



**Direct and indirect economic and health consequences of
COPD in Denmark - 1998-2010**

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Direct and indirect economic and health consequences of COPD in Denmark - 1998-2010.

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Anders Løkke: Planning, Statistics, Writing and Discussion.

Ole Hilberg: Planning, Writing and Discussion.

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Jakob Kjellberg: Planning, Statistics and Writing.

Rikke Ibsen: Statistics and Writing.

Poul Jennum: Planning, Writing and Discussion.

Abstract

Objective: Chronic Obstructive Pulmonary Disease (COPD) is among the leading causes of morbidity and mortality worldwide, but longitudinal studies of the economic consequences of COPD are scarce. This Danish study evaluated for the first time ever the economic consequences of COPD of an entire nation before and after the diagnosis.

Methods: Using records from the Danish National Patient Registry (1998-2010), 131,811 patients with COPD were identified and compared with 131,811 randomly selected controls matched for age, gender, educational level, residence, and marital status. Direct and indirect costs, including frequency of primary and secondary sector contacts and procedures, medication, unemployment benefits and social transfer payments were extracted from national databases.

Results: Patients with COPD had poor survival. The average (95% CI) 12-year survival rate was 0.364 (0.364-0.368) compared with 0.686 among controls (0.682-0.690). COPD was associated with significantly higher rates of health-related contacts, medication use and higher socioeconomic costs. The employment and the income rates of employed COPD patients were significantly lower compared to controls. The annual net costs, including social transfers were €8,572 for COPD patients. These consequences were present up to 11 years before first time diagnosis in the secondary health care sector and became more pronounced with disease advancement.

Conclusion: This study provides unique national data on direct and indirect costs before and after initial diagnosis with COPD in Denmark as well as mortality, health and economic consequences for the individual and for society. It could be speculated that early identification and intervention might contribute to the solution.

Article Summary

Article Focus:

- To show the socioeconomic impact of COPD before and after initial diagnosis.
- To provide national data regarding health and mortality of COPD patients before and after diagnosis.
- To provide extended national data regarding direct and indirect costs of COPD.

Key Messages:

- Patients with an initial primary or secondary diagnosis of COPD had poor survival. The average (95% CI) 12-year survival rate was 0.364 (0.364-0.368) compared with 0.686 among controls (0.682-0.690).
- COPD was associated with significantly higher rates of health-related contacts, medication use and higher socioeconomic costs. The employment rates and the income rates of employed COPD patients were significantly lower compared to controls.
- These consequences were present up to 11 years before first diagnosis in the secondary sector and became more pronounced with disease advancement.

Strengths and limitations:

- This study truly is unique – providing for the first time ever complete and highly relevant data regarding health and direct and indirect costs of COPD of an entire nation over a time period of 12 years.
- The 12 year time-window gives a unique possibility to look backwards and forwards from the point of initial diagnosis.
- This epidemiological study is solely based on information from national databases leading to some limitations.
- The results do not reflect the impact of COPD per se as the pronounced comorbidities of COPD patients (depression, anxiety, cardiovascular disease etc.) will have an impact, too.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is among the leading causes of morbidity and mortality worldwide, but longitudinal studies of the economic consequences of COPD are scarce (1, 2).

Smoking, though not necessarily number of pack years, is slowly declining in the Western world but continues to rise elsewhere and it is estimated that the global impact of COPD will increase in the years to come (3-5).

Estimates of COPD prevalence in industrialized countries range widely reflecting both true differences as well as differences in the definition of COPD and in the diagnostic tools used. Most studies find a 10–15% prevalence of COPD in people from 35-40 years and older (6-11). The 17.4% prevalence of COPD in Denmark reported in The Copenhagen City Heart Study is among the highest in the world (12).

The burden of COPD on the health care sector is substantial and has been described and documented in previous cost-of-illness studies concentrating on treatment of COPD and not considering comorbidity (13-20).

Furthermore, the information and assumption of costs have focused on direct costs because indirect costs have generally not been available. Thus, an estimate of total costs of COPD has not yet been achieved.

In Denmark, it is possible to calculate direct and indirect costs of any given disease because information from public and private hospitals and clinics in the primary and secondary care sectors, including medication, social factors, educational level, income and employment data from all patients is registered in central databases and be linked by the unique civil registration number assigned to all Danish citizens facilitating easy and reliable linkage of data. The aim of this study was to evaluate the direct and indirect economic burden of COPD in Denmark before and after initial diagnosis.

Methods

In Denmark, all hospital contacts (Emergency Rooms, ambulatory visits, Admittances etc.), primary and secondary diagnoses are registered in the National Patient Registry (NPR) (21). The NPR includes administrative information, diagnoses, and diagnostic and treatment procedures using

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4 several international classification systems, including the International Statistical Classification of
5 Diseases and Related Health Problems 10th Revision (ICD-10 Version: 2010).

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7 The NPR is a time-based national database that includes data from all inpatient and outpatient
8 contact, so the data that we extracted are representative of all patients in Denmark who has received
9 a first time primary and secondary diagnosis of COPD irrespective of other diagnoses. As data are
10 available for the entire observation period, we can trace patients retrospectively and prospectively
11 relative to the time of their diagnosis. Furthermore, all contacts in the primary sector (general
12 practice and specialist care) and the use of medications are recorded in the databases of the National
13 Health Security and the Danish Health and Medicines Agency, respectively.
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16 Even though the study is evaluating a relatively long period of time, there is a risk of
17 underestimating the number of patients with COPD, since those with a contact in the primary sector
18 only but not in the secondary sector are recorded as having had contact but not as having received a
19 diagnosis.
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27 We extracted the following first time primary or secondary diagnoses from the NPR in the time
28 period 1998-2010: “J44 Other chronic obstructive pulmonary disease” comprised by the
29 following sub-diagnoses: “J44.0 Chronic obstructive pulmonary disease with acute lower
30 respiratory infection”, J44.1 Chronic obstructive pulmonary disease with acute exacerbation,
31 unspecified” and “J44.9 Chronic obstructive pulmonary disease, unspecified”.
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33 “J44.8 Other specified chronic obstructive pulmonary disease” was excluded as well as “J43
34 Emphysema” and “J47 Bronchiectasis. Data on disease severity was not available.
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40 Using data from the Danish Civil Registration System including information about all partners,
41 their marital status, social factors, education level, employment, incomes, pensions etc. (22), we
42 randomly selected controls of the same age, sex and educational level as the patients.
43
44 Nor the NPR or any other of the national databases contains information about smoking status.
45
46 Social compensation was performed by selecting control subjects residing in the same area of the
47 country as the patients and with the same marital status. The ratio of control subjects to patients was
48 1:1. Data from patients and matched control subjects who could not be identified in the Income
49 Statistics database were excluded from the sample. More than 99% of the observations in the two
50 groups were successfully matched. Patients and matched controls were followed from 1998 to 2010.
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52 If a patient or control was not present in the registry on 1 January each year due to death,
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4 imprisonment or immigration, the corresponding control or patient control was not included in the
5 dataset for that year.

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7 Information about educational level is very robust for everyone between the ages of 14 and 80 with
8 only little information lacking. On the other hand there is no available information about
9 educational level for people under the age of 14 years and for a very large proportion of those aged
10 80 years or more – the latter due to lack of registration of education in the Danish Civil Registration
11 System database. This registration, based on information from the different teaching institutions, did
12 not begin until 1970.

13
14 One could argue that a huge proportion of the unregistered persons are unskilled but we cannot tell
15 and the problem is the same in the control group. To avoid bias, we excluded all persons with
16 COPD where proper matching information was missing.

17
18 Patients and matched controls were followed through the entire time period or until death. If
19 diagnosis of COPD of any given individual was made in the first year (1998) we were able to
20 follow that individual 11 years forward in time. If diagnosis of COPD of any given individual was
21 made in the last year (2010) we were able to follow that individual 11 years backwards in time. If
22 diagnosis of COPD of any given individual was made between the first and the last year we were
23 able to follow that individual both backwards and forward in time.

24
25 Municipal services such as care of the elderly (home care nursing and general home care) and
26 municipal rehabilitation is not included as they are paid by the municipals.

27
28 The economic consequences of COPD were estimated by determining the annual costs per patient
29 diagnosed with COPD and comparing these figures with the healthcare costs in a matched control
30 group. Diagnosis of COPD is presented to the NPR using information from public and private
31 hospitals. These diagnoses rely on clinical information and results of diagnostic procedures (e.g.
32 spirometry, bronchoscopy). The procedures are registered but the results of the diagnostic procedure
33 are not recorded in the NPR. The health cost was then divided into annual direct and indirect
34 healthcare costs.

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36 Direct costs included the average costs of hospitalization and outpatient treatment, for separate
37 diagnosis-related groups and specific outpatient costs. These costs were all calculated from Danish
38 Ministry of Health data using diagnosis- related groups (DRG) and average case-mix costs of
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4 hospitals or outpatient costs updated on an annual basis. The use and costs of drugs were obtained
5 from the Danish Health and Medicines Agency consisting of the retail price of each drug (including
6 dispensing costs) multiplied by the number of transactions. The frequencies and costs of
7 consultations with general practitioners and other specialists were based on National Health
8 Security data.
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13 Indirect costs included those related to reduced unemployment benefits and to social transfer
14 payments. Indirect costs were based on income figures from Income Statistics. Costs were
15 measured on an annual basis and adjusted to 2010 prices in Euros (€1: DKK 7.45).
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20 Cost-of-illness studies measure the economic burden resulting from disease and illness across a
21 defined population and include direct and indirect costs. Direct costs are the value of resources used
22 in the treatment, care, and rehabilitation of people with the condition under study. Indirect costs
23 represent the value of economic resources lost because of disease-related work disability or
24 premature mortality. As patients leave the national data registers at the time of death, the indirect
25 costs estimate comprises only the production loss related to disease-related work disability. It is
26 important to distinguish costs from monetary transfer payments such as disability and welfare
27 payments. These payments represent a transfer of purchasing power to the recipients from the
28 general taxpayers but do not represent net increases in the use of resources and, therefore, are not
29 included in the total cost estimate.
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40 Statistical analysis

41 The study was approved by the Danish Data Protection Agency. Data were anonymised and neither
42 individual consent nor ethical approval was required.
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44 The results are presented as means because some patients had a very high resource consumption
45 which, despite leading to a skewed distribution, would not be adequately represented if data were
46 presented as median values. Extreme values were manually validated and no errors were identified.
47 Statistical analysis was performed using SAS 9.1.3 (SAS, Inc., Cary, NC). Statistical significance of
48 the cost estimates was assessed by nonparametric bootstrap analysis (23, 24).
49

50 Survival was estimated using the Kaplan-Maier method. Hazard ratio was estimated using the Cox
51 proportional hazard model.
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Results

We identified and extracted 131,811 patients with COPD from the national databases (1998-2010) and compared with 131,811 randomly selected matched controls. The age distribution and education level of patients are shown in Table 1. There are a little more female than male COPD patients - probably because of the age distribution. As expected, most of the patients with an initial diagnosis of COPD are middle-aged or older.

Figure 1 shows distribution of all the included patients with COPD (in red). In blue are the excluded patients with a diagnosis of “J44.8 Other specified chronic obstructive pulmonary disease” which primarily is younger people with a diagnosis of chronic asthmatic bronchitis.

Figure 2 displays survival distribution of COPD patients and controls showing a decline in survival of COPD patients compared to controls.

The percentages of COPD patients and controls receiving various health care and income is shown in Table 2. COPD is associated with significantly higher rates of health-related contact (Outpatient and Inpatient treatment as well as Primary Care), use more medication, have more persons on various public transfer incomes and less people earning income from employment compared to controls.

The annual average health costs and income of COPD patients before and after diagnosis compared with controls are displayed in Table 3. COPD is associated with significantly higher rates of health-related costs, medication use and lower income rates compared to controls both before and increasingly so after diagnosis.

Figure 3 shows total health expenses, income from employment and public transfer income before and after diagnosis of COPD compared with controls.

For every year the total health expenses are significantly higher for COPD patients. A peak in expenses is seen at the time of diagnosis.

For COPD the income from employment is significantly lower and the total public transfer income is significantly higher than for controls – even 11 years before the diagnosis has been given.

Both effects diminish over time due to people getting older and retiring from work.

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4 In Figure 3 the x-axis begins at minus 11 and stops at 11 years. In year zero all cases and their
5 controls are present. When moving backwards from zero to minus 11, every year will hold less and
6 less cases (and controls) because the ones diagnosed with COPD in 1998 were not followed
7 backwards in time, the ones diagnosed with COPD in 1999 were only followed backwards 1 year in
8 time and so on. The same is true when moving forwards from year zero to year 11 because the ones
9 diagnosed with COPD in 2010 were not followed forward in time, the ones diagnosed with COPD
10 in 2009 were only followed forward 1 year in time and so on.

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12 One should be cautious to compare one year with another in the figures, because two neighbor years
13 will not be identical but are composed of some identical cases and some cases that differs
14 completely.

15
16 As an example: At year minus 11 the cases diagnosed with COPD in 2010 are shown (thus we are
17 11 years before the time of the diagnosis). Year minus 10 hold the cases who got diagnosed in 2010
18 plus the cases diagnosed in 2009 (thus we are 10 years before the time of the diagnosis).

29 Discussion

30 To our knowledge, this is the first epidemiological COPD study evaluates the direct and indirect
31 costs of COPD at a national level.

32
33 The 12 year time-window gives a unique possibility to look backwards and forwards from the point
34 of initial diagnosis. Including every person at a national level with a first time diagnosis of COPD
35 and randomly selected controls matched for age, gender, educational level, residence and marital
36 status provides a very large amount of persons and data making the direct and indirect results more
37 complete and robust.

38
39 The study has provided several information of interest and confirms the following general beliefs
40 about COPD:

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42 Patients with an initial primary or secondary diagnosis of COPD had poor survival. The average
43 (95% CI) 12-year survival rate was 0.364 (0.364-0.368) compared with 0.686 among controls
44 (0.682-0.690).

45
46 COPD was associated with significantly higher rates of health-related contacts, medication use and
47 higher socioeconomic costs. The employment rates and the income rates of employed COPD
48 patients were significantly lower compared to controls.

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50 The annual net costs after initial diagnosis, including social transfers were €8,572 for COPD

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4 patients.

5 These consequences were present up to 11 years before first diagnosis in the secondary sector and
6 became more pronounced with disease advancement.
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10 Determining the economic consequences of COPD is complex. With an accurate diagnosis and
11 appropriate treatment patients' risk of exacerbation decreases as well as the associated costs and
12 maybe even death (although still controversial). In addition quality of life improves. On the other
13 hand the diagnostic procedures, treatment and management of COPD add to the direct costs.
14 However, even when we include the costs associated with the diagnosis and treatment of COPD,
15 our study showed that patients with COPD incur a significant economic burden because the lower
16 employment rates and the lower income rates of employed COPD patients exceed the direct costs of
17 the disease. These factors influence costs and should be included in the disease burden.
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25 This epidemiological study is solely based on information from national databases leading to some
26 limitations.
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29 The results do not reflect the impact of COPD per se as the pronounced comorbidities of COPD
30 patients (depression, anxiety, cardiovascular disease etc.) will have an impact, too. By adjusting for
31 the above mentioned available match factor, including educational level, we have tried to minimize
32 this effect. Ideally, we would have adjusted for smoking status but this information is not registered
33 in any of the national databases in Denmark.
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37 In Denmark ICD-10 classification is only used in the secondary health sector (hospitals) not in the
38 primary health sector (general practitioners). Even though this study spans 12 years and includes all
39 with an initial primary or secondary ICD-10 diagnosis of COPD - and the majority of known COPD
40 patients are believed to be included over time - there is a risk of underestimation. COPD patients
41 that are only followed in the primary health care sector during the study period are not included and
42 this will bias the results as these patients will tend to be less sick.
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49 The accuracy of the diagnosis and management is sensitive to the diagnostic criteria used by the
50 reporting doctors. The people aged below 30-40 years with a diagnosis of COPD may – at least to
51 some extent - be due to misclassification.
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54 Furthermore, although J44 by far is the most common diagnosis used in COPD, several different
55 diagnoses deriving from J40 (bronchitis), J41 (simple and mucopurulent chronic bronchitis), J43
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4 (emphysema) and J47 bronchiectasis) are also used to some (unknown) extent. We have chosen to
5 exclude these diagnoses as well as J44.8 Other specified chronic obstructive pulmonary disease. It
6 could be argued that a large proportion of these excluded individuals are very likely to have COPD,
7 but because this is an epidemiologic study, entirely based on registry data, we decided to include
8 only those with a specific diagnosis of COPD.
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12 By allowing both primary and secondary diagnosis of COPD some correction of this problem has
13 taken place but may have opened up for adding further comorbidity.
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16 In the control group there will be a number of undiagnosed patients with COPD (approx. 10%) thus
17 introducing a bias tending to reduce the difference in costs between the two groups in our study
18 (25).
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22 **Conclusion:** This study provides unique data at a national level regarding direct and indirect costs
23 before and after initially diagnosed COPD as well as serious mortality, health and economic
24 consequences for the individual patient and for society.
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27 As the economic consequences are present years prior to the first primary or secondary diagnosis of
28 COPD in the secondary health sector one, it could be speculated that early identification and
29 intervention might be part of the solution.
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32 Adequate treatment may reduce the consequences of COPD but, if socially and economically
33 significant reductions in morbidity, mortality and social impact are to be achieved, much earlier
34 disease identification and management are needed More research and evaluation of case finding
35 strategies and disease management programs are needed (26).
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Table 1: Age, gender and education level distribution of COPD patients.

Gender	N	Percentage
Male	63,342	48.1
Female	68,469	51.9
Married or co-habiting		54.0
Age distribution		
<14	-	-
14-20	136	0.1
20-29	394	0.3
30-39	1,717	1.3
40-49	6,664	5.1
50-59	19,601	14.9
60-69	38,297	29.1
70-79	51,524	39.1
80-92	13,478	10.2
≥92	-	-
Education level		
Primary	80,483	61.1
Secondary	864	0.7
Vocational	40,050	30.4
Short college	1,824	1.4
Medium college	6,784	5.1
Master/PhD	1,806	1.4
Total	131,811	100.0

Figure 1: Distribution of included (red) and excluded cases (blue) on the basis of diagnosis according to age (x-axis) and number (y-axis).

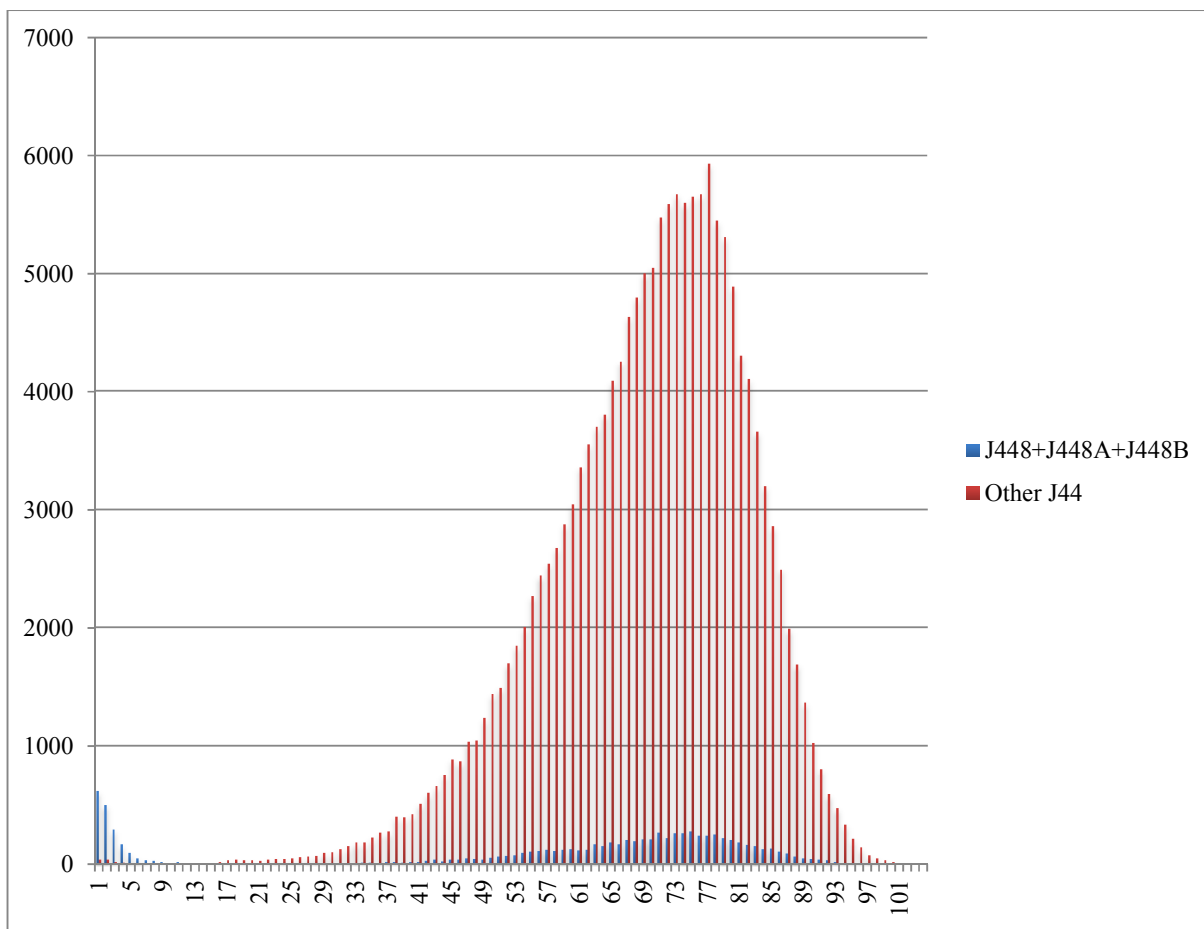
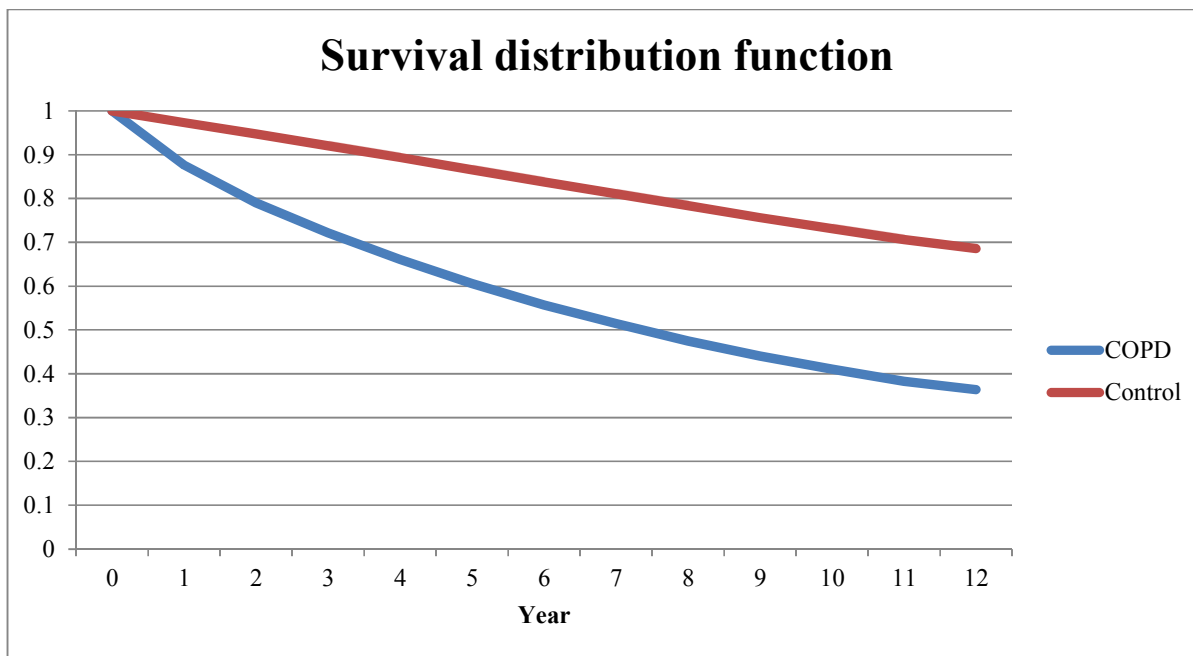


Figure 2: Kaplan-Maier survival distribution of COPD patients (blue) and controls (red) estimated using Cox proportional hazard model.



	COPD			Control			
Survival							
	Year	Survival Distribution Function Estimate	SDF Upper 95.00% Confidence Limit	SDF Lower 95.00% Confidence Limit	Survival Distribution Function Estimate	SDF Upper 95.00% Confidence Limit	SDF Lower 95.00% Confidence Limit
	0	1,000	1,000	1,000	1,000	1,000	1,000
	1	0,876	0,878	0,875	0,973	0,974	0,972
	2	0,790	0,792	0,788	0,948	0,949	0,946
	3	0,722	0,725	0,720	0,921	0,922	0,919
	4	0,661	0,664	0,659	0,894	0,895	0,892
	5	0,606	0,609	0,603	0,866	0,867	0,864
	6	0,557	0,560	0,554	0,838	0,840	0,836
	7	0,515	0,518	0,512	0,811	0,813	0,808
	8	0,475	0,478	0,472	0,784	0,786	0,781
	9	0,441	0,444	0,437	0,757	0,760	0,754
	10	0,410	0,414	0,407	0,731	0,734	0,728
	11	0,383	0,387	0,379	0,706	0,710	0,703
	12	0,364	0,368	0,360	0,686	0,690	0,682
Censored	N	131,811			131,811		
	% censored	53.5			80.2		
Hazard function	HazardRatio	0,33					
	ProbChiSq	0,00					
	StdErr	0,01					

Table 2: Percentages of COPD patients and controls that receive income and various health care services (after diagnosis).

		COPD	Controls	P-value
Outpatient treatment	%	64.9	36.2	<0.01
Inpatient treatment	%	53.8	18.8	<0.01
Medication	%	98.1	85.9	<0.01
Public health insurance	%	99.0	95.6	<0.01
Income from employment	%	16.7	23.8	<0.01
Public transfer income total	%	90.3	83.8	<0.01
<i>Pension</i>	%	60.3	63.8	<0.01
<i>Other public transfers</i>	%	27.6	18.6	<0.01
<i>Sickpay (publicly funded)</i>	%	5.5	3.6	<0.01

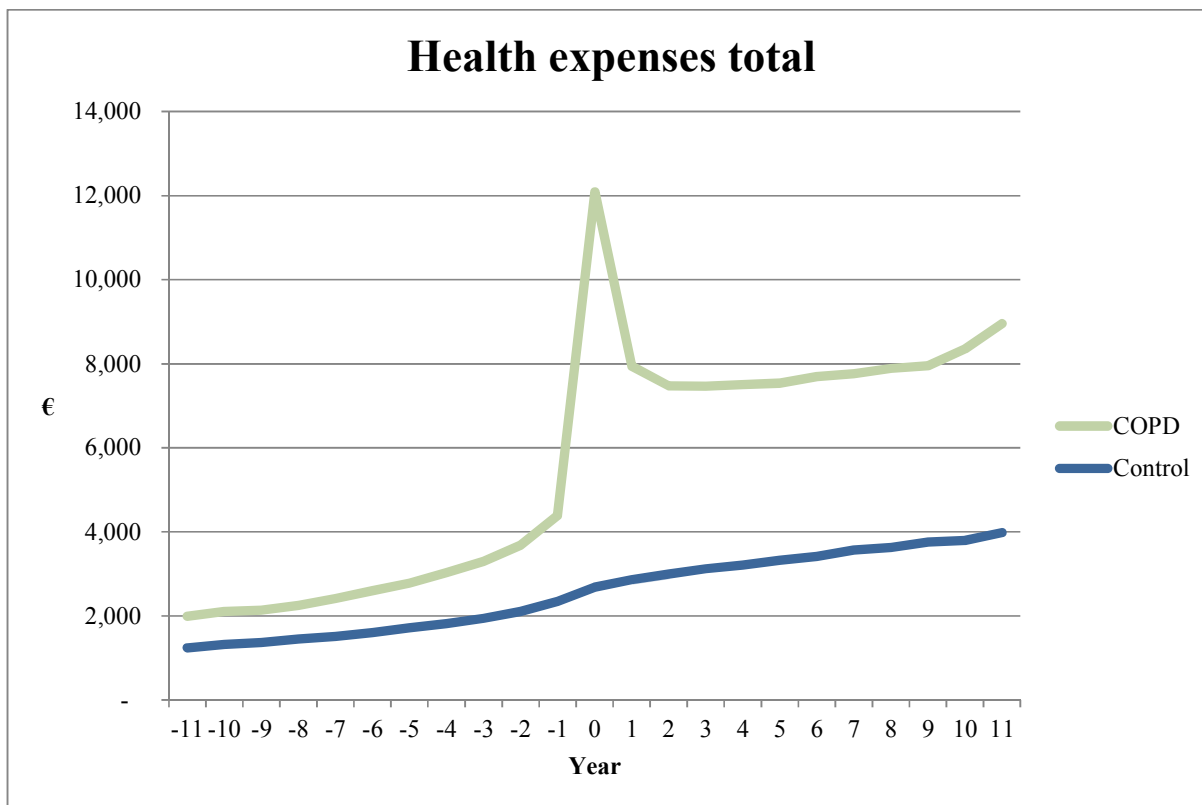
(Bootstrapped Cochran-Armitage test showing whether the fraction received is significant for each expense type). The values given are in percentages.

Table 3: Health costs and income of COPD patients before and after diagnosis compared with controls.

			COPD	Controls	P-value
Before diagnosis	N		708,329	708,343	
	Outpatient treatment	€	335	227	<0.01
	Inpatient treatment	€	1,534	904	<0.01
	Medication	€	918	434	<0.01
	Public health insurance	€	357	278	<0.01
	Income from employment	€	7,947	11,418	<0.01
	Public transfer income total	€	12,858	11,167	
	<i>Pension</i>	€	7,029	6,824	<0.01
	<i>Other public transfers</i>	€	5,450	4,104	<0.01
	<i>Sickpay (public funded)</i>	€	378	238	<0.01
	Direct health costs	€	3,144	1,843	
	Indirect costs, foregone earnings	€	3,471		
	Sum of direct and indirect costs	€	6,616	1,843	
	Net costs	€	4,773		
	Social transfer payments	€	12,858	11,167	
	Net costs including transfers	€	6,464		
After diagnosis	N	N	597,235	776,674	
	Outpatient treatment	€	789	429	<0.01
	Inpatient treatment	€	5,563	1,736	<0.01
	Medication	€	1,782	610	<0.01
	Public health insurance	€	515	361	<0.01
	Income from employment	€	4,509	6,800	<0.01
	Public transfer income total	€	13,888	13,122	
	<i>Pension</i>	€	9,171	10,317	<0.01
	<i>Other public transfers</i>	€	4,361	2,634	<0.01
	<i>Sickpay (publicly funded)</i>	€	356	171	<0.01
	Direct health costs	€	8,650	3,135	
	Indirect costs, foregone earnings	€	2,291		
	Sum of direct and indirect costs	€	10,941	3,135	
	Net costs	€	7,806		
	Social transfer payments	€	13,888	13,122	
	Net costs including transfers	€	8,572		

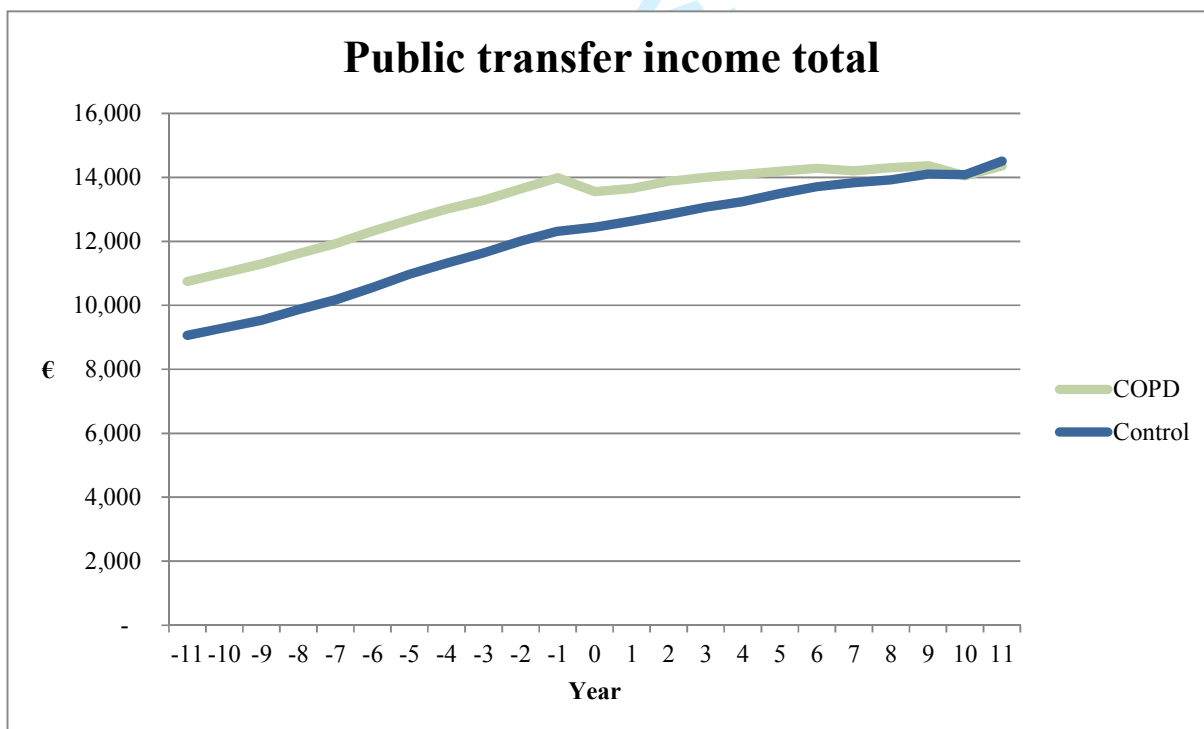
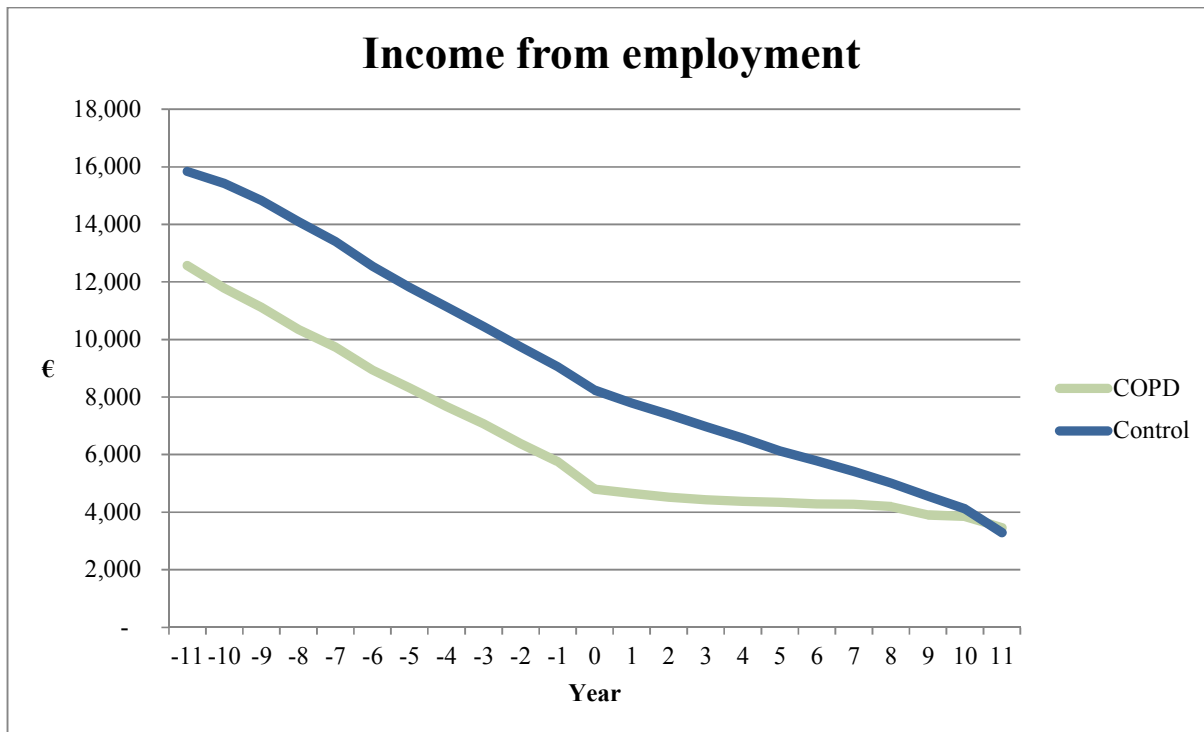
(Yearly costs calculated as the average costs with respect to income per year. N = summarized number of individuals × years observed. P-value from bootstrapped t-test. The values given are in Euros).

Figure 3: Total health expenses, income from employment and public transfer income in Euros before and after diagnosis of COPD (green) compared with control subjects (blue).



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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

1	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and
2			sensitivity analyses
3	Discussion		
4	Key results	18	Summarise key results with reference to study objectives
5	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or
6			imprecision. Discuss both direction and magnitude of any potential bias
7	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,
8			multiplicity of analyses, results from similar studies, and other relevant evidence
9	Generalisability	21	Discuss the generalisability (external validity) of the study results
10	Other information		
11	Funding	22	Give the source of funding and the role of the funders for the present study and, if
12			applicable, for the original study on which the present article is based
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*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.



Direct and indirect economic and health consequences of COPD in Denmark - A national register based study - 1998-2010.

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Manuscripts

Direct and indirect economic and health consequences of COPD in Denmark – A national register based study - 1998-2010.

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Key words:

Chronic obstructive pulmonary disease, illness costs, health costs, economic burden, employment.

Abstract

Objective: Chronic Obstructive Pulmonary Disease (COPD) is among the leading causes of morbidity and mortality worldwide, but longitudinal studies of the economic consequences of COPD are scarce. This Danish study evaluated for the first time ever the economic consequences of COPD of an entire nation before and after the diagnosis.

Methods: Using records from the Danish National Patient Registry (1998-2010), 131,811 patients with COPD were identified and compared with 131,811 randomly selected controls matched for age, gender, educational level, residence, and marital status. Direct and indirect costs, including frequency of primary and secondary sector contacts and procedures, medication, unemployment benefits and social transfer payments were extracted from national databases.

Results: Patients with COPD had poor survival. The average (95% CI) 12-year survival rate was 0.364 (0.364-0.368) compared with 0.686 among controls (0.682-0.690). COPD was associated with significantly higher rates of health-related contacts, medication use and higher socioeconomic costs. The employment and the income rates of employed COPD patients were significantly lower compared to controls. The annual net costs, including social transfers were €8,572 for COPD patients. These consequences were present up to 11 years before first time diagnosis in the secondary health care sector and became more pronounced with disease advancement.

Conclusion: This study provides unique national data on direct and indirect costs before and after initial diagnosis with COPD in Denmark as well as mortality, health and economic consequences for the individual and for society. It could be speculated that early identification and intervention might contribute to the solution.

Article Summary

Article Focus:

- To show the socioeconomic impact of COPD before and after initial diagnosis.
- To provide national data regarding health and mortality of COPD patients before and after diagnosis.
- To provide extended national data regarding direct and indirect costs of COPD.

Key Messages:

- Patients with an initial primary or secondary diagnosis of COPD had poor survival. The average (95% CI) 12-year survival rate was 0.364 (0.364-0.368) compared with 0.686 among controls (0.682-0.690).
- COPD was associated with significantly higher rates of health-related contacts, medication use and higher socioeconomic costs. The employment rates and the income rates of employed COPD patients were significantly lower compared to controls.
- These consequences were present up to 11 years before first diagnosis in the secondary sector and became more pronounced with disease advancement.

Strengths and limitations:

- This study truly is unique – providing for the first time ever complete and highly relevant data regarding health and direct and indirect costs of COPD of an entire nation over a time period of 12 years.
- The 12 year time-window gives a unique possibility to look backwards and forwards from the point of initial diagnosis.
- This epidemiological study is solely based on information from national databases leading to some limitations.
- The results do not reflect the impact of COPD per se as the pronounced comorbidities of COPD patients (depression, anxiety, cardiovascular disease etc.) will have an impact, too.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is among the leading causes of morbidity and mortality worldwide, but longitudinal studies of the economic consequences of COPD are scarce (1, 2).

Smoking, though not necessarily number of pack years, is slowly declining in the Western world but continues to rise elsewhere and it is estimated that the global impact of COPD will increase in the years to come (3-5).

Estimates of COPD prevalence in industrialized countries range widely reflecting both true differences as well as differences in the definition of COPD and in the diagnostic tools used. Most studies find a 10–15% prevalence of COPD in people from 35-40 years and older (6-11). The 17.4% prevalence of COPD in Denmark reported in The Copenhagen City Heart Study is among the highest in the world (12).

The burden of COPD on the health care sector is substantial and has been described and documented in previous cost-of-illness studies concentrating on treatment of COPD and not considering comorbidity (13-20).

Furthermore, the information and assumption of costs have focused on direct costs because indirect costs have generally not been available. Thus, an estimate of total costs of COPD has not yet been achieved.

In Denmark, it is possible to calculate direct and indirect costs of any given disease because information from public and private hospitals and clinics in the primary and secondary care sectors, including medication, social factors, educational level, income and employment data from all patients is registered in central databases and be linked by the unique civil registration number assigned to all Danish citizens facilitating easy and reliable linkage of data. The aim of this study was to evaluate the direct and indirect economic burden of COPD in Denmark before and after initial diagnosis.

Methods

In Denmark, all hospital contacts (Emergency Rooms, ambulatory visits, Admittances etc.), primary and secondary diagnoses are registered in the National Patient Registry (NPR) (21). The NPR includes administrative information, diagnoses, and diagnostic and treatment procedures using several international classification systems, including the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10 Version: 2010).

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4 The NPR is a time-based national database that includes data from all inpatient and outpatient
5 contact, so the data that we extracted are representative of all patients in Denmark who has received
6 a first time primary and secondary diagnosis of COPD irrespective of other diagnoses. As data are
7 available for the entire observation period, we can trace patients retrospectively and prospectively
8 relative to the time of their diagnosis. Furthermore, all contacts in the primary sector (general
9 practice and specialist care) and the use of medications are recorded in the databases of the National
10 Health Security and the Danish Health and Medicines Agency, respectively.

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15 Even though the study is evaluating a relatively long period of time, there is a risk of
16 underestimating the number of patients with COPD, since those with a contact in the primary sector
17 only but not in the secondary sector are recorded as having had contact but not as having received a
18 diagnosis.
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24 We extracted the following first time primary or secondary diagnoses from the NPR in the time
25 period 1998-2010: “J44 Other chronic obstructive pulmonary disease” comprised by the
26 following sub-diagnoses: “J44.0 Chronic obstructive pulmonary disease with acute lower
27 respiratory infection”, J44.1 Chronic obstructive pulmonary disease with acute exacerbation,
28 unspecified” and “J44.9 Chronic obstructive pulmonary disease, unspecified”.
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32 “J44.8 Other specified chronic obstructive pulmonary disease” was excluded as well as “J43
33 Emphysema” and “J47 Bronchiectasis. Data on disease severity was not available.
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37 Using data from the Danish Civil Registration System including information about all partners,
38 their marital status, social factors, education level, employment, incomes, pensions etc. (22), we
39 randomly selected controls of the same age, sex and educational level as the patients.
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42 Nor the NPR or any other of the national databases contains information about smoking status.
43 Social compensation was performed by selecting control subjects residing in the same area of the
44 country as the patients and with the same marital status. The ratio of control subjects to patients was
45 1:1. Data from patients and matched control subjects who could not be identified in the Income
46 Statistics database were excluded from the sample. More than 99% of the observations in the two
47 groups were successfully matched. Patients and matched controls were followed from 1998 to 2010.
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52 If a patient or control was not present in the registry on 1 January each year due to death,
53 imprisonment or immigration, the corresponding control or patient control was not included in the
54 dataset for that year.
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4 Information about educational level is very robust for everyone between the ages of 14 and 80 with
5 only little information lacking. On the other hand there is no available information about
6 educational level for people under the age of 14 years and for a very large proportion of those aged
7 80 years or more – the latter due to lack of registration of education in the Danish Civil Registration
8 System database. This registration, based on information from the different teaching institutions, did
9 not begin until 1970.
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14 One could argue that a huge proportion of the unregistered persons are unskilled but we cannot tell
15 and the problem is the same in the control group. To avoid bias, we excluded all persons with
16 COPD where proper matching information was missing.
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21 Patients and matched controls were followed through the entire time period or until death. If
22 diagnosis of COPD of any given individual was made in the first year (1998) we were able to
23 follow that individual 11 years forward in time. If diagnosis of COPD of any given individual was
24 made in the last year (2010) we were able to follow that individual 11 years backwards in time. If
25 diagnosis of COPD of any given individual was made between the first and the last year we were
26 able to follow that individual both backwards and forward in time.
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32 Municipal services such as care of the elderly (home care nursing and general home care) and
33 municipal rehabilitation is not included as they are paid by the municipals.
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37 The economic consequences of COPD were estimated by determining the annual costs per patient
38 diagnosed with COPD and comparing these figures with the healthcare costs in a matched control
39 group. Diagnosis of COPD is presented to the NPR using information from public and private
40 hospitals. These diagnoses rely on clinical information and results of diagnostic procedures (e.g.
41 spirometry, bronchoscopy). The procedures are registered but the results of the diagnostic procedure
42 are not recorded in the NPR. The health cost was then divided into annual direct and indirect
43 healthcare costs.
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49 Direct costs included the average costs of hospitalization and outpatient treatment, for separate
50 diagnosis-related groups and specific outpatient costs. These costs were all calculated from Danish
51 Ministry of Health data using diagnosis- related groups (DRG) and average case-mix costs of
52 hospitals or outpatient costs updated on an annual basis. The use and costs of drugs were obtained
53 from the Danish Health and Medicines Agency consisting of the retail price of each drug (including
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4 dispensing costs) multiplied by the number of transactions. The frequencies and costs of
5 consultations with general practitioners and other specialists were based on National Health
6 Security data.
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10 Indirect costs included those related to reduced unemployment benefits and to social transfer
11 payments. Indirect costs were based on income figures from Income Statistics. Costs were
12 measured on an annual basis and adjusted to 2010 prices in Euros (€1: DKK 7.45).
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16 Cost-of-illness studies measure the economic burden resulting from disease and illness across a
17 defined population and include direct and indirect costs. Direct costs are the value of resources used
18 in the treatment, care, and rehabilitation of people with the condition under study. Indirect costs
19 represent the value of economic resources lost because of disease-related work disability or
20 premature mortality. As patients leave the national data registers at the time of death, the indirect
21 costs estimate comprises only the production loss related to disease-related work disability. It is
22 important to distinguish costs from monetary transfer payments such as disability and welfare
23 payments. These payments represent a transfer of purchasing power to the recipients from the
24 general taxpayers but do not represent net increases in the use of resources and, therefore, are not
25 included in the total cost estimate.
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36 Statistical analysis

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38 The study was approved by the Danish Data Protection Agency. Data were anonymised and neither
39 individual consent nor ethical approval was required.
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41 The results are presented as means because some patients had a very high resource consumption
42 which, despite leading to a skewed distribution, would not be adequately represented if data were
43 presented as median values. Extreme values were manually validated and no errors were identified.
44 Statistical analysis was performed using SAS 9.1.3 (SAS, Inc., Cary, NC). Statistical significance of
45 the cost estimates was assessed by nonparametric bootstrap analysis (23, 24).
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48 Survival was estimated using the Kaplan-Maier method. Hazard ratio was estimated using the Cox
49 proportional hazard model.
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54 **Results**

55 We identified and extracted 131,811 patients with COPD from the national databases (1998-2010)
56 and compared with 131,811 randomly selected matched controls. The age distribution and
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4 education level of patients are shown in Table 1. There are a little more female than male COPD
5 patients - probably because of the age distribution. As expected, most of the patients with an initial
6 diagnosis of COPD are middle-aged or older.
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10 Figure 1 shows distribution of all the included patients with COPD (in red). In blue are the excluded
11 patients with a diagnosis of “J44.8 Other specified chronic obstructive pulmonary disease” which
12 primarily is younger people with a diagnosis of chronic asthmatic bronchitis.
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17 Figure 2 displays survival distribution of COPD patients and controls showing a decline in survival
18 of COPD patients compared to controls.
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22 The percentages of COPD patients and controls receiving various health care and income is shown
23 in Table 2. COPD is associated with significantly higher rates of health-related contact (Outpatient
24 and Inpatient treatment as well as Primary Care), use more medication, have more persons on
25 various public transfer incomes and less people earning income from employment compared to
26 controls.
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32 The annual average health costs and income of COPD patients before and after diagnosis compared
33 with controls are displayed in Table 3. COPD is associated with significantly higher rates of health-
34 related costs, medication use and lower income rates compared to controls both before and
35 increasingly so after diagnosis.
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40 Figure 3 shows total health expenses, income from employment and public transfer income before
41 and after diagnosis of COPD compared with controls.
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43 For every year the total health expenses are significantly higher for COPD patients. A peak in
44 expenses is seen at the time of diagnosis.
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46 For COPD the income from employment is significantly lower and the total public transfer income
47 is significantly higher than for controls – even 11 years before the diagnosis has been given.
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49 Both effects diminish over time due to people getting older and retiring from work.
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51 In Figure 3 the x-axis begins at minus 11 and stops at 11 years. In year zero all cases and their
52 controls are present. When moving backwards from zero to minus 11, every year will hold less and
53 less cases (and controls) because the ones diagnosed with COPD in 1998 were not followed
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4 backwards in time, the ones diagnosed with COPD in 1999 were only followed backwards 1 year in
5 time and so on. The same is true when moving forwards from year zero to year 11 because the ones
6 diagnosed with COPD in 2010 were not followed forward in time, the ones diagnosed with COPD
7 in 2009 were only followed forward 1 year in time and so on.

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9 One should be cautious to compare one year with another in the figures, because two neighbor years
10 will not be identical but are composed of some identical cases and some cases that differs
11 completely.

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13 As an example: At year minus 11 the cases diagnosed with COPD in 2010 are shown (thus we are
14 11 years before the time of the diagnosis). Year minus 10 hold the cases who got diagnosed in 2010
15 plus the cases diagnosed in 2009 (thus we are 10 years before the time of the diagnosis).
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23 Discussion

24 To our knowledge, this is the first epidemiological COPD study evaluates the direct and indirect
25 costs of COPD at a national level.
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27 The 12 year time-window gives a unique possibility to look backwards and forwards from the point
28 of initial diagnosis. Including every person at a national level with a first time diagnosis of COPD
29 and randomly selected controls matched for age, gender, educational level, residence and marital
30 status provides a very large amount of persons and data making the direct and indirect results more
31 complete and robust.
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38 The study has provided several information of interest and confirms the following general beliefs
39 about COPD:

40 Patients with an initial primary or secondary diagnosis of COPD had poor survival. The average
41 (95% CI) 12-year survival rate was 0.364 (0.364-0.368) compared with 0.686 among controls
42 (0.682-0.690).
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46 COPD was associated with significantly higher rates of health-related contacts, medication use and
47 higher socioeconomic costs. The employment rates and the income rates of employed COPD
48 patients were significantly lower compared to controls.
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50 The annual net costs after initial diagnosis, including social transfers were €8,572 for COPD
51 patients.
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53 These consequences were present up to 11 years before first diagnosis in the secondary sector and
54 became more pronounced with disease advancement.
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6 Determining the economic consequences of COPD is complex. With an accurate diagnosis and
7 appropriate treatment patients' risk of exacerbation decreases as well as the associated costs and
8 maybe even death (although still controversial). In addition quality of life improves. On the other
9 hand the diagnostic procedures, treatment and management of COPD add to the direct costs.
10
11 However, even when we include the costs associated with the diagnosis and treatment of COPD,
12 our study showed that patients with COPD incur a significant economic burden because the lower
13 employment rates and the lower income rates of employed COPD patients exceed the direct costs of
14 the disease. These factors influence costs and should be included in the disease burden.
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21 This epidemiological study is solely based on information from national databases leading to some
22 limitations.
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24 The results do not reflect the impact of COPD per se as the pronounced comorbidities of COPD
25 patients (depression, anxiety, cardiovascular disease etc.) will have an impact, too. By adjusting for
26 the above mentioned available match factor, including educational level, we have tried to minimize
27 this effect. Especially educational level is a good parameter to use if one wants to level out
28 economical differences. However social factors that we are not aware of can have an impact on the
29 outcome and explain some of the observed differences.
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32 Ideally, we would have adjusted for smoking status but this information is not registered in any of
33 the national databases in Denmark.
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37 In Denmark ICD-10 classification is only used in the secondary health sector (hospitals) not in the
38 primary health sector (general practitioners). Even though this study spans 12 years and includes all
39 with an initial primary or secondary ICD-10 diagnosis of COPD - and the majority of known COPD
40 patients are believed to be included over time - there is a risk of underestimation. COPD patients
41 that are only followed in the primary health care sector during the study period are not included and
42 this will bias the results as these patients will tend to be less sick. This fact will tend to overestimate
43 the direct and indirect costs of COPD.
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50 The accuracy of the diagnosis and management is sensitive to the diagnostic criteria used by the
51 reporting doctors. The people aged below 30-40 years with a diagnosis of COPD may – at least to
52 some extent - be due to misclassification.
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55 Furthermore, although J44 by far is the most common diagnosis used in COPD, several different
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4 diagnoses deriving from J40 (bronchitis), J41 (simple and mucopurulent chronic bronchitis), J43
5 (emphysema) and J47 bronchiectasis) are also used to some (unknown) extent. We have chosen to
6 exclude these diagnoses as well as J44.8 Other specified chronic obstructive pulmonary disease. It
7 could be argued that a large proportion of these excluded individuals are very likely to have COPD,
8 but because this is an epidemiologic study, entirely based on registry data, we decided to include
9 only those with a specific diagnosis of COPD.
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14 By allowing both primary and secondary diagnosis of COPD some correction of this problem has
15 taken place but may have opened up for adding further comorbidity.
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17 In the control group there will be a number of undiagnosed patients with COPD (approx. 10%) thus
18 introducing a bias tending to reduce the difference in costs between the two groups in our study
19 (25).
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24 **Conclusion:** This study provides unique data at a national level regarding direct and indirect costs
25 before and after initially diagnosed COPD as well as serious mortality, health and economic
26 consequences for the individual patient and for society.
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29 As the economic consequences are present years prior to the first primary or secondary diagnosis of
30 COPD in the secondary health sector one, it could be speculated that early identification and
31 intervention might be part of the solution.
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34 Adequate treatment may reduce the consequences of COPD but, if socially and economically
35 significant reductions in morbidity, mortality and social impact are to be achieved, much earlier
36 disease identification and management are needed More research and evaluation of case finding
37 strategies and disease management programs are needed (26).
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Conflicts of interest:

None of the authors have any conflicts of interest, nor do they have any financial disclosures to make.

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Competing interests: None.

Ethics approval:

The study was approved by the Danish Data Protection Agency. Because data handling was anonymous, individual and ethical approval was not mandatory.

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Author Contribution:

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Philip Tønnesen: Writing and Discussion.

Jakob Kjellberg: Planning, Statistics and Writing.

Rikke Ibsen: Statistics and Writing.

Poul Jennum: Planning, Writing and Discussion.

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Table 1: Age, gender and education level distribution of COPD patients.

Gender	N	Percentage
Male	63,342	48.1
Female	68,469	51.9
Married or co-habiting		54.0
Age distribution		
<14	-	-
14-20	136	0.1
20-29	394	0.3
30-39	1,717	1.3
40-49	6,664	5.1
50-59	19,601	14.9
60-69	38,297	29.1
70-79	51,524	39.1
80-92	13,478	10.2
≥92	-	-
Education level		
Primary	80,483	61.1
Secondary	864	0.7
Vocational	40,050	30.4
Short college	1,824	1.4
Medium college	6,784	5.1
Master/PhD	1,806	1.4
Total	131,811	100.0

Figure 1: Distribution of included (red) and excluded cases (blue) on the basis of diagnosis according to age (x-axis) and number (y-axis).

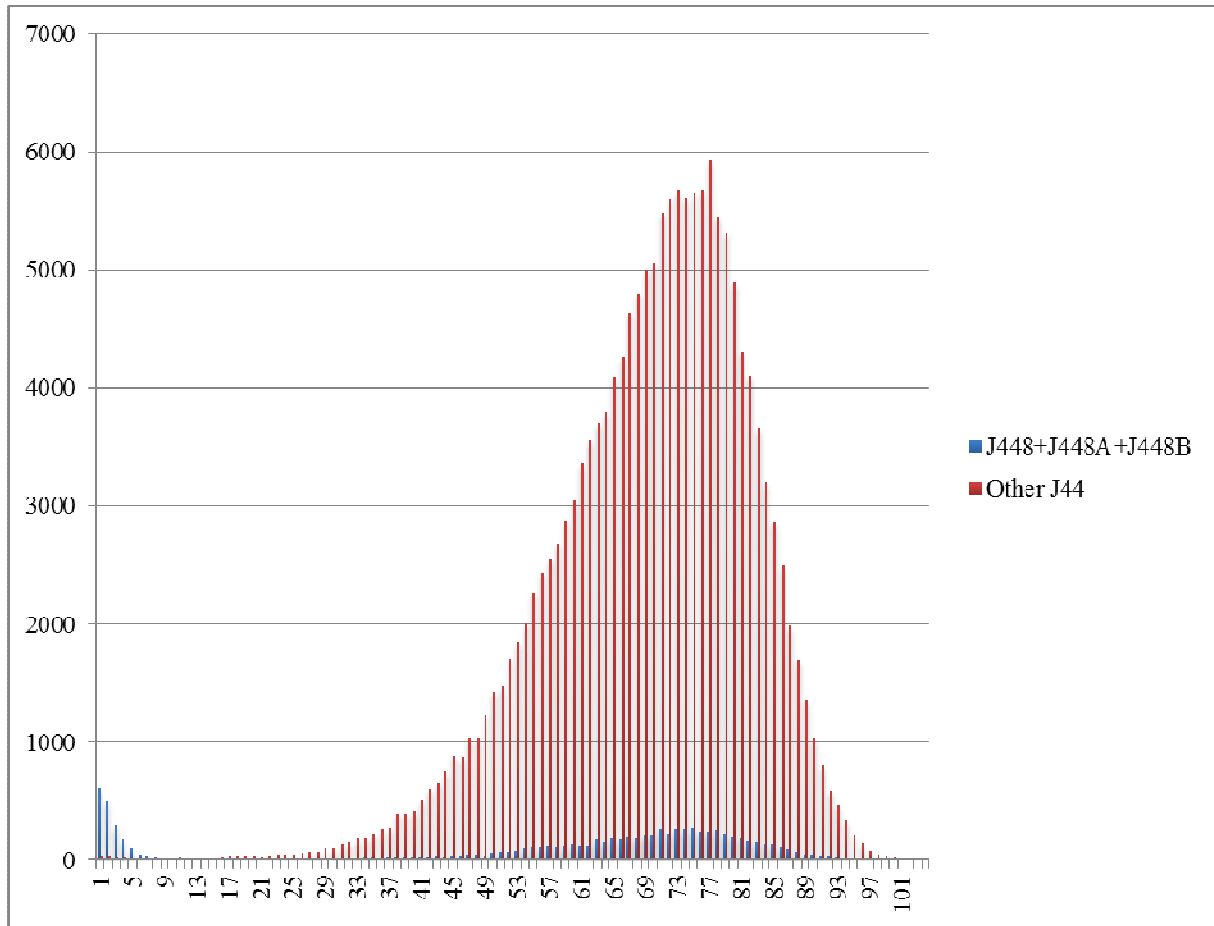
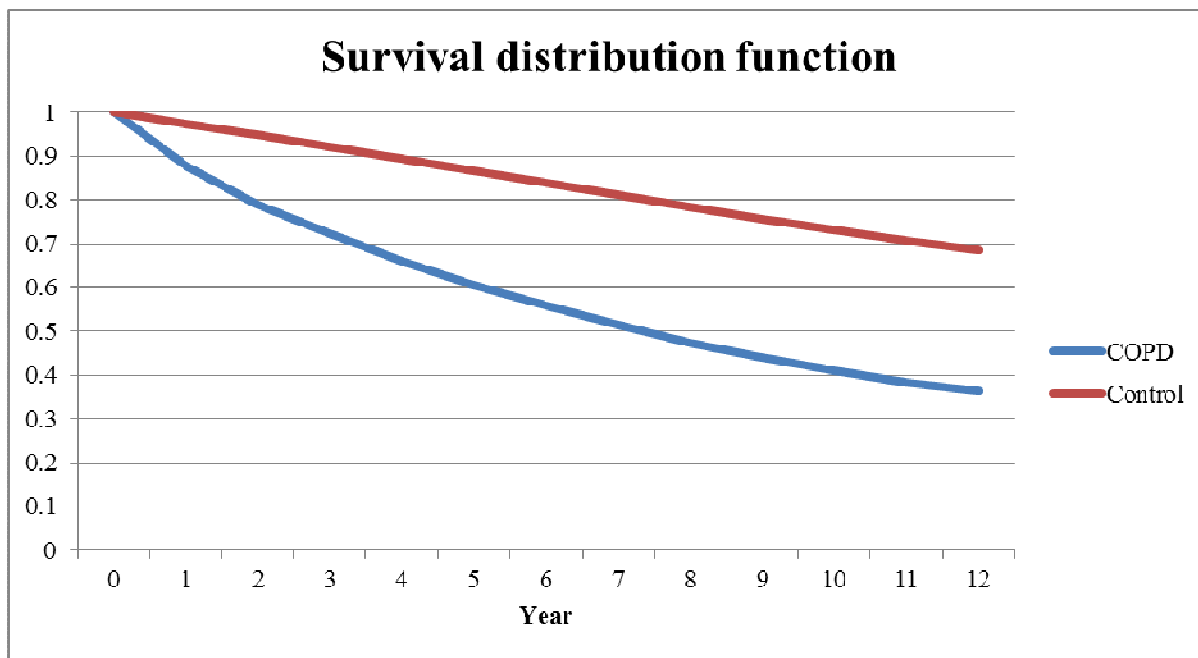


Figure 2: Kaplan-Maier survival distribution of COPD patients (blue) and controls (red) estimated using Cox proportional hazard model.



	COPD			Control			
Survival							
	Year	Survival Distribution Function Estimate	SDF Upper 95.00% Confidence Limit	SDF Lower 95.00% Confidence Limit	Survival Distribution Function Estimate	SDF Upper 95.00% Confidence Limit	SDF Lower 95.00% Confidence Limit
	0	1,000	1,000	1,000	1,000	1,000	1,000
	1	0,876	0,878	0,875	0,973	0,974	0,972
	2	0,790	0,792	0,788	0,948	0,949	0,946
	3	0,722	0,725	0,720	0,921	0,922	0,919
	4	0,661	0,664	0,659	0,894	0,895	0,892
	5	0,606	0,609	0,603	0,866	0,867	0,864
	6	0,557	0,560	0,554	0,838	0,840	0,836
	7	0,515	0,518	0,512	0,811	0,813	0,808
	8	0,475	0,478	0,472	0,784	0,786	0,781
	9	0,441	0,444	0,437	0,757	0,760	0,754
	10	0,410	0,414	0,407	0,731	0,734	0,728
	11	0,383	0,387	0,379	0,706	0,710	0,703
	12	0,364	0,368	0,360	0,686	0,690	0,682
Censored	N	131,811			131,811		
	% censored	53.5			80.2		
Hazard function	HazardRatio	0,33					
	ProbChiSq	0,00					
	StdErr	0,01					

Table 2: Percentages of COPD patients and controls that receive income and various health care services (after diagnosis).

		COPD	Controls	P-value
Outpatient treatment	%	64.9	36.2	<0.01
Inpatient treatment	%	53.8	18.8	<0.01
Medication	%	98.1	85.9	<0.01
Public health insurance	%	99.0	95.6	<0.01
Income from employment	%	16.7	23.8	<0.01
Public transfer income total	%	90.3	83.8	<0.01
<i>Pension</i>	%	60.3	63.8	<0.01
<i>Other public transfers</i>	%	27.6	18.6	<0.01
<i>Sickpay (publicly funded)</i>	%	5.5	3.6	<0.01

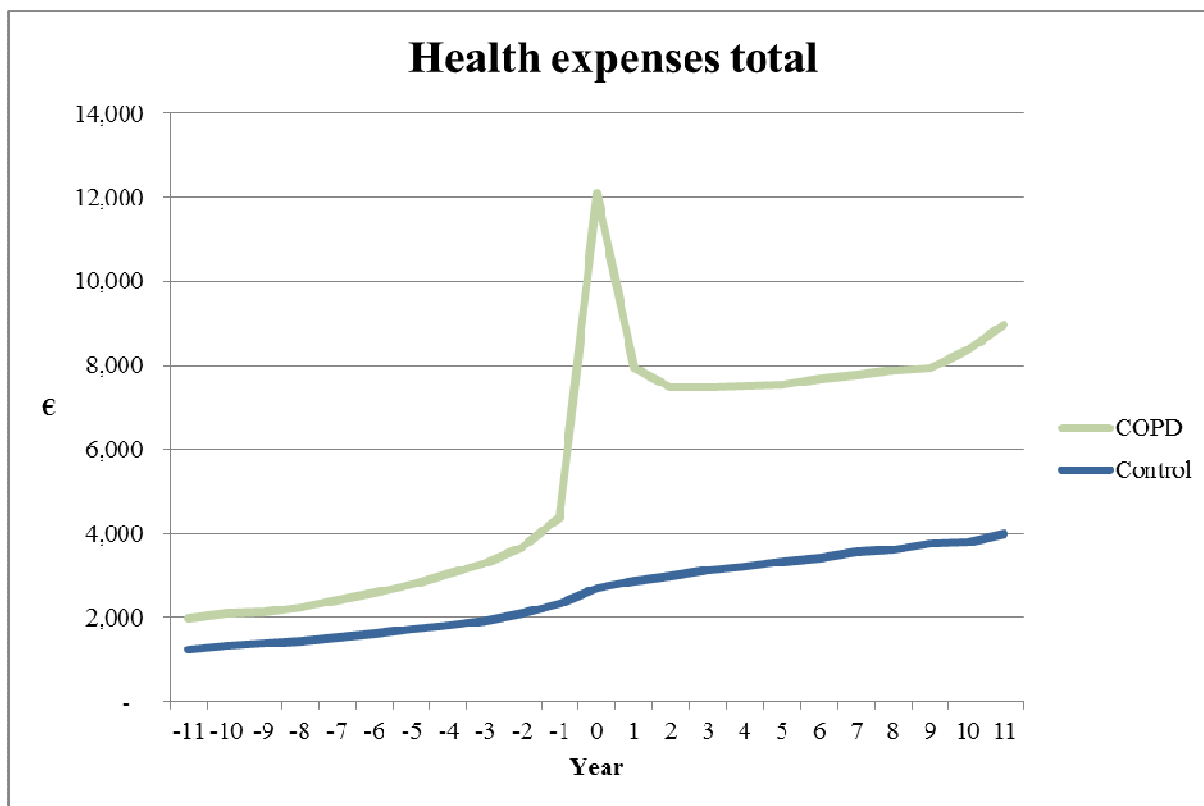
(Bootstrapped Cochran-Armitage test showing whether the fraction received is significant for each expense type). The values given are in percentages.

Table 3: Health costs and income of COPD patients before and after diagnosis compared with controls.

			COPD	Controls	P-value
Before diagnosis	N		708,329	708,343	
	Outpatient treatment	€	335	227	<0.01
	Inpatient treatment	€	1,534	904	<0.01
	Medication	€	918	434	<0.01
	Public health insurance	€	357	278	<0.01
	Income from employment	€	7,947	11,418	<0.01
	Public transfer income total	€	12,858	11,167	
	Pension	€	7,029	6,824	<0.01
	Other public transfers	€	5,450	4,104	<0.01
	Sickpay (public funded)	€	378	238	<0.01
	Direct health costs	€	3,144	1,843	
	Indirect costs, foregone earnings	€	3,471		
	Sum of direct and indirect costs	€	6,616	1,843	
	Net costs	€	4,773		
	Social transfer payments	€	12,858	11,167	
	Net costs including transfers	€	6,464		
After diagnosis	N	N	597,235	776,674	
	Outpatient treatment	€	789	429	<0.01
	Inpatient treatment	€	5,563	1,736	<0.01
	Medication	€	1,782	610	<0.01
	Public health insurance	€	515	361	<0.01
	Income from employment	€	4,509	6,800	<0.01
	Public transfer income total	€	13,888	13,122	
	Pension	€	9,171	10,317	<0.01
	Other public transfers	€	4,361	2,634	<0.01
	Sickpay (publicly funded)	€	356	171	<0.01
	Direct health costs	€	8,650	3,135	
	Indirect costs, foregone earnings	€	2,291		
	Sum of direct and indirect costs	€	10,941	3,135	
	Net costs	€	7,806		
	Social transfer payments	€	13,888	13,122	
	Net costs including transfers	€	8,572		

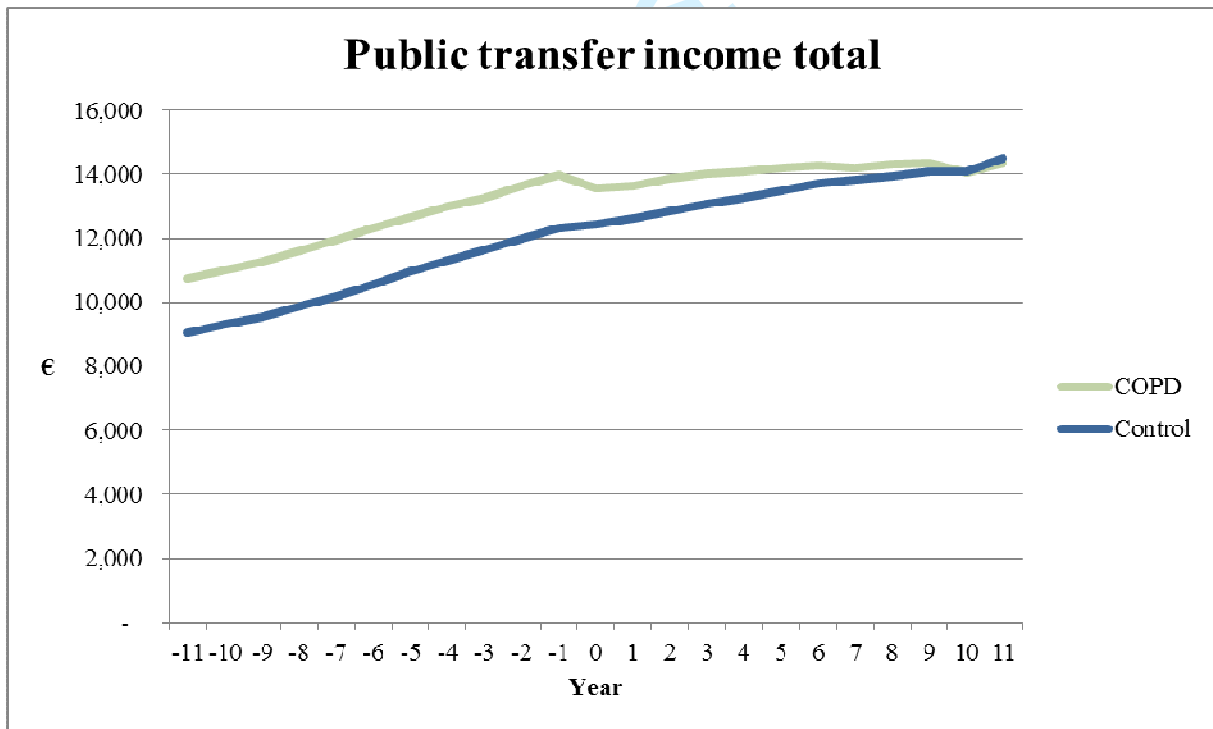
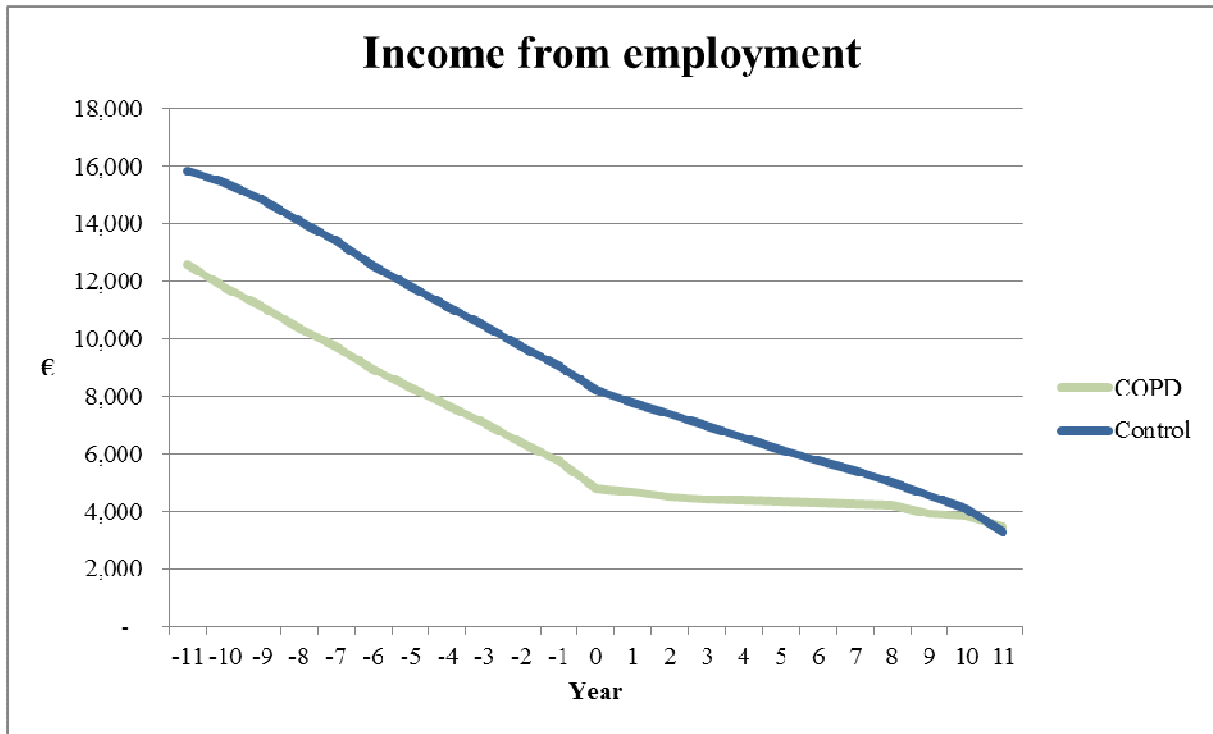
(Yearly costs calculated as the average costs with respect to income per year. N = summarized number of individuals × years observed. P-value from bootstrapped t-test. The values given are in Euros).

Figure 3: Total health expenses, income from employment and public transfer income in Euros before and after diagnosis of COPD (green) compared with control subjects (blue).



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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is among the leading causes of morbidity and mortality worldwide, but longitudinal studies of the economic consequences of COPD are scarce (1, 2).

Smoking, though not necessarily number of pack years, is slowly declining in the Western world but continues to rise elsewhere and it is estimated that the global impact of COPD will increase in the years to come (3-5).

Estimates of COPD prevalence in industrialized countries range widely reflecting both true differences as well as differences in the definition of COPD and in the diagnostic tools used. Most studies find a 10–15% prevalence of COPD in people from 35-40 years and older (6-11). The 17.4% prevalence of COPD in Denmark reported in The Copenhagen City Heart Study is among the highest in the world (12).

The burden of COPD on the health care sector is substantial and has been described and documented in previous cost-of-illness studies concentrating on treatment of COPD and not considering comorbidity (13-20).

Furthermore, the information and assumption of costs have focused on direct costs because indirect costs have generally not been available. Thus, an estimate of total costs of COPD has not yet been achieved.

In Denmark, it is possible to calculate direct and indirect costs of any given disease because information from public and private hospitals and clinics in the primary and secondary care sectors, including medication, social factors, educational level, income and employment data from all patients is registered in central databases and be linked by the unique civil registration number assigned to all Danish citizens facilitating easy and reliable linkage of data. The aim of this study was to evaluate the direct and indirect economic burden of COPD in Denmark before and after initial diagnosis.

Methods

In Denmark, all hospital contacts (Emergency Rooms, ambulatory visits, Admittances etc.), primary and secondary diagnoses are registered in the National Patient Registry (NPR) (21). The NPR includes administrative information, diagnoses, and diagnostic and treatment procedures using several international classification systems, including the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10 Version: 2010).

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8 The NPR is a time-based national database that includes data from all inpatient and outpatient
9 contact, so the data that we extracted are representative of all patients in Denmark who has received
10 a first time primary and secondary diagnosis of COPD irrespective of other diagnoses. As data are
11 available for the entire observation period, we can trace patients retrospectively and prospectively
12 relative to the time of their diagnosis. Furthermore, all contacts in the primary sector (general
13 practice and specialist care) and the use of medications are recorded in the databases of the National
14 Health Security and the Danish Health and Medicines Agency, respectively.
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16 Even though the study is evaluating a relatively long period of time, there is a risk of
17 underestimating the number of patients with COPD, since those with a contact in the primary sector
18 only but not in the secondary sector are recorded as having had contact but not as having received a
19 diagnosis.
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25 We extracted the following first time primary or secondary diagnoses from the NPR in the time
26 period 1998-2010: "J44 Other chronic obstructive pulmonary disease" comprised by the
27 following sub-diagnoses: "J44.0 Chronic obstructive pulmonary disease with acute lower
28 respiratory infection", J44.1 Chronic obstructive pulmonary disease with acute exacerbation,
29 unspecified" and "J44.9 Chronic obstructive pulmonary disease, unspecified".
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31 "J44.8 Other specified chronic obstructive pulmonary disease" was excluded as well as "J43
32 Emphysema" and "J47 Bronchiectasis. Data on disease severity was not available.
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36 Using data from the Danish Civil Registration System including information about all partners,
37 their marital status, social factors, education level, employment, incomes, pensions etc. (22), we
38 randomly selected controls of the same age, sex and educational level as the patients.
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40 Nor the NPR or any other of the national databases contains information about smoking status.
41
42 Social compensation was performed by selecting control subjects residing in the same area of the
43 country as the patients and with the same marital status. The ratio of control subjects to patients was
44 1:1. Data from patients and matched control subjects who could not be identified in the Income
45 Statistics database were excluded from the sample. More than 99% of the observations in the two
46 groups were successfully matched. Patients and matched controls were followed from 1998 to 2010.
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48 If a patient or control was not present in the registry on 1 January each year due to death,
49 imprisonment or immigration, the corresponding control or patient control was not included in the
50 dataset for that year.
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8 Information about educational level is very robust for everyone between the ages of 14 and 80 with
9 only little information lacking. On the other hand there is no available information about
10 educational level for people under the age of 14 years and for a very large proportion of those aged
11 80 years or more – the latter due to lack of registration of education in the Danish Civil Registration
12 System database. This registration, based on information from the different teaching institutions, did
13 not begin until 1970.

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16 One could argue that a huge proportion of the unregistered persons are unskilled but we cannot tell
17 and the problem is the same in the control group. To avoid bias, we excluded all persons with
18 COPD where proper matching information was missing.
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22 Patients and matched controls were followed through the entire time period or until death. If
23 diagnosis of COPD of any given individual was made in the first year (1998) we were able to
24 follow that individual 11 years forward in time. If diagnosis of COPD of any given individual was
25 made in the last year (2010) we were able to follow that individual 11 years backwards in time. If
26 diagnosis of COPD of any given individual was made between the first and the last year we were
27 able to follow that individual both backwards and forward in time.
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32 Municipal services such as care of the elderly (home care nursing and general home care) and
33 municipal rehabilitation is not included as they are paid by the municipalities.
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36 The economic consequences of COPD were estimated by determining the annual costs per patient
37 diagnosed with COPD and comparing these figures with the healthcare costs in a matched control
38 group. Diagnosis of COPD is presented to the NPR using information from public and private
39 hospitals. These diagnoses rely on clinical information and results of diagnostic procedures (e.g.
40 spirometry, bronchoscopy). The procedures are registered but the results of the diagnostic procedure
41 are not recorded in the NPR. The health cost was then divided into annual direct and indirect
42 healthcare costs.
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46 Direct costs included the average costs of hospitalization and outpatient treatment, for separate
47 diagnosis-related groups and specific outpatient costs. These costs were all calculated from Danish
48 Ministry of Health data using diagnosis- related groups (DRG) and average case-mix costs of
49 hospitals or outpatient costs updated on an annual basis. The use and costs of drugs were obtained
50 from the Danish Health and Medicines Agency consisting of the retail price of each drug (including
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8 dispensing costs) multiplied by the number of transactions. The frequencies and costs of
9 consultations with general practitioners and other specialists were based on National Health
10 Security data.
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13 Indirect costs included those related to reduced unemployment benefits and to social transfer
14 payments. Indirect costs were based on income figures from Income Statistics. Costs were
15 measured on an annual basis and adjusted to 2010 prices in Euros (€1: DKK 7.45).
16

17
18 Cost-of-illness studies measure the economic burden resulting from disease and illness across a
19 defined population and include direct and indirect costs. Direct costs are the value of resources used
20 in the treatment, care, and rehabilitation of people with the condition under study. Indirect costs
21 represent the value of economic resources lost because of disease-related work disability or
22 premature mortality. As patients leave the national data registers at the time of death, the indirect
23 costs estimate comprises only the production loss related to disease-related work disability. It is
24 important to distinguish costs from monetary transfer payments such as disability and welfare
25 payments. These payments represent a transfer of purchasing power to the recipients from the
26 general taxpayers but do not represent net increases in the use of resources and, therefore, are not
27 included in the total cost estimate.
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33 34 35 Statistical analysis

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37 The study was approved by the Danish Data Protection Agency. Data were anonymised and neither
38 individual consent nor ethical approval was required.

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40 The results are presented as means because some patients had a very high resource consumption
41 which, despite leading to a skewed distribution, would not be adequately represented if data were
42 presented as median values. Extreme values were manually validated and no errors were identified.
43
44 Statistical analysis was performed using SAS 9.1.3 (SAS, Inc., Cary, NC). Statistical significance of
45 the cost estimates was assessed by nonparametric bootstrap analysis (23, 24).
46

47 Survival was estimated using the Kaplan-Maier method. Hazard ratio was estimated using the Cox
48 proportional hazard model.
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50 **Results**

51 We identified and extracted 131,811 patients with COPD from the national databases (1998-2010)
52 and compared with 131,811 randomly selected matched controls. The age distribution and
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8 education level of patients are shown in Table 1. There are a little more female than male COPD
9 patients - probably because of the age distribution. As expected, most of the patients with an initial
10 diagnosis of COPD are middle-aged or older.
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13 Figure 1 shows distribution of all the included patients with COPD (in red). In blue are the excluded
14 patients with a diagnosis of “J44.8 Other specified chronic obstructive pulmonary disease” which
15 primarily is younger people with a diagnosis of chronic asthmatic bronchitis.
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19 Figure 2 displays survival distribution of COPD patients and controls showing a decline in survival
20 of COPD patients compared to controls.
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24 The percentages of COPD patients and controls receiving various health care and income is shown
25 in Table 2. COPD is associated with significantly higher rates of health-related contact (Outpatient
26 and Inpatient treatment as well as Primary Care), use more medication, have more persons on
27 various public transfer incomes and less people earning income from employment compared to
28 controls.
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32 The annual average health costs and income of COPD patients before and after diagnosis compared
33 with controls are displayed in Table 3. COPD is associated with significantly higher rates of health-
34 related costs, medication use and lower income rates compared to controls both before and
35 increasingly so after diagnosis.
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39 Figure 3 shows total health expenses, income from employment and public transfer income before
40 and after diagnosis of COPD compared with controls.
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42 For every year the total health expenses are significantly higher for COPD patients. A peak in
43 expenses is seen at the time of diagnosis.
44

45 For COPD the income from employment is significantly lower and the total public transfer income
46 is significantly higher than for controls – even 11 years before the diagnosis has been given.
47

48 Both effects diminish over time due to people getting older and retiring from work.

49 In Figure 3 the x-axis begins at minus 11 and stops at 11 years. In year zero all cases and their
50 controls are present. When moving backwards from zero to minus 11, every year will hold less and
51 less cases (and controls) because the ones diagnosed with COPD in 1998 were not followed
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8 backwards in time, the ones diagnosed with COPD in 1999 were only followed backwards 1 year in
9 time and so on. The same is true when moving forwards from year zero to year 11 because the ones
10 diagnosed with COPD in 2010 were not followed forward in time, the ones diagnosed with COPD
11 in 2009 were only followed forward 1 year in time and so on.

12
13 One should be cautious to compare one year with another in the figures, because two neighbor years
14 will not be identical but are composed of some identical cases and some cases that differs
15 completely.

16
17 As an example: At year minus 11 the cases diagnosed with COPD in 2010 are shown (thus we are
18 11 years before the time of the diagnosis). Year minus 10 hold the cases who got diagnosed in 2010
19 plus the cases diagnosed in 2009 (thus we are 10 years before the time of the diagnosis).
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23 24 **Discussion**

25
26 To our knowledge, this is the first epidemiological COPD study evaluates the direct and indirect
27 costs of COPD at a national level.

28
29 The 12 year time-window gives a unique possibility to look backwards and forwards from the point
30 of initial diagnosis. Including every person at a national level with a first time diagnosis of COPD
31 and randomly selected controls matched for age, gender, educational level, residence and marital
32 status provides a very large amount of persons and data making the direct and indirect results more
33 complete and robust.
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36
37 The study has provided several information of interest and confirms the following general beliefs
38 about COPD:

39
40 Patients with an initial primary or secondary diagnosis of COPD had poor survival. The average
41 (95% CI) 12-year survival rate was 0.364 (0.364-0.368) compared with 0.686 among controls
42 (0.682-0.690).

43
44 COPD was associated with significantly higher rates of health-related contacts, medication use and
45 higher socioeconomic costs. The employment rates and the income rates of employed COPD
46 patients were significantly lower compared to controls.

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48 The annual net costs after initial diagnosis, including social transfers were €8,572 for COPD
49 patients.
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51 These consequences were present up to 11 years before first diagnosis in the secondary sector and
52 became more pronounced with disease advancement.
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Determining the economic consequences of COPD is complex. With an accurate diagnosis and appropriate treatment patients' risk of exacerbation decreases as well as the associated costs and maybe even death (although still controversial). In addition quality of life improves. On the other hand the diagnostic procedures, treatment and management of COPD add to the direct costs. However, even when we include the costs associated with the diagnosis and treatment of COPD, our study showed that patients with COPD incur a significant economic burden because the lower employment rates and the lower income rates of employed COPD patients exceed the direct costs of the disease. These factors influence costs and should be included in the disease burden.

This epidemiological study is solely based on information from national databases leading to some limitations.

The results do not reflect the impact of COPD per se as the pronounced comorbidities of COPD patients (depression, anxiety, cardiovascular disease etc.) will have an impact, too. By adjusting for the above mentioned available match factor, including educational level, we have tried to minimize this effect. Especially educational level is a good parameter to use if one wants to level out economical differences. However social factors that we are not aware of can have an impact on the outcome and explain some of the observed differences.

Ideally, we would have adjusted for smoking status but this information is not registered in any of the national databases in Denmark.

In Denmark ICD-10 classification is only used in the secondary health sector (hospitals) not in the primary health sector (general practitioners). Even though this study spans 12 years and includes all with an initial primary or secondary ICD-10 diagnosis of COPD - and the majority of known COPD patients are believed to be included over time - there is a risk of underestimation. COPD patients that are only followed in the primary health care sector during the study period are not included and this will bias the results as these patients will tend to be less sick. This fact will tend to overestimate the direct and indirect costs of COPD.

The accuracy of the diagnosis and management is sensitive to the diagnostic criteria used by the reporting doctors. The people aged below 30-40 years with a diagnosis of COPD may – at least to some extent - be due to misclassification.

Furthermore, although J44 by far is the most common diagnosis used in COPD, several different

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8 diagnoses deriving from J40 (bronchitis), J41 (simple and mucopurulent chronic bronchitis), J43
9 (emphysema) and J47 bronchiectasis) are also used to some (unknown) extent. We have chosen to
10 exclude these diagnoses as well as J44.8 Other specified chronic obstructive pulmonary disease. It
11 could be argued that a large proportion of these excluded individuals are very likely to have COPD,
12 but because this is an epidemiologic study, entirely based on registry data, we decided to include
13 only those with a specific diagnosis of COPD.
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16 By allowing both primary and secondary diagnosis of COPD some correction of this problem has
17 taken place but may have opened up for adding further comorbidity.
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19 In the control group there will be a number of undiagnosed patients with COPD (approx. 10%) thus
20 introducing a bias tending to reduce the difference in costs between the two groups in our study
21 (25).
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25 **Conclusion:** This study provides unique data at a national level regarding direct and indirect costs
26 before and after initially diagnosed COPD as well as serious mortality, health and economic
27 consequences for the individual patient and for society.
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29 As the economic consequences are present years prior to the first primary or secondary diagnosis of
30 COPD in the secondary health sector one, it could be speculated that early identification and
31 intervention might be part of the solution.
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33 Adequate treatment may reduce the consequences of COPD but, if socially and economically
34 significant reductions in morbidity, mortality and social impact are to be achieved, much earlier
35 disease identification and management are needed More research and evaluation of case finding
36 strategies and disease management programs are needed (26).
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Table 1: Age, gender and education level distribution of COPD patients.

Gender	N	Percentage
Male	63,342	48.1
Female	68,469	51.9
Married or co-habiting		54.0
Age distribution		
<14	-	-
14-20	136	0.1
20-29	394	0.3
30-39	1,717	1.3
40-49	6,664	5.1
50-59	19,601	14.9
60-69	38,297	29.1
70-79	51,524	39.1
80-92	13,478	10.2
≥92	-	-
Education level		
Primary	80,483	61.1
Secondary	864	0.7
Vocational	40,050	30.4
Short college	1,824	1.4
Medium college	6,784	5.1
Master/PhD	1,806	1.4
Total	131,811	100.0

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Figure 1: Distribution of included (red) and excluded cases (blue) on the basis of diagnosis according to age (x-axis) and number (y-axis).

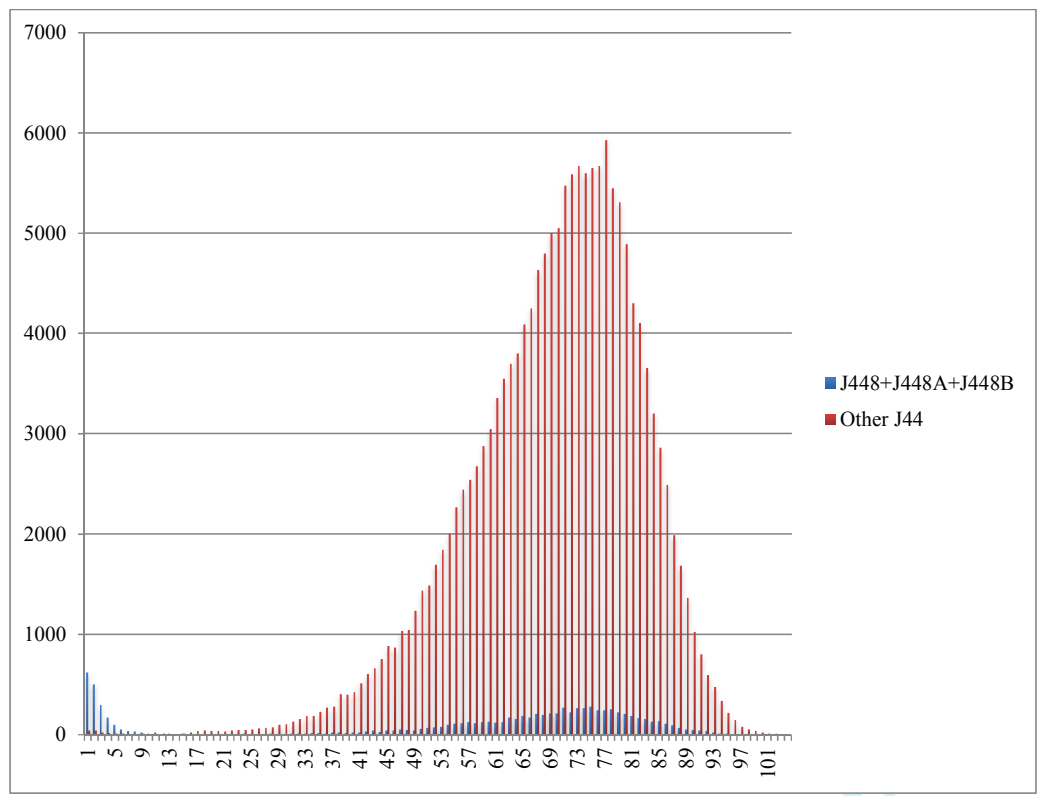
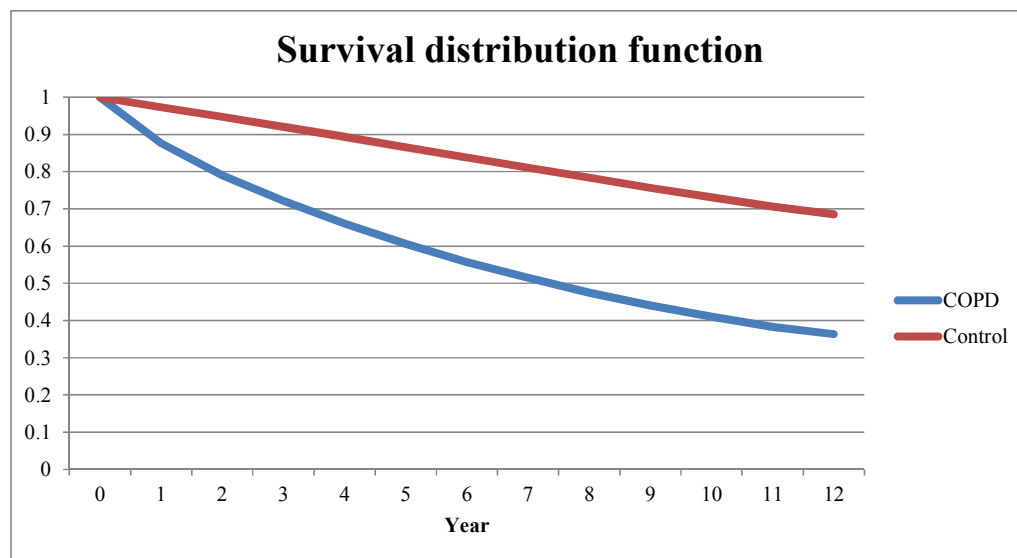


Figure 2: Kaplan-Maier survival distribution of COPD patients (blue) and controls (red) estimated using Cox proportional hazard model.



		COPD			Control		
Survival	Year	Survival Distribution Function Estimate	SDF Upper 95.00% Confidence Limit	SDF Lower 95.00% Confidence Limit	Survival Distribution Function Estimate	SDF Upper 95.00% Confidence Limit	SDF Lower 95.00% Confidence Limit
	0	1,000	1,000	1,000	1,000	1,000	1,000
	1	0,876	0,878	0,875	0,973	0,974	0,972
	2	0,790	0,792	0,788	0,948	0,949	0,946
	3	0,722	0,725	0,720	0,921	0,922	0,919
	4	0,661	0,664	0,659	0,894	0,895	0,892
	5	0,606	0,609	0,603	0,866	0,867	0,864
	6	0,557	0,560	0,554	0,838	0,840	0,836
	7	0,515	0,518	0,512	0,811	0,813	0,808
	8	0,475	0,478	0,472	0,784	0,786	0,781
	9	0,441	0,444	0,437	0,757	0,760	0,754
	10	0,410	0,414	0,407	0,731	0,734	0,728
	11	0,383	0,387	0,379	0,706	0,710	0,703
12	0,364	0,368	0,360	0,686	0,690	0,682	
Censored	N	131,811			131,811		
	% censored	53.5			80.2		
Hazard function	HazardRatio	0,33					
	ProbChiSq	0,00					
	StdErr	0,01					

Table 2: Percentages of COPD patients and controls that receive income and various health care services (after diagnosis).

		COPD	Controls	P-value
Outpatient treatment	%	64.9	36.2	<0.01
Inpatient treatment	%	53.8	18.8	<0.01
Medication	%	98.1	85.9	<0.01
Public health insurance	%	99.0	95.6	<0.01
Income from employment	%	16.7	23.8	<0.01
Public transfer income total	%	90.3	83.8	<0.01
<i>Pension</i>	%	60.3	63.8	<0.01
<i>Other public transfers</i>	%	27.6	18.6	<0.01
<i>Sickpay (publicly funded)</i>	%	5.5	3.6	<0.01

(Bootstrapped Cochran-Armitage test showing whether the fraction received is significant for each expense type). The values given are in percentages.

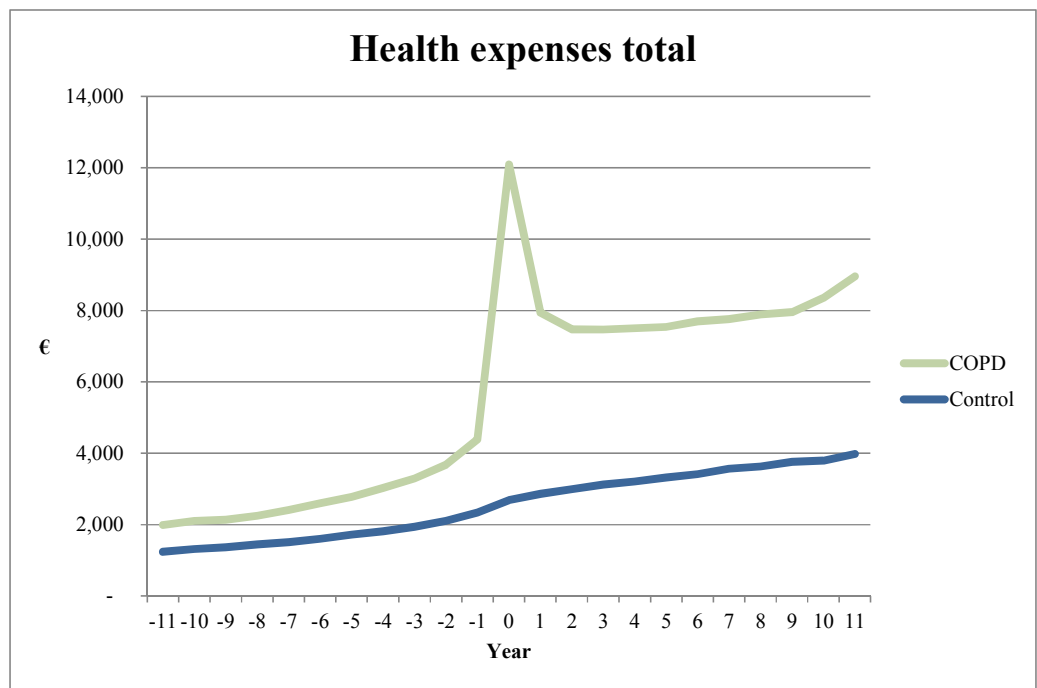
Table 3: Health costs and income of COPD patients before and after diagnosis compared with controls.

			COPD	Controls	P-value
Before diagnosis	N		708,329	708,343	
	Outpatient treatment	€	335	227	<0.01
	Inpatient treatment	€	1,534	904	<0.01
	Medication	€	918	434	<0.01
	Public health insurance	€	357	278	<0.01
	Income from employment	€	7,947	11,418	<0.01
	Public transfer income total	€	12,858	11,167	
	Pension	€	7,029	6,824	<0.01
	Other public transfers	€	5,450	4,104	<0.01
	Sickpay (public funded)	€	378	238	<0.01
	Direct health costs	€	3,144	1,843	
	Indirect costs, foregone earnings	€	3,471		
	Sum of direct and indirect costs	€	6,616	1,843	
	Net costs	€	4,773		
	Social transfer payments	€	12,858	11,167	
	Net costs including transfers	€	6,464		
After diagnosis	N	N	597,235	776,674	
	Outpatient treatment	€	789	429	<0.01
	Inpatient treatment	€	5,563	1,736	<0.01
	Medication	€	1,782	610	<0.01
	Public health insurance	€	515	361	<0.01
	Income from employment	€	4,509	6,800	<0.01
	Public transfer income total	€	13,888	13,122	
	Pension	€	9,171	10,317	<0.01
	Other public transfers	€	4,361	2,634	<0.01
	Sickpay (publicly funded)	€	356	171	<0.01
	Direct health costs	€	8,650	3,135	
	Indirect costs, foregone earnings	€	2,291		
	Sum of direct and indirect costs	€	10,941	3,135	
	Net costs	€	7,806		
	Social transfer payments	€	13,888	13,122	
	Net costs including transfers	€	8,572		

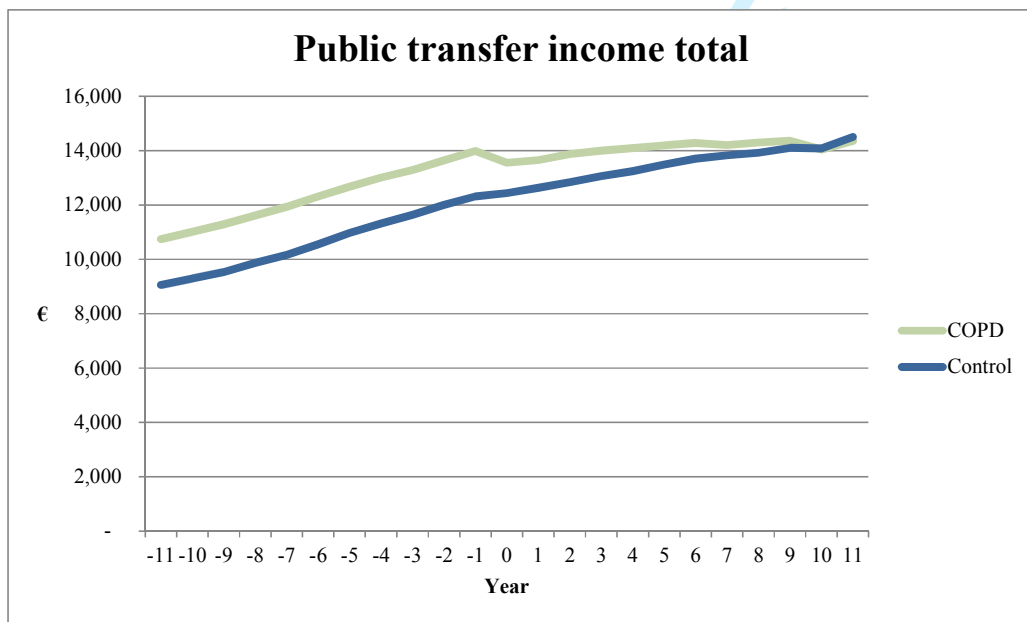
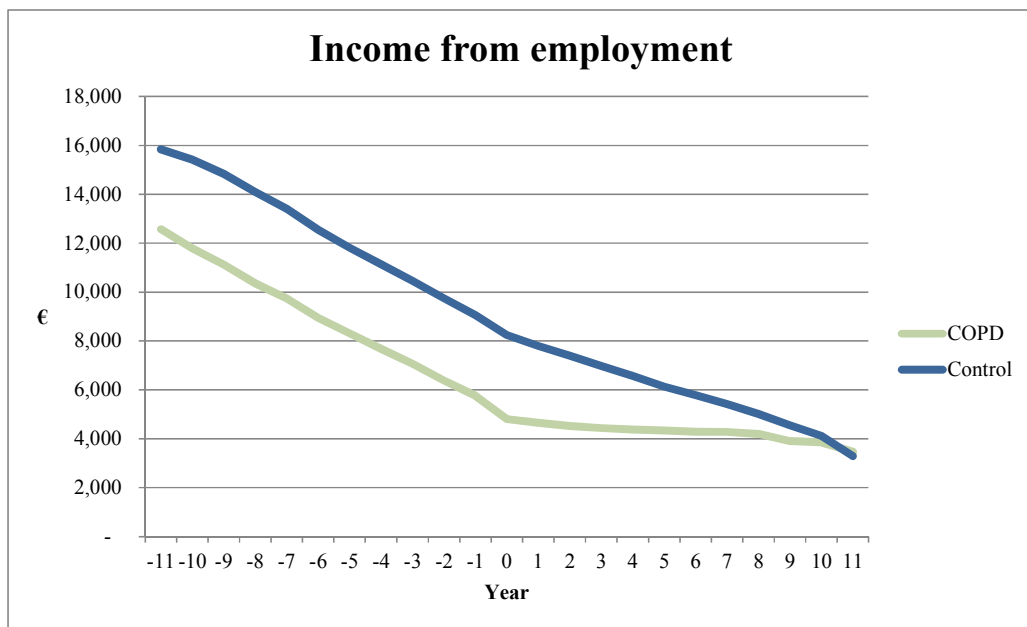
(Yearly costs calculated as the average costs with respect to income per year. N = summarized number of individuals × years observed. P-value from bootstrapped t-test. The values given are in Euros).

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Figure 3: Total health expenses, income from employment and public transfer income in Euros before and after diagnosis of COPD (green) compared with control subjects (blue).



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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.