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nceRegular Physical Activity reduces Hospital Admission and Mortality in Chronic Obstructive Pulmonary Disease. A Population-Based Cohort Study

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ABSTRACT

Background: Information about the influence of regular physical activity on the course of chronic obstructive pulmonary disease (COPD) is scarce. We studied the association between regular physical activity and both hospital admissions for COPD and all-cause and specific mortality in COPD subjects.

Methods: From a population-based sample recruited in Copenhagen in 1981-3 and 1991-4, 2,386 individuals with COPD (according to lung function tests) were identified and followed until 2000. Self-reported regular physical activity at baseline was classified into four categories (very low, low, moderate, and high). Dates and causes of hospital admissions and mortality were obtained from Danish registers. Adjusted associations between physical activity and hospital admissions for COPD and mortality were obtained using negative binomial and Cox regression models, respectively.

Results: After adjustment for relevant confounders, subjects reporting low, moderate or high physical activity had lower risk of COPD admission during follow-up than those who reported very low physical activity (Incidence Rate Ratio 0.72, 95% confidence interval 0.53 to 0.97). Low, moderate and high levels of regular physical activity were associated with an adjusted lower risk of all-cause mortality (Hazard Ratio 0.76, 0.65 to 0.90) and respiratory mortality (0.70, 0.48 to 1.02). No effect modification was found for gender, age group, COPD severity or a background of ischaemic heart disease.

Conclusions: COPD subjects who perform some level of regular physical activity have lower risk of both COPD admissions and mortality. The recommendation that COPD patients be encouraged to maintain or increase their levels of regular physical activity should be considered in future COPD guidelines, since it is likely to result in a relevant public health benefit.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD), with a prevalence in adults of around 6-7%[1], is one of the main causes of morbidity, and a leading cause of death worldwide[2]. Reducing admissions to hospital due to the exacerbation of COPD is a prime aim in the management of the disease[3][4] due to its high economic and social costs[5]. Currently only oxygen therapy, some bronchodilators and glucocorticoids, and influenza vaccinations are considered effective in improving the course of the disease, either reducing the frequency of hospital admission for COPD or mortality[3][4]. In a previous study, conducted in a cohort of 346 patients with moderate to severe COPD followed-up for one year in Barcelona, Spain, we found a reduced risk of admission for the exacerbation of COPD in subjects with COPD who reported physical activity equivalent to walking at least one hour daily, compared to those who reported physical activity equivalent to walking only 20 minutes a day or less[6]. The finding was considered important because of its potentially significant beneficial impact and its implications with regard to reducing health costs[7]. Indeed, among the current internationally recognised COPD guidelines, only those edited by the British Thoracic Society[8] recommend that COPD patients be encouraged to increase their levels of regular physical activity, a recommendation which as yet is not evidence-based. From a Public Health point of view, and considering the large amount of health benefits associated with the practice of physical activity[9], the possibility that higher levels of regular physical activity, such as walking or cycling, could be associated with an improvement in the course of COPD is worthy of further investigation. The lack of research on the influence of regular physical activity in the natural history of COPD is in contrast to that existing for other chronic diseases such as type 2 diabetes[10] or cancer[11][12], in which, among subjects with the disease, higher levels of physical activity [the equivalent to walking 3 to 5 hours per week) have even been related to a reduced risk of death from the chronic disease in question[13]. In the present study, we assessed the association between regular physical activity and both hospital admission due to COPD and all-cause and specific mortality in a large prospective cohort study of COPD subjects sampled from the general population in Copenhagen and followed-up for a mean of 12.0 years. The study is part of the Copenhagen City Heart Study, which has already provided relevant information about the course of COPD[14][15][16].

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METHODS

Study design and population

The Copenhagen City Heart Study (CCHS) involves the study of an on-going prospective cohort of adults recruited from the general population, with repeated examinations every 5-10 years. A random age-stratified sample of the general population aged 20 years or more was drawn from the Copenhagen Population Register as of January 1st 1976, and a first examination (n=14,223) took place in 1976-1978. At the second examination five years later (1981-1983), the cohort was supplemented with a new sample of subjects aged 20 to 24 years (total n=12,698). In the third examination (1991-1994) the sample was supplemented with 20 to 49 year old subjects (total n=10,135)[17][18]. The institutional review board and Danish regional ethics committees approved the research protocol. Participants gave written informed consent.

Since the first CCHS examination provided limited information about regular physical activity, for the present study we selected all participants included in the second (1981-1983) together with the complementary sample of the third (1991-94) CCHS examinations. Of these (n=15,563), 2,386 subjects met the criteria for COPD and were included in the present analysis. COPD was defined, based on the results of lung function tests including the measurement of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC), as the presence of airway obstruction: $FEV_1/FVC \leq 70\%$, and classified according to the degree of airway obstruction[3][4]: mild ($FEV_1 \geq 80\%$), moderate ($FEV_1 < 80\%$ & $\geq 50\%$), severe ($FEV_1 < 50\%$ & $\geq 30\%$), and very severe ($FEV_1 < 30\%$). Subjects who, in addition to COPD, reported having suffered asthma, (n=268) were initially included, although later sensitivity analysis excluding this group was carried out. The date of participation in the second CCHS examination or, in those newly recruited from the third CCHS examination, the date of participation in the third CCHS examination, was considered the start of follow-up. Subjects were followed-up either to the time of death, or to Dec 28th 2000, with a mean of 12 years follow-up (range 0.5-20 years), providing a total of 28,747 person years.

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Measurements

Identical methods were applied in the second and third CCHS examination and have been previously described in detail[17][18]. For the present analysis only the measurements of physical activity and other independent variables obtained at the start of follow-up were used. A self-administered questionnaire on regular physical activity over the previous 12 months, current smoking and alcohol consumption, socio-economic factors (sex, age, education, marital status, cohabitation, income), current symptoms (dyspnea[19], sputum, chest pain, leg pain and intermittent claudication), a diagnosis of comorbidity at any time (asthma, ischaemic heart disease, myocardial infarction, stroke, diabetes), and health service use over the previous 12 months was completed and checked by the CCHS staff. Blood pressure, plasma cholesterol, glucose concentrations and body mass index were also measured. Clinical records were reviewed to obtain information about comorbidity.

Physical activity was measured using a questionnaire originally developed by Saltin and Grimby[20], which discriminates between sedentary persons and their more active counterparts with respect to maximal oxygen uptake[21], and has been widely used to describe the effects of physical activity on health outcomes in similar types of populations[22][23]. Physical activity variables included physical activity at work, physical activity during leisure time, jogging, cycling in winter, and cycling in summer. The level of physical activity was classified as previously reported[24]: 1) low: engaging in light physical activity such as walking or biking for less than 2 hours per week; 2) moderate: engaging in light physical activity for 2–4 hours per week; and 3) high: engaging in light physical activity for more than 4 hours per week, or in more vigorous activity for any frequency. Given that in a previous paper[6] we reported differences in the risk of hospital admission for COPD between subjects who reported low levels of physical activity and those who reported very low physical activity, in the present analysis the “low” category was split into: very low physical activity, corresponding to those who reported mainly sitting during work, no activity during leisure time, and no jogging or cycling; and low levels of physical activity, for the remaining subjects.

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Lung function parameters (FEV_1 and FVC) were measured at the second CCHS examination with an electronic spirometer (model N 403;Monaghan, Littleton, CO), which was calibrated daily with a 1-l syringe and weekly against a water-sealed Godard spirometer. At the third examination a dry wedge spirometer (Vitalograph, Maidenhead, UK), calibrated daily with a 1-l syringe, was used. At each examination three sets of values were obtained and at least two measurements differing by less than 5% had to be produced. The highest measurements of FEV_1 and FVC were used in the analyses as absolute values and as percentage of predicted values, using internally derived reference values based on a sub-sample of healthy never smokers[25]. Information about hospital admissions (dates and diagnoses on discharge) both prior to start and during follow-up was obtained from the National Patient Register, which covers all Danish hospitals and is administered by the National Board of Health. COPD admission was defined as any admission classified as ICD-8 codes 490-492 or ICD-10 codes J40-J44 for the main diagnosis. Data on deaths, and the causes thereof, were obtained from the Danish National Board of Health. Cause of death was defined according to the following ICD codes for the immediate cause of death: COPD deaths 490-492 (ICD-8) or J40-J44 (ICD-10); respiratory deaths 460-519 (ICD-8) or J00-J99 (ICD-10), and cardiovascular deaths 390-458 (ICD-8) or I00-I99 (ICD-10).

Statistical analysis

Kaplan Meier curves and log-rank tests of both COPD admission and mortality were performed after stratifying by levels of regular physical activity. In multivariate analysis, physical activity categories were a priori combined into “very low” and “low, moderate or high” level, according to results of a previous study[6].

For the study of the association between physical activity and COPD admission, the use of Poisson regression[26] was ruled out due to the presence of overdispersion in our data and a high proportion of subjects not experiencing hospital admission. Instead, zero-inflated negative binomial regression with the number of COPD admissions as the outcome was used since it takes into account individuals more prone to repeated admission, and provides more conservative confidence intervals and P values than does Poisson regression[27]. In addition, Cox proportional hazards regression, modelling time from recruitment to first event, was used

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with COPD admission and mortality (all-cause, respiratory and cardiovascular) as the outcomes, checking the proportionality of multivariate models.

Among the variables detailed in the Measurements section, those considered as potential confounders of the association between physical activity and COPD admission or mortality were tested, and were maintained in the final multivariate models if they were independently associated both with the outcome and exposure (p value<0.05), or if they modified the risk ratio estimate for any of the remaining covariates (≥5% change[28]). Final models were built keeping the most parsimonious model that still explains the data.

The final multivariate models for both COPD admission and mortality were stratified according to gender, age, COPD severity, and history of ischaemic heart disease. If differences in the risk estimate were found, interaction terms among variables where effect modification was plausible were tested for. For the sensitivity analyses, the final models for admission and mortality were run excluding subjects with self-reported asthma, excluding subjects who had never smoked, or excluding subjects lower than 40 years of age. The analysis was performed using Stata, release 8.0 (StataCorp, 2003, College Station, TX, USA).

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RESULTS

Description of the sample and events (COPD admission, death) during follow-up

A total of 2,386 subjects with COPD were included. At baseline, half were men, the mean age was 60 years, the mean BMI was 24.9 kg/m^2, 12% reported having at some time suffered asthma, and 71% were current smokers (Table 1).

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Table 1. Description of 2,386 COPD subjects recruited from the general population in Copenhagen, Denmark, by gender.

		All subjects* n=2386	Women n=1100	Men n=1286
Gender	n (%)		1100 (46.1)	1286 (53.9)
Age (years)	m (SD)	59.5 (10.9)	59.3 (10.8)	59.7 (11.0)
Education (years at school)	m (SD)	8.3 (1.9)	8.3 (1.8)	8.4 (2.0)
Low income†	n (%)	946 (40.9)	498 (47.8)	448 (35.2)
BMI (kg/m^2)	m (SD)	24.9 (4.2)	24.2 (4.5)	25.6 (3.8)
Ischaemic heart disease†	n (%)	634 (26.6)	249 (22.6)	385 (29.9)
Asthma†	n (%)	268 (11.8)	131 (12.5)	137 (11.3)
Dyspnea†				
0 – no dyspnea	n (%)	978 (41.1)	421 (38.5)	557 (43.4)
1 – dyspnea in effort	n (%)	841 (35.4)	410 (37.5)	431 (33.6)
2 – dyspnea walking	n (%)	240 (10.1)	119 (10.9)	121 (9.4)
3 – dyspnea at rest	n (%)	318 (13.4)	144 (13.1)	174 (13.6)
Sputum†	n (%)	939 (39.4)	381 (34.7)	558 (43.5)
Smoking				
Never	n (%)	230 (9.7)	174 (15.9)	56 (4.3)
Ex	n (%)	459 (19.3)	184 (16.8)	275 (21.4)
Current	n (%)	1692 (71.0)	737 (67.3)	955 (74.3)
COPD severity (GOLD Stages†)				
I – Mild (FEV_1≥80%)	n (%)	833 (35.1)	363 (33.1)	470 (36.7)
II – Moderate (FEV_1<80% & ≥50%)	n (%)	1095 (46.1)	521 (47.6)	574 (44.8)
III – Severe (FEV_1 <50% & ≥30%)	n (%)	354 (14.9)	166 (15.2)	188 (14.7)
IV – Very severe (FEV_1<30%)	n (%)	94 (3.9)	45 (4.1)	49 (3.8)
Any medical visit to any doctor in previous year†	n (%)	1871 (78.8)	911 (83.2)	960 (74.9)

* The numbers do not always add up to 2,386 as some values are missing for certain variables: 11 in education, 5 in cohabitation, 72 in income, 12 in BMI, 117 in asthma, 9 in dyspnea, 5 in sputum, 5 in smoking, 10 in lung function, and 10 in visits to doctors.

† Low household income was defined as income lower than 4,000 Danish kroner per month. Ischaemic heart disease and asthma were self-reported and obtained from medical records. Dyspnea was self-reported and categorised according to the Modified British Medical Research Council questionnaire (reference 19). Sputum was considered present if subjects answered positively to the question “Do you usually bring up phlegm from your chest in the morning or during the day?”. COPD severity was classified according to GOLD stages (reference 3). Any medical visit to any doctor in previous year includes visits to the general practitioner, specialist, emergency room or private doctor.

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Classification of severity according to GOLD stages showed a high prevalence of mild (35%) and moderate (46%) COPD. Regarding the level of regular physical activity (Table 2), 9%, 12%, 46% and 33% of subjects reported very low, low, moderate and high physical activity levels, respectively. Subjects with more severe COPD presented lower levels of physical activity.

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Table 2. Regular physical activity in 2,386* COPD subjects recruited from the general population in Copenhagen, Denmark, by COPD severity (GOLD stages).

	All subjects n=2386	GOLD I Mild n=833	GOLD II Moderate n=1095	GOLD III Severe n=354	GOLD IV Very severe n=94	p (Chi^2)
Physical activity at work						
Mainly sitting	824 (40.0)	280 (38.7)	365 (37.9)	129 (43.7)	44 (61.1)	0.003
Sitting & standing	763 (37.0)	254 (35.1)	376 (39.0)	111 (37.6)	20 (27.8)	
Walking & lifting	392 (19.0)	156 (21.6)	182 (18.9)	48 (16.3)	6 (8.3)	
Heavy activity	83 (4.0)	33 (4.6)	41 (4.2)	7 (2.4)	2 (2.8)	
Physical activity during leisure time						
Light activity <2h/wk and no heavy activity	540 (22.7)	123 (14.8)	246 (22.6)	124 (35.2)	42 (45.2)	<0.001
Light activity 2-4h/wk and no heavy activity	1073 (45.2)	385 (46.4)	506 (46.4)	143 (40.6)	37 (39.8)	
Light activity >4h/wk and/or heavy activity <2h/wk	713 (30.0)	296 (35.7)	318 (29.2)	82 (23.3)	14 (15.0)	
Heavy activity >4h/wk	49 (2.1)	26 (3.1)	20 (1.8)	3 (0.9)	0 (0)	
Jogging	39 (1.6)	20 (2.4)	17 (1.6)	2 (0.6)	0 (0)	0.068
Cycling winter (hours/week)						
No	1839 (77.5)	582 (70.4)	865 (79.4)	299 (84.9)	83 (89.2)	<0.001
<1/2 h/wk	224 (9.5)	108 (13.1)	85 (7.8)	25 (7.1)	6 (6.5)	
½ – 1 h/wk	180 (7.6)	79 (9.5)	79 (7.3)	19 (5.4)	3 (3.2)	
1-2 h/wk	97 (4.1)	41 (4.9)	49 (4.5)	6 (1.7)	1 (1.1)	
>2 h/wk	31 (1.3)	17 (2.1)	11 (1.0)	3 (0.9)	0 (0)	
Cycling summer (hours/week)						
No	1481 (62.5)	429 (51.9)	705 (64.7)	260 (74.0)	78 (84.8)	<0.001
<1/2 h/wk	273 (11.5)	124 (15.0)	114 (10.4)	29 (8.2)	6 (6.5)	
½ – 1 h/wk	291 (12.3)	136 (16.4)	122 (11.2)	29 (8.2)	3 (3.2)	
1-2 h/wk	195 (8.2)	86 (10.4)	90 (8.3)	17 (4.8)	2 (2.2)	
>2 h/wk	131 (5.5)	52 (6.3)	59 (5.4)	17 (4.8)	3 (3.3)	
Physical Activity Summary score						
Very low	219 (9.2)	45 (5.4)	97 (8.9)	54 (15.3)	20 (21.5)	<0.001
Low	294 (12.4)	69 (8.3)	138 (12.7)	65 (18.5)	20 (21.5)	
Moderate	1089 (45.8)	389 (46.9)	511 (46.9)	148 (42)	39 (41.9)	
High	773 (32.6)	327 (39.4)	344 (31.5)	85 (24.2)	14 (15.1)	

* The numbers do not always add up to 2,386 as some values are missing for certain variables: 324 in physical activity at work, 11 in physical activity during leisure time, 8 in jogging, 15 in cycling in winter, 15 in cycling in summer, and 10 in lung function (GOLD stage).

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During follow-up (mean 12.0 years, SD 5.9 years), 22% of participants had at least one hospital admission due to COPD (median of 3, interquartile range: 1 to 5 for those with an admission). As expected, the subjects admitted to hospital were older, had a higher proportion of cardiovascular disease and asthma, presented lower levels of physical activity, and suffered more severe COPD. The time to first COPD admission during follow-up was shorter for the subjects presenting lower levels of physical activity (Figure 1a).

During follow-up 1,425 (60%) subjects died. Death from respiratory and cardiovascular diseases constituted 18% and 32% of all deaths respectively, with 14% of deaths due to COPD. The subjects who died were older, had a higher proportion of cardiovascular disease and diabetes, presented lower levels of physical activity and also suffered more severe COPD. The time to death was shorter in subjects with lower levels of physical activity (Figure 1b).

Association between physical activity and both COPD hospital admission and mortality

In the multivariate negative binomial model with the number of COPD admissions as the outcome, subjects who reported low, moderate or high level of physical activity, compared with those who reported a very low level of physical activity, showed a reduced risk of a COPD admission, after adjusting for confounders (Incidence Rate Ratio (IRR) 0.72, 95% CI 0.53-0.97, p=0.033)(Table 3). Using time to first COPD admission as the outcome in a multivariate Cox regression model yielded very similar results (Hazard Ratio (HR) 0.76, 0.58-0.99, p=0.039).

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Table 3. Crude and adjusted associations between physical activity and number of COPD admissions in COPD subjects (zero-inflated negative binomial regression).

	N*	Crude IRR (95%CI)	p	Adjusted† IRR (95%CI)	p
Physical Activity – combined					
Very low	219	1		1	
Low & Moderate & High	2155	0.63 (0.46-0.86)	0.004	0.72 (0.53-0.97)	0.033
Physical activity – categories					
Very low	219	1		1	
Low	294	0.73 (0.49-1.08)	0.113	0.77 (0.53-1.14)	0.192
Moderate	1089	0.63 (0.45-0.88)	0.006	0.68 (0.49-0.93)	0.018
High	772	0.57 (0.40-0.82)	0.002	0.76 (0.53-1.08)	0.121
p for linear trend			*0.002*		*0.104*

* The number of subjects may be lower in the multivariate models as some values are missing for certain variables (see Tables 1 and 2). One subject was excluded from the zero-inflated negative binomial regression model for recording 65 COPD admissions during follow-up (outlier value).

† Multivariate model adjusted for sputum and FEV_1 in the count component, and for age, ischaemic heart disease, smoking habit, sputum, visits to doctor, and FEV_1 in the zero-inflated component of the zero-inflated negative binomial regression.

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Regarding mortality, after adjusting for all relevant confounders and taking the group with very low physical activity as the reference, subjects who reported low, moderate or high physical activity showed a lower risk of death by all-cause (HR 0.76, 0.65-0.90, p=0.001), respiratory causes (HR 0.70, 0.48-1.02, p=0.060), and cardiovascular causes (HR 0.77, 0.58-1.02, p=0.065) (Table 4).

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Table 4. Crude and adjusted associations between physical activity and mortality in COPD subjects (Cox regression).

	ALL-CAUSE MORTALITY (n=2386, 1425 deaths)*				RESPIRATORY MORTALITY (n=2386, 254 deaths)*				CARDIOVASCULAR MORTALITY (n=2386, 461 deaths)*			
	Crude		Adjusted†		Crude		Adjusted‡		Crude		Adjusted§	
	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p
Physical Activity – combined												
Very low	1		1		1		1		1		1	
Low & Moderate & High	0.53 (0.45-0.62)	<0.001	0.76 (0.65-0.90)	0.001	0.40 (0.29-0.57)	<0.001	0.70 (0.48-1.02)	0.060	0.47 (0.36-0.62)	<0,001	0.77 (0.58-1.02)	0.065
Physical Activity – categories												
Very low	1		1		1		1		1		1	
Low	0.77 (0.63-0.94)	0.009	1.04 (0.84-1.27)	0.744	0.68 (0.44-1.06)	0.089	0.89 (0.55-1.44)	0.622	0.55 (0.38-0.79)	0,001	0.84 (0.58-1.23)	0.372
Moderate	0.52 (0.44-0.61)	<0.001	0.73 (0.61-0.86)	<0.001	0.41 (0.28-0.59)	<0.001	0.64 (0.43-0.95)	0.028	0.47 (0.36-0.63)	<0,0001	0.73 (0.54-0.98)	0.035
High	0.48 (0.40-0.57)	<0.001	0.72 (0.59-0.86)	<0.001	0.31 (0.21-0.46)	<0.001	0.72 (0.46-1.12)	0.142	0.45 (0.34 -0.61)	<0,0001	0.81 (0.59-1.11)	0.194
p for linear trend		*<0.001*		*<0.001*		*<0.001*		*0.072*		*<0.001*		*0.195*

* The number of subjects may be lower in the multivariate models as some values are missing for certain variables (see Tables 1 and 2).

† Each row is a multivariate model adjusted for: sex, age, income, BMI, smoking, glucose, systolic blood pressure and FEV_1

‡ Each row is a multivariate model adjusted for: sex, age, BMI, myocardial infarction, asthma, sputum, smoking, asthma*smoking interaction and FEV_1.

§ Each row is a multivariate model adjusted for: sex, age, income, ischaemic heart disease, myocardial infarction, stroke, smoking, glucose, systolic blood pressure and FEV_1

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After stratification for gender, age, COPD stage, and history of ischaemic heart disease, subjects who reported low, moderate or high level of physical activity, compared with very low level of physical activity, showed a reduced risk of both hospital admission for COPD and death due to any cause in all subgroups of subjects, although statistical significance was lost in many models, most likely due to a reduction in statistical power (data not shown, available from the authors).

Sensitivity analyses yielded very similar results. After excluding the subjects who reported having suffered asthma at some time, the adjusted IRR of a COPD admission for those with low, moderate or high physical activity compared to those reporting very low physical activity was 0.72 (0.50-1.04, p=0.082); correspondingly, the adjusted HR of all-cause mortality was 0.76 (0.63-0.91, p=0.003). After exclusion of never smokers, the adjusted IRR of a COPD admission was 0.70 (0.52-0.96, p=0.026), and the adjusted HR of all-cause mortality was 0.76 (0.64-0.90, p=0.001). After exclusion of subjects lower than 40 years of age, the adjusted IRR of a COPD admission was 0.72 (0.53-0.98, p=0.037), and the adjusted HR of all-cause mortality was 0.77 (0.65-0.91, p=0.002).

Given the results of the bivariate analysis (Figures 1a and 1b), all analyses were run taking together those reporting a very low or low level of physical activity (n=513) as the reference category, providing an adjusted IRR of a COPD admission of 0.80 (0.64-1.01, p=0.065), and the following adjusted HR of mortality: all-cause 0.71 (0.63-0.80, p<0.001), respiratory causes 0.71 (0.53-0.95, p=0.021), and cardiovascular causes 0.82 (0.66-1.03, p=0.084).

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DISCUSSION

The present 20-year follow-up study of 2,386 subjects with COPD shows that, for these subjects, a level of physical activity equivalent to walking or cycling 2 hours per week or more was associated with a 30 to 40% reduction in the risk of both hospital admission due to COPD and respiratory mortality. This is the first population-based cohort study showing that a relatively small amount of physical activity may have important beneficial effects in the course of COPD. To date, only the British guidelines for COPD[8] advise that COPD patients be encouraged to exercise (page S-12), a recommendation that so far was not evidence-based. The present results provide both robust evidence in favour of this recommendation, and support for its consideration in future COPD guidelines.

The present results are highly consistent with our previous observation of a reduction in COPD hospital admissions among the COPD patients recruited from tertiary hospitals in Barcelona who reported a level of physical activity equivalent to walking one hour daily[6]. The important environmental and climatic differences between Copenhagen and Barcelona are likely to result in different patterns of physical activity, reinforcing the external validity of the reported associations.

Some respiratory rehabilitation trials have shown a reduced risk of COPD admission[29][30][31]. Since the majority of respiratory rehabilitation programs include a component of exercise training, it could be considered that the effects reported in our study and those reported in respiratory rehabilitation studies are consistent. However, respiratory rehabilitation also incorporates other pharmacological and non-pharmacological interventions and the effect of exercise training can not be isolated[32]. Whereas respiratory rehabilitation should be considered in specific COPD patients, our results suggest the convenience of incorporating the advice of increasing or mantaining a moderate level of physical activity at any medical encounter with all-stage COPD patients. Further interventional studies should test the efficacy and effectiveness of physical activity advice in COPD subjects.

The mechanisms underlying the potential beneficial effects of regular physical activity in COPD are not known, although some evidence regarding muscle function, exercise capacity, and inflammation, may give support to its biological plausibility. Regarding muscles, physical

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activity improves peripheral muscle function [33], which have been related to reduced health service utilization in cases of COPD[34]. At the cell level, exercise training improves the bioenergetics of skeletal muscle in COPD patients[35], which, through a reduction in lactate production during exercise, could reduce symptoms[36]. Exercise capacity has, on the other hand, been associated with a lower risk of hospital admission for COPD exacerbation[37] and a lower risk of mortality[38][39] in COPD cohorts. To what extent exercise capacity in COPD patients is influenced by regular physical activity and vice versa is not known, although a cross-sectional association between the two has been reported[40]. Finally, important anti-inflammatory and anti-oxidant effects have been reported both in healthy subjects exposed to moderate levels of exercise[41][42] and in COPD patients participating in rehabilitation programs[43][44].

As with any observational study, ours may be affected by several limitations. Since losses to follow-up are the main cause of selection bias in longitudinal studies[45], and only 4 subjects (0,2%) were lost to follow-up in our study, it is unlikely that selection will have biased the estimates of the effects of physical activity in the course of COPD. It is most likely that we will have measured regular physical activity with a degree of non-differential misclassification, both because of the inherent limited validity of the questionnaire and the omission of changes in physical activity during follow-up. In either case, the resulting effect was most probably a reduced estimate of the effects of physical activity[22] [45]. Given that the present study was not specifically designed to examine the effects of physical activity, direct measures were not available but should be considered in future studies. Our study was designed to test the hypothesis that physical activity may reduce the risk of COPD admission or respiratory related death in COPD patients and consequently our study population included only patients with COPD. The inclusion of a reference group without COPD would have not been appropriate since the control subjects exposed to physical activity would not have had the opportunity of experiencing the expected effects.

We considered the possibility of dyspnea acting as a confounder since it was not included in the final models, even though its presence was associated with both physical activity and the outcomes. The inclusion of dyspnea in the regression models did not change the magnitude of the associations between physical activity and COPD admission or mortality (IRR of COPD admission 0.82, 0.60-1.11; HR of mortality 0.80, 0.68-0.95), with the magnitude of the

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potential confounding effect being virtually null[45]. In addition, since dyspnea could also be an intermediate variable between reduced levels of physical activity and an increased risk of admission or mortality, and as dyspnea was correlated with physical activity, its inclusion in our multivariate models was avoided. We are currently exploring the applicability of marginal structural models to disentangle the individual effects of physical activity and dyspnea[46].

It should also be considered whether the group of subjects who reported very low physical activity represent a specific group with an unhealthy lifestyle, which could partially account for an increased risk of COPD admission and mortality. However, multivariate models already included smoking and income as covariates, and the inclusion of alcohol consumption or other sociodemographic factors (education, marital status or cohabitation), did not change the estimates for physical activity (results available from the authors). Other markers of lifestyle such as diet were not available but should be explored in further studies.

The lack of a linear dose-response relationship between levels of physical activity and hospitalisation or mortality may cast some doubts upon the observed estimates. The lack of a clear dose-response relationship between physical activity and health related outcomes has been reported for hypertension, obesity, cancer, osteoporosis, quality of life, depression and anxiety, amongst other disorders[47]. Whether the lack of a clear dose-response association is due to a real lack of dose-response relationship, a lack of sensitivity in determining the dose of physical activity or uncontrolled confounders is generally not known[47]. However, because the kind of dose-response relationship is important for public health, it is recommended to address this issue in further research by using more accurate measures of physical activity including frequency, duration and intensity[47].

In summary, our results provide robust evidence that the performance of regular physical activity by COPD patients is associated with an important reduction in the risk of both COPD admission and all-cause and respiratory mortality. The magnitude of this effect, and the fact that the type of physical activity required to achieve it can be easily recommended without the need for additional training or specialized supervision, make these findings particularly promising. Our results provide evidence for the consideration, in future COPD guidelines, of the recommendation that COPD patients be encouraged to maintain or increase their levels of regular physical activity. Given that COPD is a chronic disease associated with high a socio-

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economic burden and health consequences, such a measure is likely to result in a relevant public health benefit.

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AUTHORS' CONTRIBUTIONS

Judith Garcia-Aymerich, Peter Lange, Peter Schnohr and Josep M Antó participated in the design of the study. Peter Lange and Peter Schnohr coordinated data collection in Copenhagen. Judith Garcia-Aymerich, Peter Lange, Marta Benet, and Josep M Antó performed the statistical analysis and interpreted the results. Judith Garcia-Aymerich prepared the first draft of the paper. All authors contributed to the writing of paper.

DATA ACCESS AND RESPONSIBILITY

Judith Garcia-Aymerich had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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COMPETING INTERESTS

All authors declare that the answer to the questions on your competing interest form bmj.com/cgi/content/full/317/7154/291/DC1 are all No and therefore have nothing to declare.

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Figure 1a. Kaplan-Meier curve of time to first COPD admission during follow-up, according to level of regular physical activity.

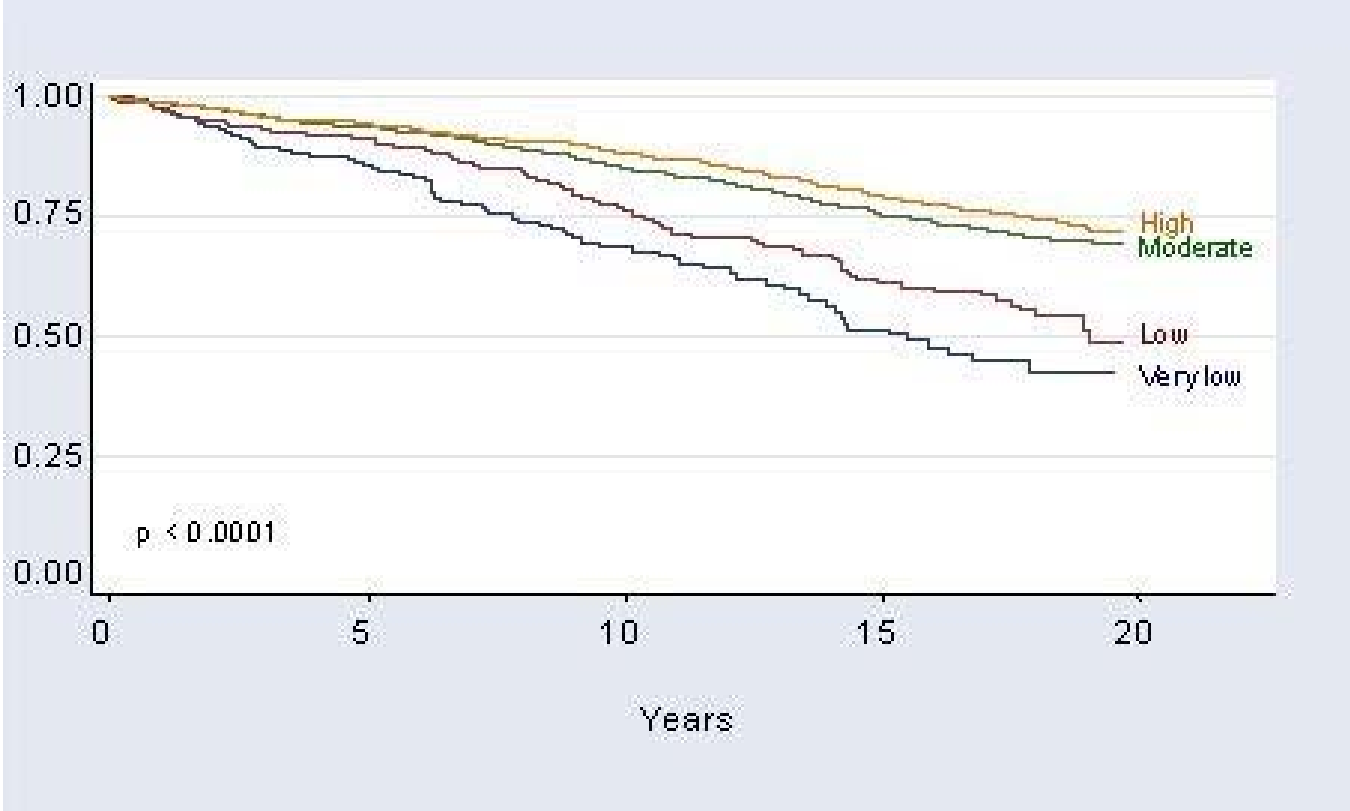

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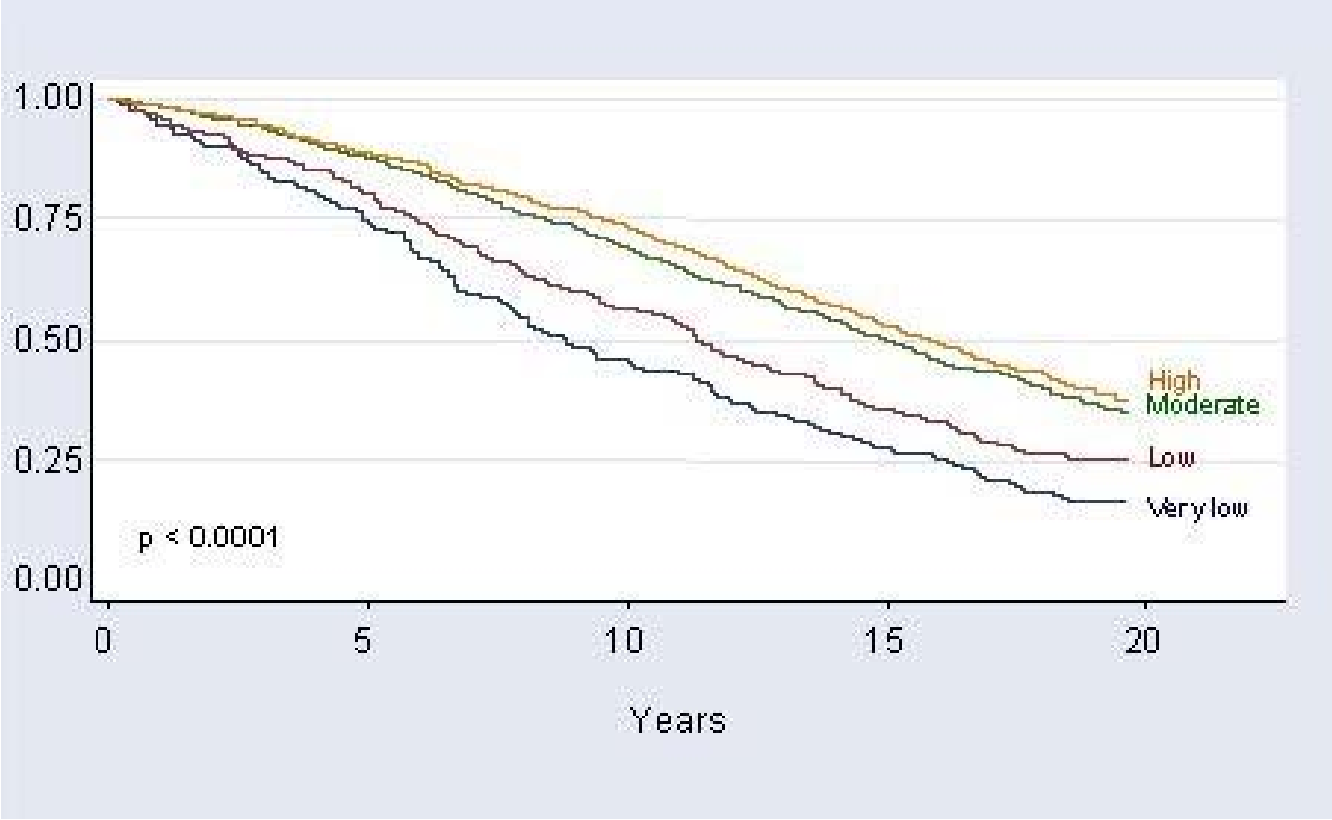
Figure 1b. Kaplan-Meier curve of time to death (all-cause mortality), according to level of regular physical activity.



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