years) than in those over 74 years both in males and in females. Unfortunately, these conclusions are heavily influenced by differences in sex and in age observed between the population of hospitalised patients we used as the source of concurrent causes. We found fewer very old patients than expected among concurrent COPD deaths. This fact could be explained by the use of hospital discharge records. In fact, comparing those who died in the hospital with all patients who died

with an underlying cause of COPD we found that the older the patients were, the less likely they were to be hospitalised.

Another limit in using the HDR as the source of concurrent causes of death is that the concurrent/underlying cause ratio has been estimated in similar but non-equal populations, the former being estimated only in hospitalised patients and the latter among all deaths. This prevents us from estimating a cumulative multiple cause of death rate. The original ratio proposed by Israel et al.<sup>1</sup> uses the frequency with which a cause of death is reported on the death certificate, compared with the frequency the cause is selected as the underlying cause of death in the same population.

Finally, we obtained a PPV of concurrent COPD mortality estimated from hospital diagnoses as low as 54.3%, which means we detected among the concurrent causes of COPD almost 45.7% of deaths for which COPD had not been reported on the death certificate. Therefore, our method compared to the death certificates may have over-estimated concurrent mortality. Adding respiratory failure allowed us to get a PPV of 76.4%, but this approach would require changing the definition of COPD as concurrent cause of death.

## Conclusions

An additional 62.3% of COPD mortality as concurrent cause must be added to COPD mortality as underlying cause in our region, to correctly determine the whole burden of COPD mortality. Moreover, the multiple cause-of-death approach assures more valid national comparisons of COPD mortality as it takes into account geographical differences and time variations in codifying causes of deaths.

The method we present to estimate concurrent mortality using the discharge diagnoses registry gets estimate very close to those reported in other countries and assures a good reproducibility over time, although it may overestimate the real concurrent mortality as estimated from death certificates and may cause a negative selection of males and very old patients. Further applications of this method could help to identify its potential and its limits.

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