Natural history data in economic modelling for COPD: a focus on hospitalisation

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Abstract

Background: to date, all information on Chronic Obstructive Pulmonary Disease (COPD) exacerbations used within decision analytic models have come from clinical trials. The authors have available to them, a unique longitudinal dataset with a sizeable COPD population, followed up for over 30 years, with linked hospitalisation and death records.

Aim: to derive information on COPD hospitalisations and mortality from a longitudinal dataset in order to inform an economic model for COPD.

Data: a Scottish prospective cohort (Renfrew/Paisley (MIDSPAN) study) of 15 402 men and women followed up for up to 34 years was used (1). Between 1972 and 1976, all residents aged 45-64 years within Renfrew and Paisley were asked to complete a health questionnaire and to attend a physical examination. Hospital admissions were recorded and indirect follow up of mortality via the Registrar General for Scotland was established.

Methods: the study was split by baseline disease severity. Rates of hospitalisation and rates of mortality by disease severity were derived. The frequency of hospital admissions (severe exacerbations) and length of stay in hospital were derived from the longitudinal dataset. All analyses were conducted on men and women separately.

Results: of the study population, 78% of the men and 66% were deceased, giving an extensive and complete follow up for the majority of those in the study. Eleven percent of the study population had either a COPD hospitalisation and/or a COPD coded death. Hospitalisation rates and mortality rates were seen to increase with disease severity in both men and women. Most of those hospitalised during the follow up period had just one hospitalisation and length of stay in hospital was found to be nine days or fewer for 50% of those with a COPD hospitalisation.

Conclusion: epidemiological data provides useful and important information that can be used to inform the design and inputs into an economic model for COPD. Additional thoughts on ways in which the data can be mined are welcomed for discussion.

Introduction

The respiratory disease, Chronic Obstructive Pulmonary Disease (COPD) has been defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as:

"…a preventable and treatable disease…characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with abnormal inflammatory response of the lung to noxious particles or gases."(2)

COPD is a major cause of morbidity and mortality worldwide and is the only major cause of morbidity that is increasing.

Total costs to the NHS for COPD have been estimated somewhere between £486 million (3;4) and £848 million (5;6) per year. The major drivers of this cost are disease severity and severe exacerbations, for example, COPD patients have been found to occupy approximately one million bed days annually.(7)

Severe exacerbations have been described as when the patient (or caregiver) recognizes an obvious and/or a rapid deterioration in their condition and requires hospitalisation.(9) They are typified by one or more of: increased shortness of breath; increased volume and purulence of sputum; increased cough and shallow/rapid breathing.(9) According to expert opinion, an exacerbation is the main reason why a COPD patient would attend hospital.

Reducing or preventing disease progression and/or hospital admission (severe exacerbations) will have a direct effect on: the total cost burden for COPD,(8) and on quality of life for patients. Because of this, reducing or preventing disease progression and/or hospital admissions are often principal outcome measures for clinical trials in COPD.

Because of the physical detriment and economic cost associated with exacerbations, exacerbations are modelled within cost effectiveness analyses of COPD. Exacerbations are predominantly built into the disease states (usually mild, moderate and severe).(10-14) Each health state has an exacerbation (usually mild and severe) probability attached which varies by disease state and by treatment group.(10-14) Cycle lengths have been assumed to

either be one month,(10-12) or three months,(13;14) during which only one exacerbation can take place. To date all information on COPD exacerbations used within decision analytic models have come from clinical trials.(10-14)

The authors have available to them, a unique longitudinal dataset with a sizeable COPD population, followed up for over 30 years, with linked hospitalisation and death records. Because the study group were middle aged at the start of the study, the majority of the population are now deceased. As such it is possible to study the natural history of the disease and to use this information to partially inform an economic model of the disease. The aim of this initial analysis of the dataset is to determine severe exacerbation frequency, the rate of hospitalisation and mortality and length of stay in hospital for severe exacerbations, all by disease severity. Additional future analyses of the dataset will be described.

Methods

Study sample

A Scottish prospective cohort (Renfrew/Paisley (MIDSPAN) study) of 15 402 men and women followed up for over 30 years (until the end of December 2005) was used.(1) Between 1972 and 1976, all residents aged between 45 and 64 years within the two conurbations of Renfrew and Paisley were asked to complete a health questionnaire and to attend a physical examination (78% participated,(15)).

Respiratory symptoms of: phlegm, breathlessness, and wheeze were self-reported as were smoking history (including pack years) and social class (derived from occupation).(16) Body mass index (BMI), diastolic blood pressure, and plasma cholesterol were recorded within the physical examination.(17) Forced Expiratory Volume in one second (FEV_1) and Forced Vital Capacity (FVC) were measured using a vitalograph spirometer whilst the participant was standing. A practice blow was first carried out, followed by two expirations into the spirometer. The higher of the two values was recorded.

Percentage predicted FEV_1 was obtained for each participant by dividing actual FEV_1 by predicted FEV_1. Predicted FEV_1 was determined by a linear regression on age and height

by sex using a cohort of healthy participants, 870 men and 2792 women (non smokers, who said no to questions on: wheeze, breathlessness, asthma, and phlegm). The equations were:

Men: FEV_1 = -187.32-2.87 x age + 3.69 x height
Women: FEV_1 = -25.15-2.89 x age + 2.37 x height

These slightly differ from previously published equations,(18) due to improved data recording in the dataset. Twenty three participants were lost to follow up and were excluded from all analyses.

Linked data

The Midspan cohort are linked to information held by the General Register's Office (GRO) for Scotland on all deaths in the United Kingdom,(2) and to all acute hospital discharges (SMR1 recording scheme) in Scotland between 1972 and Dec 1995.(19)

Clinical opinion regards exacerbations as the main reason why a COPD patient would attend hospital and given that severe exacerbations occur when the patient (or caregiver) recognizes an obvious and/or a rapid deterioration in their condition and requires hospitalisation (Roberto Rodriguez), all COPD coded hospital admissions within the dataset were regarded as severe exacerbations.

COPD hospital admissions and mortality (ICD8 491-492, ICD9 490-492 & 496, ICD10 J40-J44) were identified, in any diagnostic position (in any of the principal or secondary (up to five) diagnostic coding positions). Hospital admission stays of more than 200 days (N=11) were removed from the dataset as these were unlikely to represent (acute) COPD hospital exacerbations.

COPD definition

The NICE guidelines recommend that a diagnosis of COPD should be considered in patients: aged over 35, with a risk factor (usually smoking), who present with one or more of the symptoms: exertional breathlessness, chronic cough, regular sputum production, frequent winter 'bronchitis' or wheeze,(20) and who have airflow obstruction, considered present when both FEV_1 /FVC<0.7 and FEV_1 <80% predicted.(20)

Assumptions about a COPD case were made to allow for the application of the NICE definition to the dataset:
1) Airflow obstruction: FEV_1 /FVC<0.7 and FEV_1 <80% predicted.
2) Respiratory symptom: one or more of, breathlessness, wheeze, phlegm.
3) Risk factor: either a smoking history of ten pack years or more, or a pipe/cigar smoker.
This interpretation represents a close match to the definition given by NICE. All participants meeting these criteria were defined as COPD cases.
Disease severity was established for each COPD case using percentage predicted FEV_1
Mild COPD was defined as 50≤ FEV_1< 80 percent predicted, moderate COPD as 30≤ FEV_1< 50 percent predicted and severe COPD as FEV_1<30 percent predicted.

Statistical analysis

For the variables integral to the analysis (lung function, respiratory symptoms and height), participants were removed from further analyses if missing data on these variables existed. The amount of missing data was small at less than two percent: FEV_1 (N missing=22), FVC (29), phlegm (5), phlegm over three months (50), phlegm and cough (71), breathlessness (61), wheeze, (73) and height (13). For the secondary variables used within the analysis, missing values (by sex) were replaced by the mean value for age at starting smoking (current/ex) and by the modal value for social class (410).

The percentage of participants in each COPD severity group (at baseline) with a COPD hospitalisation at any point within 34years of follow up was identified from the data. The percentage of participants within each COPD severity group with a COPD coded death was also determined.

Hospitalisation rates were calculated by first summing the frequency of hospitalisations in each severity group and then simply dividing this value by the number of person years at risk for that severity group.

Kaplan Meier survival curves were derived by the standard method, using age in study along the x axis. Because age is used along the x axis, information at both ends of the curves should be interpreted with caution, and at the extremes, disregarded.

All cause mortality rates were calculated in a similar fashion to the hospitalisation rates, with the frequency of deaths in each severity group divided by the total number of person years at risk in that group .

The number of times each participant was hospitalised over the 34 years of follow up was determined and depicted by a histogram.

Length of stay in hospital was derived from the data and illustrated using a histogram. Length of stay was calculated by subtracting the date of discharge from the admission date (once any transfers had been accounted for). A value of one was added to all length of stay values to adjust for day cases (ie where admission date is equal to the discharge date).

Results

The study population comprised of 6920 men and 8202 women (table 1). Of the men (women) 78% (66%) were deceased. Many of the participants were smokers or had smoked: 77% (46%) had ten or more pack years and a substantial minority, 39% (29%), had one or more respiratory symptom. Overall prevalence of COPD within the population was found to be eight percent: twelve percent in men and five percent in women.

Of those with a COPD hospitalisation at baseline: 61% had respiratory symptoms, 85% had smoked ten or more pack years, 58% had a percentage predicted FEV_1 of less than 0.8 and 54% had an FEV_1/FVC of <0.7.

Out of the 15 122 participants within the study, nine percent (N=1314) had a COPD hospital admission (10% men 8% women), six percent died of COPD (8% men 5% women) and eleven percent (N=1660) either died from COPD and/or were hospitalised for COPD within the 34 years of follow up (13% men 9% women) (table 1).

The proportion of study participants with a COPD hospital admission and/or COPD mortality was shown to increase in line with baseline disease severity (table 2). Looking to the no COPD group, four percent had COPD as a cause of death and seven percent were admitted to hospital for COPD. Of the 94 participants diagnosed with severe COPD at

baseline, 50% went into hospital, 50% had COPD recorded on their death certificate and 69% either had a hospital admission and/or COPD coded mortality.

Hospitalisation rates were seen to increase with disease severity in both men and women (table 3). In the male (female) group, for every 100 person years at risk in the severe COPD group, there were 14 (11) hospitalisations, compared to 4 (4) in every 100 person years at risk in the mild group and 1(1) in the no COPD group.

The survival curves for all-cause mortality showed clear separation by disease severity (figure 1). The most severe COPD group had the lowest survival probability in both men and women and the no COPD group the highest. The median age of survival can be read off these curves: the median age of survival is reduced as the participant becomes more severely diseased, by more than 20 years between the very severe compared to the no COPD group.

All-cause mortality rates increased with disease severity, with a larger association in men between mortality and disease severity than in women (table 4). In the male severe COPD group, 13 deaths occurred in 100 person years at risk in comparison to 6 in the female group. In the mild COPD group, 6 deaths occurred for every 100 person years at risk in the male group and 4 in the female group.

Of those hospitalised with COPD, the modal number of hospital admissions in both men and women was one (figure 2): 51% of men and 47% of women had just one hospital admissions over the follow up period. The distribution of the number of hospitalisations was positively skewed in both men and women. The largest number of COPD hospital admissions was seen in the female group, with one woman having 39 admissions compared to one man having 34 admissions. Nevertheless, most of the participants (98%) had 11 or fewer hospital admissions over the follow up period of 34 years. The mean number of COPD hospitalisations was 2.53 (sd 3.14) in men and 2.89 (sd 4.05) in women.

For length of stay in hospital, 50% of the men (women) had a length of stay of 8 (9) days or fewer and 90% of hospital stays were less than or equal to 28 (27) days. The distribution of

length of stay was positively skewed. Less than 4% of hospital stays in both men and women were for more than 50 days.

Discussion

Information elicited from longitudinal data on resource utilisation (hospitalisation) and mortality provides an alternative and useful source to data collected from randomised controlled trials, in informing economic models.

The extensive follow up period of the Midspan study provides a unique source of information on the natural history of the disease not otherwise available. Of the study population, 78% of the men and 66% were deceased, giving an extensive and complete follow up for the majority of those in the study. Eleven percent of the study population had either a COPD hospitalisation and/or a COPD coded death.

Hospitalisation rates and mortality rates were seen to increase with disease severity in both men and women. Most of those hospitalised during the follow up period had just one hospitalisation and length of stay in hospital was found to be nine days or fewer for 50% of those with a COPD hospitalisation.

Further analyses of the data will be carried out and any further suggestions or advice from the interested reader will be much appreciated.

A significant proportion of participants diagnosed with COPD did not experience a hospital admission. In the economic model that the authors are considering, questions have been raised as to whether there should be post exacerbation states built into the model that reflect altered probabilities of mortality and disease progression once a severe exacerbation has occurred. The data will be split by disease severity and by those who have and who have not experienced a COPD hospital admission. The hazard rates for all-cause mortality between those who have and haven't been hospitalised for COPD will be compared, by disease severity.

From initial exploratory analysis of the data, it was seen that exacerbations tend to occur in bundles, thus implying that after experiencing one exacerbation, there may be an increased

probability of having a further exacerbation. It would be of interest to examine if this was indeed the case.

COPD costs given by HRG codes were £1106 for a non elective stay in 2005/06 and £1490 for an elective stay. Hospitalisation costs will be estimated by disease severity.

One of the biggest issues with the dataset is that information on the participants was only collected at one time point. Therefore as the study population grew older, lung function was bound to deteriorate and a proportion of them were likely to develop respiratory symptoms. The extent to which any participant with no COPD went on to develop COPD is unknown, but is likely to, in part explain the four percent of the no COPD group who had COPD recorded on their death certificate and the seven percent of the same group with a COPD hospitalisation.

Of those with mild or moderate COPD at baseline, the proportion that developed more severe disease is unknown and is a limitation of the study. One way of attempting to get around this issue is to do regression analysis with year of study included as an explanatory variable. In further work, this technique will be used to examine the independent effect of disease severity on the risk of hospitalisation (accounting for any within participant variability).

Conclusion

Epidemiological data provides useful and important information that can be used to inform the design and inputs into an economic model for COPD. Additional thoughts on ways in which the data can be mined are welcomed for discussion.

Table 1 Summary statistics. Figures are in numbers (percentages) unless stated otherwise

	Men	Women
Participants	6920 (46)	8202 (54)
Deceased	5426 (78)	5400 (66)
Yrs of follow up (mean)	19.8	23.2
Yrs of follow up (range)	0-34	0-34
Time at risk (days)	137 044	190 313
Age (mean)	54.1	54.4
Social Class (mode)	IIIM	IV
Body Mass Index (mean)	25.9	25.8
Smoking $\geq$ 10yr pack yrs	5320 (77)	3780 (46)
Respiratory symptoms	2667 (39)	2397 (29)
COPD prevalence	857 (12)	382 (5)
Hospital admission	698 (10.1)	616 (7.5)
COPD mortality	545 (7.9)	376 (4.6)
Hospital admission and/or COPD mortality	915 (13.2)	745 (9.1)

Table 2 Percentage of participants with: a COPD hospital admission; COPD mortality; COPD hospital admissions and/or COPD mortality, by COPD disease severity at baseline (over follow up period, max 34yrs).

		N	Hosp Admission	COPD mortality	Hosp ad and/or COPD mortality
All					
	No COPD	13 883	7	4	8
	Mild	843	27	21	35
	Moderate	302	38	44	53
	Severe	94	50	50	69
Men					
	No COPD	6063	7	5	9
	Mild	582	25	21	33
	Moderate	205	36	45	53
	Severe	70	49	57	73
Women					
	No COPD	820	6	3	7
	Mild	261	33	21	39
	Moderate	97	42	41	53
	Severe	24	54	29	58

N= total number in severity group

Table 3 Hospitalisation rates by disease severity, men and women

		N	Person years at risk	Rate per person yr	Rate per 100 person yrs	Rate per 1000 person yrs
All						
	No COPD	2448	307711.9	0.01	0.80	7.96
	mild	598	14621	0.04	4.09	40.90
	moderate	386	4127	0.09	9.35	93.53
	severe	118	897	0.13	13.15	131.55
Men						
	No COPD	1104	124383.57	0.01	0.89	8.88
	mild	370	9517.93	0.04	3.89	38.87
	moderate	219	2615.53	0.08	8.37	83.73
	severe	76	527.04	0.14	14.42	144.20
Women						
	No COPD	1344	183327.47	0.01	0.73	7.33
	mild	228	5103.38	0.04	4.47	44.68
	moderate	167	1511.63	0.11	11.05	110.48
	severe	42	370.22	0.11	11.34	113.45

N=number of events (hospitalisations) in each disease severity group

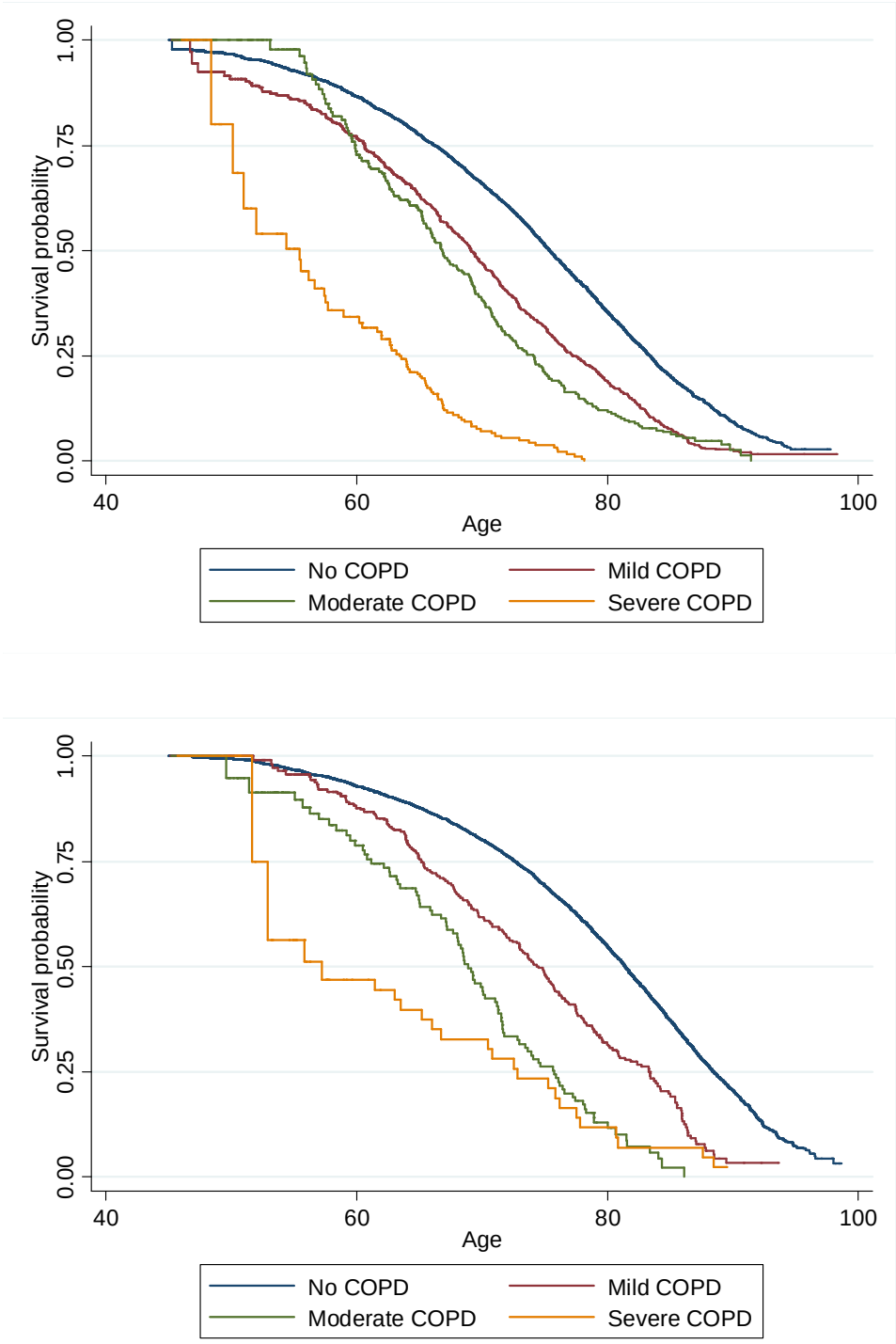

Figure 1 Survival curves for all cause mortality for men (top) and women (bottom) by COPD disease severity

Table 4 Mortality rates by disease severity, men and women

	N	Person years at risk	Rate per person yr	Rate per 100 person yrs	Rate per 1000 person yrs
All					
No COPD	9700	307711.53	0.03	3.15	31.52
mild	751	14621.30	0.05	5.14	51.36
moderate	283	4127.15	0.07	6.86	68.57
severe	92	897.26	0.10	10.25	102.53
Men					
No COPD	4629	124383.41	0.04	3.72	37.22
mild	535	9517.93	0.06	5.62	56.21
moderate	193	2615.53	0.07	7.38	73.79
severe	69	527.04	0.13	13.09	130.92
Women					
No COPD	5071	183327.97	0.03	2.77	27.66
mild	216	5103.38	0.04	4.23	42.32
moderate	90	1511.63	0.06	5.95	59.54
severe	23	370.22	0.06	6.21	62.12

N=number of events (mortality) in each disease severity group

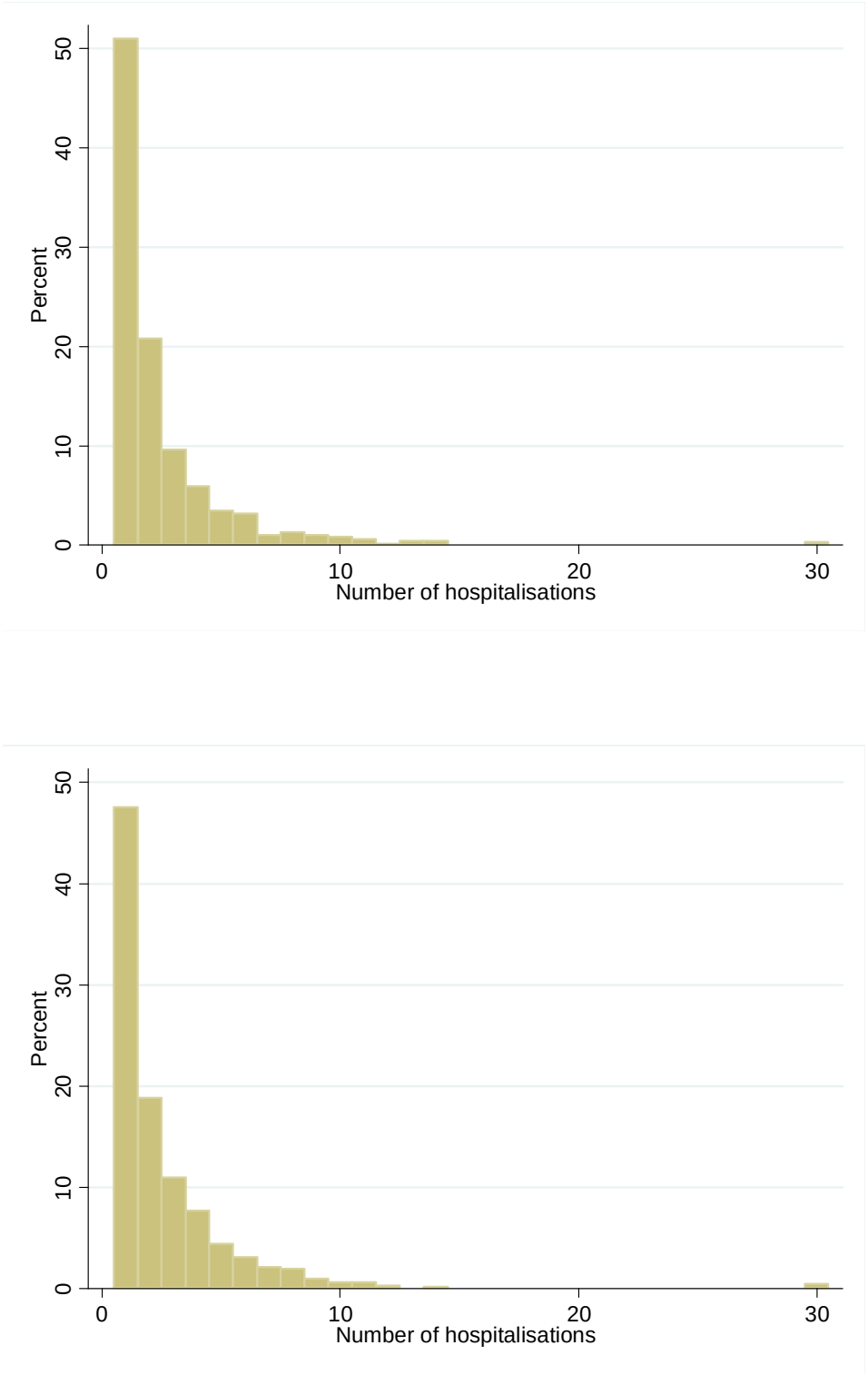

Figure2 Number of times hospitalised (over maximum 34yrs follow up), men (top) women (bottom)

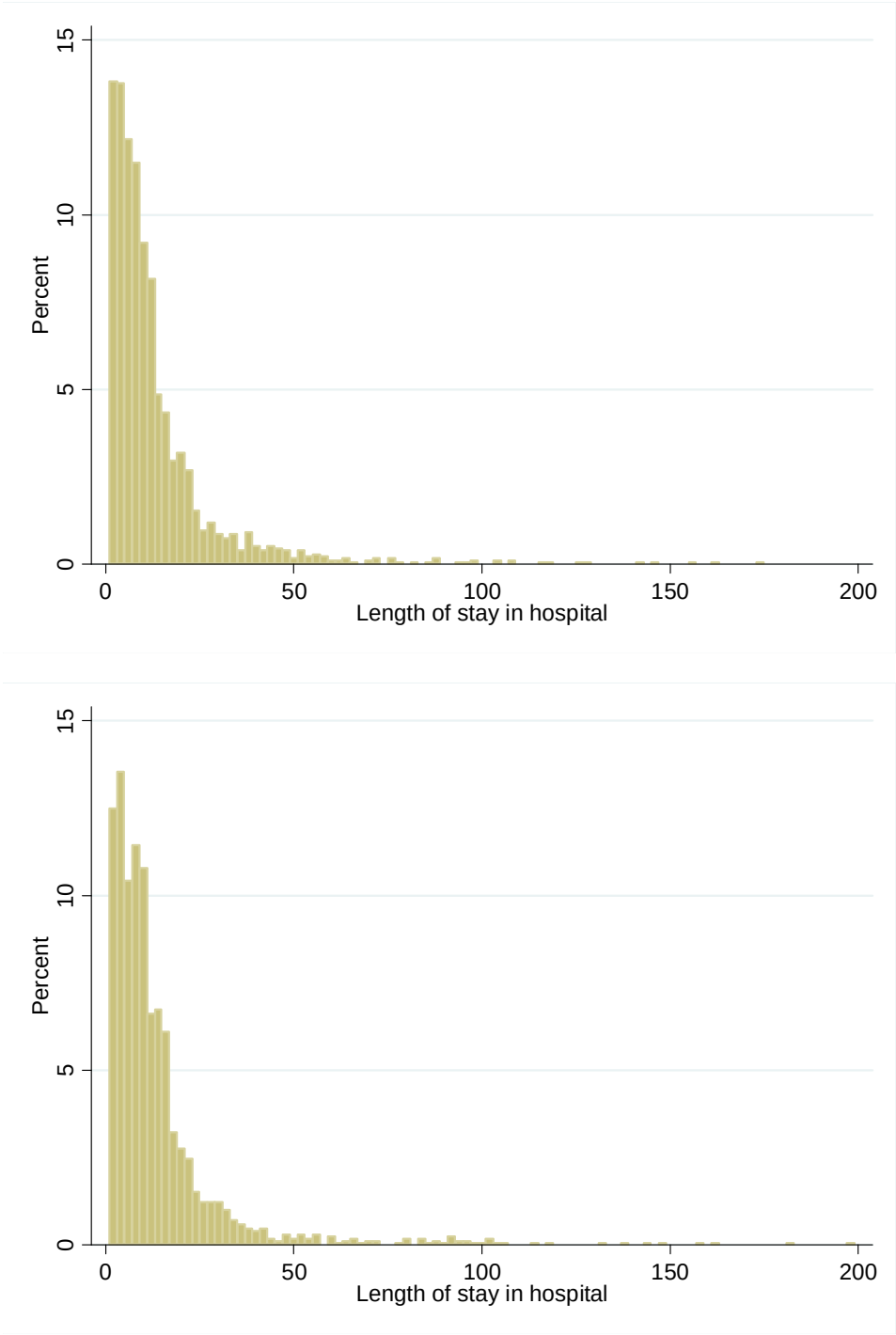

Figure 3 length of stay in hospital, men (top) women (bottom)

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