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Prognostic value of weight change in chronic obstructive pulmonary disease: results from the Copenhagen City Heart Study

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ABSTRACT: An association between low body mass index (BMI) and poor prognosis in patients with chronic obstructive pulmonary disease (COPD) has been found in a number of studies. The prevalence and prognostic importance of weight change in unselected subjects with COPD was examined.

Subjects with COPD, defined as forced expiratory volume in one second/forced vital capacity <0.7 in the Copenhagen City Heart Study and who attended two examinations 5 yrs apart, were followed for 14 yrs for COPD-related and all-cause mortality.

The proportion of subjects who lost >1 unit BMI (~3.8 kg) between the two examinations was significantly associated with level of COPD, reaching ~30% in subjects with severe COPD. After adjusting for age, smoking habits, baseline BMI and lung function, weight loss was associated with higher mortality in both persons with and without COPD (rate ratio (RR) for weight loss >3 BMI units 1.71 (95% confidence interval (CI): 1.32–2.23) and 1.63 (95% CI 1.38–1.92), respectively). Weight gain was associated with increased mortality, but not significantly so in subjects with COPD. Risk of COPD-related death increased with weight loss (RR 2.14 (95% CI 1.18–3.89)), but not with weight gain (RR 0.95 (95% CI 0.43–2.08)). In subjects without COPD or with mild-to-moderate COPD, the effect of weight change was the same irrespective of initial weight. In subjects with severe COPD, there was a significant risk ratio modification (p=0.045) between effect of baseline BMI and weight change: in the normal-to-underweight (BMI<25), best survival was seen in those who gained weight, whereas for the overweight and obese (BMI ⩾25), best survival was seen in stable weight.

A high proportion of subjects with chronic obstructive pulmonary disease experienced a significant weight loss, which was associated with increased mortality. The results support further intervention studies that aim at avoiding weight loss in normal-to-underweight chronic obstructive pulmonary disease patients.

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In patients with chronic obstructive pulmonary disease (COPD), a number of observational studies have shown that a low body mass index (BMI) is associated with a poor prognosis independent of the degree of ventilatory impairment [1–3]. Consequently, nutritional support has been advocated as a useful part of the care of COPD patients with low BMI. A number of nutritional intervention studies with pulmonary function, exercise capacity or weight increase as outcome have been performed [4–7]. However, a recent meta-analysis reviewed the effect of these studies and concluded that the studies did not document a beneficial effect of nutritional support in patients with COPD [8]. So far, no controlled intervention study with mortality as outcome has tested the effect of nutritional support in these patients.

A different way of addressing this question is in an epidemiological setting to study mortality rates of subjects with COPD and relate these to changes in body weight. In a previous study, the present authors have shown that low BMI was an independent risk factor for both all-cause and COPD-related mortality in subjects with COPD [3]. In mild-to-moderate COPD, the best prognosis was found in normal weight or overweight subjects, whereas in severe COPD, being overweight and even obese was associated with a better survival.

The aim of the present study was to prospectively study whether changes in BMI in subjects with COPD independently predict mortality. The analysis is based on a large sample of the general Danish population, where BMI was determined on two occasions with an interval of 5 yrs and subjects were thereafter followed for mortality for up to 18–20 yrs.

Methods

Population and design

The study is based on data from the Copenhagen City Heart Study, which has previously been

described in detail [9]. The population was derived from a random, age-stratified sample of 19,329 individuals aged $\geq$20 yrs recruited in 1976 among 90,000 people living in a defined area in Copenhagen. A total of 14,223 subjects (response rate 74%) attended the first examination in 1976/78. After 5 yrs (1981/83), 11,135 subjects were re-examined, representing a response rate of 83% among subjects still alive. Exclusion of subjects with self-reported asthma at either examination (n=329) or missing data on crucial variables (forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) or BMI; n=382) left a total of 10,424 subjects available for the analyses. Among these, 1,612 subjects with COPD were identified based on a ratio of FEV_1 to FVC of <0.7 at the second examination, 736 females and 876 males.

Variables of interest

The variables of main interest were BMI measured at two examinations and ventilatory function at the second examination. BMI was calculated as weight·height^{-2} (kg·m^{-2}) and categorised into four groups: underweight (<20 kg·m^{-2}), normal weight (20–24.9 kg·m^{-2}), overweight (25–29.9 kg·m^{-2}) and obese ($\geq$30 kg·m^{-2}). Changes in BMI between the first and second examinations were categorised into five groups: BMI decrease of >3 units, 1–3 units, between 1 unit decrease and 1 unit increase (defined as stable weight and used as reference), increase of 1–3 units, and increase of >3 units. One unit BMI depends on height in metres squared, *i.e.*, for a subject 170 cm high, 1 unit change in BMI is equal to 3.89 kg. For tests of effect modification baseline BMI was dichotomised with cut-off point of 25 kg·m^{-2} and changes in BMI collapsed into 3 groups with cut-off points of ±1 BMI, respectively. This was done to retain sufficient statistical power.

FEV_1 and FVC were obtained using a spirometer, which was calibrated daily. As a criterion for correct performance, at least two measurements differing by <5% had to be produced. The largest volume was used in the analyses. Predicted values of FEV_1 were based on internally derived values, generated from a subgroup of lifetime nonsmokers without diabetes mellitus, bronchial asthma, heart disease, or pulmonary symptoms and with a daily consumption of alcohol of less than five drinks. Linear regression of age and height on FEV_1 was performed separately for each sex. For each participant, the observed FEV_1 as a percentage of the predicted was calculated (FEV_1 % pred). Subjects were classified into three categories according to severity of ventilatory impairment: severe COPD (FEV_1 % pred <50), moderate COPD (FEV_1 % pred 50–69), and mild COPD (FEV_1 % pred $\geq$70). Cut-off limits were chosen according to the European Respiratory Society guidelines on COPD [10].

In addition to BMI and ventilatory function, age, sex, and tobacco consumption were included as potential risk factors. Based on data from the first survey, subjects were classified as never-smokers, exsmokers or current smokers. Furthermore, duration of smoking (yrs) and the current amount of tobacco consumed (g·day^{-1}) was reported; one cigarette equals 1, one cheroot 3, and one cigar 5 g of tobacco. Three categories of current smokers were defined; light smokers (1–14 g·day^{-1}), medium smokers (15–24 g·day^{-1}), and heavy smokers (>24 g·day^{-1}). Smokers also reported whether they inhaled.

Follow-up

Notification of deaths and cause of death were obtained from the National Board of Health. COPD deaths were defined as deaths where the immediate or contributory cause of death was registered as codes 490–493 according to the International Classification of Diseases, 8th revision (ICD-8) until January 1, 1994 and as codes J429–J449 according to the 10th revision (ICD-10) for the remaining period; ICD-9 was never used in Denmark. All subjects were followed until September 2000 for all-cause mortality and until January 1, 1998 for COPD-related mortality.

Statistical analyses

To assess the independent contribution of changes in BMI to mortality in COPD, the Cox proportional hazards model was used [11]. Age was thought to be most closely associated with the outcome and was chosen as the underlying time scale with subjects entering the analyses with their age at the second examination. This ensured optimal adjustment for age. Time since weight change could also be associated with survival and analyses were repeated using time since second examination as timescale and adjusting for age categorically in 10-yr age bands. Analyses were adjusted for FEV_1 % pred, current smoking status, inhalation, and duration of smoking. FEV_1 % pred was entered as a continuous covariate after testing that a linear association between FEV_1 % pred and outcome did not violate the data. Initial analyses were performed separately by sex. The association between BMI and both all-cause and COPD-related mortality did not differ between males and females. Further analyses were performed on the pooled sample stratified by sex, thus assuming the same effect of covariates in males and females, but allowing for different baseline hazards. The present study tested whether effects were similar in males and females by including interaction terms between sex and each covariate separately. Only interaction terms that reached statistical significance using the likelihood ratio test were included in the final model.

The results of regression analyses are given in terms of estimated rate ratio (hazard ratios) with corresponding 95% confidence intervals.

Results

Baseline characteristics of subjects by presence of airways obstruction for males and females separately are shown in table 1. In both males and females,

Table 1. – Baseline data of the 10,424 subjects in the Copenhagen City Heart Study by sex and presence of airway obstruction[#]

	Females		Males	
	COPD	No COPD	COPD	No COPD
Subjects n	736	5096	876	3716
Age yrs	55.8±9.0	51.8±11.2	56.6±9.7	50.9±11.9
FEV1 % pred	67.3±21.7	90.0±18.1	66.3±20.6	89.6±17.9
Never-smokers	131 (17.8)	1539 (30.2)	34 (3.9)	490 (13.2)
Heavy smokers[¶]	274 (52.3)	1235 (44.4)	506 (72.1)	1555 (64.0)
Age at smoking debut[¶]	24.8±9.0	24.8±9.4	18.4±6.7	18.8±6.3
Deaths	422 (57.3)	1620 (31.8)	600 (68.5)	1667 (44.9)
COPD-related deaths	72 (9.8)	46 (0.9)	93 (10.6)	52 (1.4)

Data are presented as mean±SD or number (%). FEV1: forced expiratory volume in one second; COPD: chronic obstructive pulmonary disease. All values differed significantly ($p<0.001$) between groups in both sexes except age at smoking debut: females $p=0.98$, males $p=0.15$. [#]: COPD defined as FEV1/forced vital capacity (FVC) <0.7; [¶]: among current smokers.

subjects with COPD were older, more were smokers, and the proportion of heavy smokers was higher. During follow-up, 4,309 subjects died, 2,042 females and 2,267 males. A large proportion of subjects with COPD died during the 19 yrs of follow-up, 57.3% of the females and 68.5% of the males. A total of 263 subjects died from COPD-related causes, 165 of these occurred in subjects with COPD at baseline as defined.

Table 2 shows distribution of baseline weight and subsequent weight changes by severity of COPD as well as in subjects without COPD. In females baseline BMI was lower in subjects with impaired lung function, whereas no differences were found in males. In both males and females, weight changes differed with lung function with mean weight loss seen in subjects with the poorest lung function and mean weight gain seen in subjects without airways obstruction. The proportion of subjects that lost >1 unit BMI (~3.8 kg) increased with decreasing lung function reaching 35.3% and 27.4%, respectively, in females and males with severe COPD.

The results of the survival analyses regarding all-cause mortality are shown in table 3. Among subjects with COPD all-cause mortality was increased in subjects who lost ≥ 1 BMI unit. An excess mortality of 70% was seen in subjects who lost >3 units BMI (~10 kg). Mortality in subjects, who gained weight, did not differ significantly from those with a stable weight. Effect of weight change on mortality did not differ with severity of COPD (test for interaction $p=0.67$, 4 degrees of freedom (df)). Results were similar for subjects without COPD at baseline, although a significantly increased risk was seen in subjects who gained ≥ 3 BMI units. The effect of baseline BMI was U-shaped in both groups, with excess mortality associated with both under- and overweight. The rate ratio (RR) associated with weight loss was higher in non-COPD subjects <70 yrs at baseline (results not shown). No such age differences were found for subjects with COPD.

Further analyses were concerned with whether effect of weight changes on survival was dependent on initial weight (*i.e.* effect modification). In subjects with moderate or mild COPD and in subjects without COPD, no modification of the effect of baseline BMI on weight change was found. Among subjects with severe COPD (FEV1 % pred <50) effect of weight change differed with baseline weight (test for interaction: $p=0.045$, df 2) as shown in figure 1. In all groups, weight loss was associated with increased mortality.

Table 2. – Weight and weight change by baseline lung function in males and females in the Copenhagen City Heart Study

	COPD FEV1/FVC<0.7			No COPD FEV1/FVC≥0.7	p-value
	<50% pred	50–70% pred	>70% pred		
Females					
Subjects n	156	260	320	5096	
Baseline BMI kg·m^{-2}	23.8±4.3	24.1±4.2	24.3±4.2	24.7±4.2	0.009
BMI increase kg·m^{-2}[#]	-0.20±2.11	0.08±2.37	0.17±1.92	0.40±2.21	<0.001
Weight loss >-1 kg·m^{-2} %	35.3	26.9	19.7	17	<0.001
Males					
Subjects n	190	316	370	3716	
Baseline BMI kg·m^{-2}	26.0±4.2	25.6±3.5	25.5±3.2	25.8±3.21	0.43
BMI increase kg·m^{-2}[#]	-0.16±2.03	0.29±1.70	0.00±1.49	0.35±1.76	<0.001
Weight loss >-1 kg·m^{-2} %	27.4	19.9	22.4	15.7	<0.001

Data are presented as mean±SD unless otherwise stated. COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; BMI: body mass index. [#]: one unit BMI is equivalent of height in metres squared, *i.e.*, in a subject 170 cm high one unit change in BMI is equal to 3.89 kg.

Table 3. – All-cause mortality in relation to weight change in 1,612 subjects with chronic obstructive pulmonary disease (COPD) and 8,812 subjects without COPD at baseline in the Copenhagen City Heart Study. Estimated rate ratios (RR) derived from proportional hazards models of Cox are stratified by sex. In addition to covariates shown, models included an interaction term sex*tobacco consumption (2*5 categories) and inhalation

	COPD FEV1/FVC<0.7	No COPD FEV1/FVC⩾0.7
Subjects n	1612	8812
Deaths	1022	3287
Weight change in BMI units#		
>-3 kg·m^{-2}	1.71 (1.32–2.23)	1.63 (1.38–1.92)
-1–3 kg·m^{-2}	1.18 (1.00–1.39)	1.20 (1.08–1.32)
-1–+1 kg·m^{-2}	ref	ref
+1–3 kg·m^{-2}	1.07 (0.91–1.26)	0.99 (0.90–1.08)
>+3 kg·m^{-2}	1.26 (0.93–1.72)	1.39 (1.19–1.61)
Initial BMI		
<20 kg·m^{-2}	1.24 (0.98–1.57)	1.31 (1.11–1.54)
20–24.9 kg·m^{-2}	ref	ref
25–29.9 kg·m^{-2}	1.04 (0.91–1.21)	1.08 (1.00–1.17)
⩾30 kg·m^{-2}	1.23 (0.99–1.54)	1.28 (1.14–1.43)
FEV1 % pred (per 10% decrease)	1.15 (1.11–1.19)	1.09 (1.07–1.11)

Data are presented as RR (95% confidence interval). #: One unit body mass index (BMI) is equivalent of height in metres squared, *i.e.*, in a subject 170 cm high one unit change in BMI is equal to 3.89 kg. FEV1: forced expiratory volume in one second; FVC: forced vital capacity; ref: reference group.

However, normal and underweight subjects (BMI<25) with severe COPD differed from the remaining in experiencing increased survival after weight gain. The reverse was found in the overweight and obese (BMI⩾25), among whom the best survival was seen in subjects who had stable weight or who decreased their weight.

The estimated relative mortality rates from COPD among subjects with COPD at baseline are given in table 4. The highest risks were found in subjects who lost weight between examinations whereas weight increase did not seem to increase risk of COPD-related death. Unlike all-cause mortality, the risk function for baseline BMI seemed to be linear rather than u-shaped with the lowest risk seen in subjects who increased their weight. Results were similar in subjects without COPD at baseline (results not shown).

In separate analyses, the first 2 yrs of follow-up to control for weight loss related to terminal illness was excluded. This excluded 263 deaths, 74 of these among subjects with COPD. Results did not differ from those given in table 3. In the repeated analyses using time

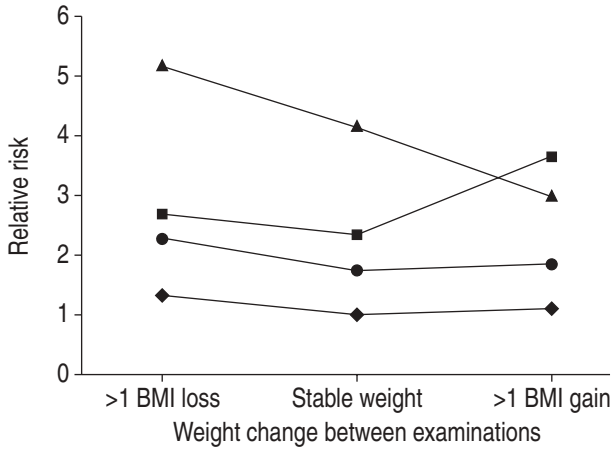

Fig. 1. – All-cause mortality by weight change in subjects with no/mild chronic obstructive pulmonary disease (COPD), moderate COPD and severe COPD. Subjects with no/mild COPD with stable weight were used for reference. ▲: severe COPD body mass index (BMI) <25; ■: severe COPD BMI >25; ●: moderate COPD; ◆: no/mild COPD.

Table 4. – Mortality from chronic obstructive pulmonary disease (COPD) in relation to weight change in 1,612 subjects with COPD at baseline in the Copenhagen City Heart Study. Estimated rate ratios (RR) derived from proportional hazards models of Cox are stratified by sex. In addition to covariates shown, models included an interaction term between sex and tobacco consumption (2*5 categories) and inhalation

	COPD FEV1/FVC<0.7
Weight change in BMI units#	
>-3 kg·m^{-2}	2.14 (1.18–3.89)
-1–3 kg·m^{-2}	1.31 (0.89–1.92)
-1–+1 kg·m^{-2}	ref
+1–3 kg·m^{-2}	0.83 (0.53–1.32)
>+3 kg·m^{-2}	0.95 (0.43–2.08)
Test for linear trend	p=0.01
Initial BMI	
<20 kg·m^{-2}	1.68 (1.06–2.66)
20–24.9 kg·m^{-2}	ref
25–29.9 kg·m^{-2}	0.66 (0.44–0.98)
>=30 kg·m^{-2}	0.72 (0.38–1.35)
Test for linear trend	p=0.002
FEV1 % pred (per 10% decrease)	1.50 (1.37–1.65)

Data are presented as RR (95% confidence interval). FEV1: forced expiratory volume in one second; FVC: forced vital capacity; ref: reference group. #: One unit body mass index (BMI) is equivalent of height in metres squared, *i.e.*, in a subject 170 centimetres high one unit change in BMI is equal to 3.89 kg.

since study entry as underlying time-scale and adjusting for age, results were also similar.

Discussion

This is the first epidemiological study to examine the relationship between changes in weight and mortality in subjects with COPD. The most important findings were the large proportion of subjects with COPD experiencing a weight loss and the increased mortality associated with this weight loss.

The present study has the advantage of being based on a large population sample followed prospectively. However, a conspicuous shortcoming was that no information on reasons for changing weight between examinations was available. Hence, it could be argued that the explanation for the increased mortality in those subjects losing weight was terminal illness, *e.g.* advanced cancer. If so, the results would be biased. In order to address this problem, the initial analysis was repeated after having excluded the first 2 yrs of follow-up, and thus the deaths among subjects who were already terminally ill at the second follow-up. This gave essentially the same result. Consequently, increased mortality associated with weight loss is not likely only to be due to terminal illness.

Another limitation to the study is that no information on body composition was obtained. This has implications for effect of baseline BMI, but even more so for changes in body composition. Losing fat tissue in an obese patient is not expected to have the same prognostic implication as losing fat free-mass, particularly muscle mass, in a lean patient with COPD. However, weight loss was associated with increased mortality in all subjects, irrespective of baseline BMI and severity of COPD, perhaps because loss of weight in an observational study such as this is most likely to be caused by loss of fat-free mass, including in the overweight and obese.

In a previous study of the same population [3], the present authors have shown that being underweight is an independent risk factor for all-cause mortality in subjects with COPD, particularly in severe COPD. In mild-to-moderate COPD the best prognosis was found in normal-weight or overweight subjects, whereas in severe COPD being overweight, and even obese, was associated with a better survival. The present results show the same relation to baseline BMI. A considerable number of subjects with COPD, particularly moderate and severe COPD spontaneously lost weight between examinations. This weight loss was associated with an increased risk of both all-cause and COPD-related mortality.

Weight loss in general was associated with increased mortality, and the results for all-cause mortality did not differ significantly between subjects with and without COPD. This indicates that the impact of weight loss in COPD may not differ from other chronic diseases, which could suggest a common pathway for weight loss and development of cachexia. This is supported by a recent study showing similar skeletal muscle dysfunction in COPD and chronic heart failure [12]. However, given the high proportion of subjects with COPD who lost weight between examinations, this will have a high impact on mortality in subjects with COPD.

Results for COPD-related mortality were also similar to the previous study [3] in that the best survival was found in subjects who were overweight or obese. Furthermore, weight increase did not increase COPD-related mortality. Due to a limited number of study subjects, the present study could not analyse COPD-related mortality according to degree of COPD.

A number of studies have found that in patients with COPD, low BMI is associated with increased mortality independent of other established risk factors. Consequently it has been argued, that patients with COPD and low BMI should receive nutritional support. However, in the randomised trials reported so far it has been difficult to demonstrate a beneficial effect of this [8]. Either systematic bias in the observation studies or improper design of the intervention studies could explain the discrepancy between the observation studies and the intervention studies.

In patients with severe COPD with normal or low weight for height, loss of weight was associated with increased mortality, whereas weight gain was associated with reduced mortality. These results are in agreement with those reported by SCHOLS *et al.* [13], who studied patients with severe COPD participating in an 8-week study of the effect of nutritional support. After following subjects for ~4 yrs, they found that patients who increased their weight by >2 kg had a significantly better survival, independently of their initial BMI. Taken together, these two studies support the view that the result of the previous observational studies is not a bias. Moreover, these results suggest that an effect of nutritional support can be expected, but most likely only in COPD patients with low or normal weight and with moderate-to-severe ventilatory impairment.

The intervention studies carried out so far have been of relatively short duration and the nutritional support given modest, typically the energy content of the support has amounted to 400–500 kcal·day^{-1}. Also, it has not been properly controlled whether the total energy content in those receiving nutritional support actually increased or if the nutritional support lead to a reduction in the ordinary food intake, resulting in similar total energy intake in those supported and those not supported.

The reasons for either spontaneously losing weight, or not gaining weight during nutritional support have to some degree been investigated during recent years. One study found that when comparing COPD patients with unintentional weight loss to patients with stable weight, the group with weight loss had increased tumour necrosis factor (TNF)-α levels. Hence, it was suggested that one possible reason for weight loss in these patients might be systemic inflammation [14]. In line with this, another study reported that resting energy expenditure is related to plasma levels of TNF-α [15]. In a recent study, 24 patients with advanced COPD (FEV_1 <40% of expected) were studied with regard to body composition, resting energy expenditure, and indicators of chronic inflammatory activity, before entering an 8-week course of nutritional

support with 500–750 kcal·day^{-1}. On the basis of achieved weight gain, they were separated into three groups. It was found that those who did not gain weight were characterised by higher age, higher levels of indicators of systemic inflammation, and a lower ratio between spontaneous energy intake and energy expenditure [16]. As there were no differences in the energy expenditure between the three groups, the authors suggested that a reason for not gaining weight is relative anorexia, which results in a reduced spontaneous food intake during nutritional support. Thus, it is likely that nutritional support is beneficial in some groups of COPD patients, and that in order to achieve such an effect it is necessary to overcome the relative anorexia of these patients so that a substantial increase in energy intake can been maintained for a long period.

In conclusion, the present study has shown that weight loss is common in chronic obstructive pulmonary disease and is an independent risk factor for all-cause mortality. In addition, weight gain seems to have a protective effect in under and normal-weight subjects with severe chronic obstructive pulmonary disease. These results should be tested in an intervention study.

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