ERJ Express. Published on March 12, 2009 as doi: 10.1183/09031936.00162608

Sex-specific Effect of Body Weight Gain on Systemic Inflammation in Subjects with COPD

Results from the SAPALDIA cohort study 2

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Short title: COPD, weight gain and systemic inflammation

Word Count : Abstract: 200 Text: 3126

Online Supplementary Table: 5 tables

Keywords: Chronic obstructive pulmonary disease, FEV_1 decline, Gender differences, Obesity, Systemic inflammation

ABSTRACT

Systemic inflammation may mediate the association between COPD and extra-pulmonary comorbidities. We measured high-sensitivity C-reactive protein (hs-CRP) in COPD and quantified the effect modification by body weight change and gender.

Using data from the Swiss Cohort Study on Air Pollution and Lung Diseases in Adults (n=5479) with measurements of Forced Expiratory Volume in 1 second (FEV_1), body weight and hs-CRP, we examined the association of hs-CRP and categories of body weight change (lost weight, gained 0-5%, 5-9%, 9-14%, >14%) to fast FEV_1 decline.

Hs-CRP was elevated both in association with fast FEV_1 decline and body weight gain. Subjects with fast FEV_1 decline and weight gain (>14%) had higher hs-CRP (2.0 mg/L for women vs 1.6 mg/L for men). After adjustment for age, smoking, physical activity, hormonal therapy and diabetes, elevated hs-CRP (>3mg) was more likely in subjects with fast FEV_1 decline, (OR_{men} 1.38, OR_{women} 1.42) and in those with weight gain (>14%), (OR_{men} 2.04, OR_{women} 4.51).

The association of weight gain and fast FEV_1 decline predicts higher level of systemic inflammation. Because the effect of weight gain on systemic inflammation is larger in women than in men, weight gain may be a risk factor for extra-pulmonary comorbidities in women with COPD.

INTRODUCTION

Worldwide, chronic obstructive pulmonary disease (COPD) is a prevalent disease which is projected to become the fourth leading cause of death by 2020[1], even though most patients with COPD are classified into the mild or moderate categories according to recent studies[2, 3]. COPD prevalence and related mortality are increasing in women: in 2000, women dying with COPD outnumbered men dying with the condition in the United States[4]. Women may have increased susceptibility to COPD and once the disease is established, its prognosis may be worse for them, even after adjustments for smoking, forced expiratory volume in 1 second (FEV_1) and age[5, 6]. This phenomenon remains unexplained.

Inflammatory processes, related to COPD, extend beyond the lungs and explain a higher level of systemic inflammation, as measured by high-sensitivity C-Reactive Protein (hs-CRP), fibrinogen, TNF-α, leucocytes, Interleukin-6 or 8[7]. In fact, systemic inflammation may contribute to diverse extra-pulmonary co-morbidities frequently seen in COPD patients, such as skeletal muscle wasting or cardiovascular disease[8, 9], for which COPD is an independent risk factor [10]. Indeed, a leading cause of death in COPD includes cardiovascular disease, which is more frequent than respiratory failure in mild or moderate disease [11].

Hs-CRP, a marker of systemic inflammation, is increased in association with several factors such as smoking, diabetes or obesity [12, 13]. Inversely, physical activity, smoking cessation or dietary interventions may reduce hs-CRP and have been associated with slower lung function decline [14-16]. Elevated CRP (>3mg/l) is strongly associated with cardiovascular morbidity and mortality and it has been hypothesized that systemic inflammation mediates the relation between mild COPD and cardiovascular mortality [9, 17, 18]. Thus, reducing systemic inflammation and, henceforth, cardiovascular morbidity and mortality would be a major objective of COPD management. Observational studies suggested that statins may decrease serum levels of hs-CRP and have a protective effect independent of the effect on

lipid metabolism in COPD patients [19]. To date, however, no single medication has proved to be efficacious in reducing mortality in patients with COPD. This suggests that the multiple origins of systemic inflammation in COPD (eg obesity, smoking or lung inflammation) need to be better understood in order to propose efficient therapeutic interventions. Because the prevalence of obesity is growing, a cumulative effect of COPD and obesity on systemic inflammation is possible.

Whether the excess of death related to COPD in women, as described in previous studies, could be related to higher levels of systemic inflammation compared to men is unknown [4]. The aim of this study was to examine the complex relationship between weight gain and systemic inflammation in subjects with COPD, as defined by fast FEV_1 decline. Specifically, we sought to determine whether body weight gain modifies systemic inflammation in COPD and, if so, whether this effect different in men and women.

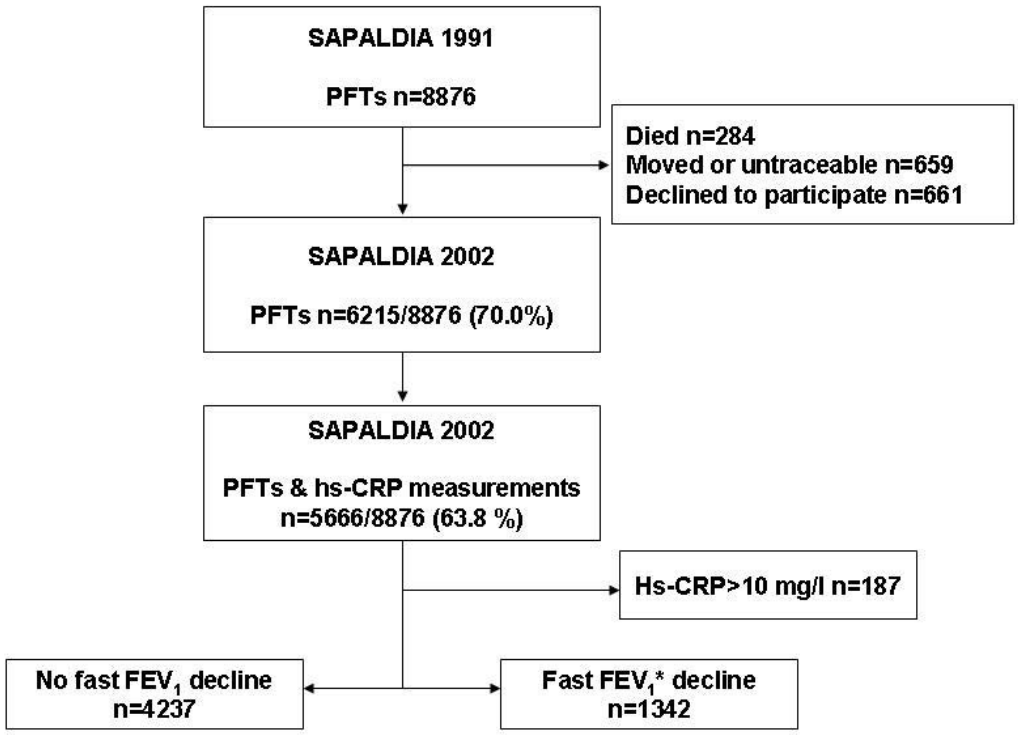
METHODS

Study Population

The SAPALDIA (Swiss Study on Air Pollution and Lung Diseases in Adults) cohort was initiated in 1991 to assess the effect of air pollution on respiratory health in Switzerland. Detailed descriptions of the cohort can be found elsewhere [20-22]. Briefly, in 1991, 9651 randomly selected adults in eight geographically and culturally diverse areas were included and followed on average over 10.9 year (Basel, Aarau, Geneva, Montana, Davos, Wald, Payerne and Lugano). Of those, 8876 had pulmonary function tests. In 2002, the follow-up study enrolled 8047 subjects from the 1991 sample (83.4%). For the present study, we included subjects who had pulmonary function tests at both surveys (SAPALDIA 1 [1991], SAPALDIA 2 [2002]) and who provided blood for high-sensitivity C reactive Protein measurements in 2002. We excluded 187 subjects in whom elevated hs-CRP (>10mg/L),

could be related to a current infection. (**figure 1**).

Figure 1: Flow chart of participants included in the present study (SAPALDIA, 1991-2002)



PFTs : Pulmonary functions tests, Hs-CRP : High-sensitivity C-reactive Protein,
FEV_1: Forced Expiratory Volume in 1 sec *upper quartile of FEV_1 decline (% baseline FEV_1)

Pulmonary function tests

Pulmonary function tests were performed according to the American Thoracic Society standards, using the same spirometers (SensorMedics 2200 SP Yorba Linda, CA) at both surveys. This was done in order to limit systematic bias error in volume measurement[23]. FEV_1 and forced vital capacity (FVC) were obtained without bronchodilators. We used the European Respiratory Society equation to calculate the predicted value of FEV_1 and FVC [24]. FEV_1 decline was calculated as the difference between the 2 measurements divided by baseline (1991) FEV_1. Each subject was classified into a quartile of FEV_1 decline and those in the highest quartile were defined as fast decliners. This definition of COPD was chosen because the rate of FEV_1 decline is a key-marker of COPD [25].

Weight change

Weight and height were recorded immediately before pulmonary function tests. Body weight change was calculated as the difference in weight between the 2 surveys divided by baseline (1991) weight. Body weight change was divided into 5 groups. "Weight loss" group included subjects who lost ≥0.1 % of their baseline weight between the two surveys. "Gained ≤5%" group encompassed subjects, whose weight change was between 0% and ≤5%. "Gained ≤9%" group had weight change between >5% and ≤9%. "Gained ≤14%" and "Gained >14%" groups corresponded to a weight gain of >9% to ≤14% and more than 14%, respectively. Categories of weight change were chosen such as to examine a wide range of individual weight changes while preserving sufficient numbers of subjects in each category.

Covariates

Smoking status (current, former or never smoker) and lifetime smoking (packs of cigarettes/day * smoking duration [years]) were recorded at both surveys.

Level of physical activity was assessed at SAPALDIA 2 with questions addressing the frequency and the intensity of physical activity. Results of these questions were combined into a single variable which defined subjects as "physically active" if they fulfilled the following criteria: a) exercise one or more hours per week and b) twice or more times per week. Categorization of physical activity into two broad groups is in accordance with published literature [26, 27]. (see online supplemental data for detailed questions and subjects classification). Highest education reached, use of hormone replacement therapy and co-morbid conditions were self-reported and extracted from the questionnaire administered by trained interviewers.

High-sensitivity C reactive protein

Serum hs-CRP was determined at SAPALDIA 2 (2002) from frozen serum by the Institute for Clinical Chemistry of the University Hospital Zürich using a new latex-enhanced immunoturbidimetric assay. (Roche Diagnostics, Mannheim, Germany)

Statistical analyses

Statistical analyses were carried out with Stata version 10 (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA). As the main variable of interest, hs-CRP, was not normally distributed, it was log-transformed and described by its geometric mean. Predictors of interest were body weight change categories in subjects with or without fast FEV_1 decline. Linear regression models were used to investigate the relation between body weight change categories and log-transformed hs-CRP in subjects with or without fast FEV_1 decline.
We tested the interactions between fast FEV_1 decline and the following variables: weight change (continuous variable or group variable), smoking status, physical activity and hormonal therapy. For the purpose of the analyses and according to the published literature, we dichotomized hs-CRP into a low and high hs-CRP level (>3mg/l). Logistic regression was applied to measure the association between fast FEV_1 decline, weight change groups and high hs-CRP (dependent variable). Hosmer and Lemeshow goodness-of-fit tests were performed. Adjustments were made for age, age squared, smoking status, lifetime smoking (pack*years), physical activity, diabetes and study area as a random effect variable. In women, hormone replacement therapy was also included in the models.

Sensitivity analysis

All analyses were repeated with the following changes:

First, subjects with hs-CRP≥10mg were included. Second, subjects with a restrictive pattern (FEV_1/FVC ratio ≥0.7 and FVC <80% predicted) were excluded. Third, the following potential confounders were included in the models: physician-diagnosed asthma, hypertension, cardiac disease or education level. Fourth, absolute body weight change and absolute FEV_1 decline were used as predictors of hs-CRP instead of relative changes. Fifth, we restricted further the definition of COPD by adding the mandatory presence of respiratory symptoms (chronic cough, phlegm or shortness of breath by walking) to the group of subjects with fast FEV_1 decline. Sixth, we also tested our models using the modified (without bronchodilation) Global Initiative on Obstructive Lung Disease (GOLD) 2-4 category to define COPD and seventh using modified GOLD 1-4 definition & fast FEV_1 decline as predictor.

RESULTS

Of the 6215 adults participants who had pulmonary function tests at both SAPALDIA 1 and 2, 5666 (91.1%) had determination of hs-CRP. Characteristics of the subjects by sex and FEV_1 decline are shown in **table 1** and in the online supplement. Fast FEV_1 decline was associated with older age, lower education, higher smoking exposure, higher FEV_1 at baseline, more symptoms and lower health-related quality of life. Men with fast FEV_1 decline reported hypertension and cardiac disease more frequently. At follow-up, weight gain was larger for fast FEV_1 decliners. The mean yearly FEV_1 losses were 3-times larger among fast FEV_1 decliners compared to non-fast decliners. Abnormal FEV_1/FVC ratio (i.e. <0.7), according to the GOLD criterion was met in 46.0% of men and 36.1% of women with fast FEV_1 decline versus 17.4% and 12.8% respectively in non fast FEV_1 decliners.

Table 1: Subjects characteristics by categories of FEV1 decline in SAPALDIA

Characteristics at SAPALDIA 2 (2002) n=5479	Men n=2616			Women n= 2863		
	Non fast FEV_1 decliners n=2016	Fast FEV_1 decliners n=600	*P*-value (t-test or χ^2)	Non fast FEV_1 decliners n=2121	Fast FEV_1 decliners n=742	*P*-value (t-test or χ^2)
Age, mean (SD)	50 (11)	56 (10)	<0.001	50 (11)	57 (10)	<0.001
Weight, kg (SD)	81.0 (12.1)	83.3 (13.1)	<0.001	65.8 (12.1)	67.8 (13.2)	<0.001
Weight change, kg (SD)	+5.5 (6.1)	+6.3 (6.59	0.003	+5.1(5.9)	+6.0 (6.4)	<0.001
Weight change (% baseline), mean (SD)	+7.3 (8.1)	+8.2 (8.2)	0.026	+8.4 (9.1)	+9.6 (9.9)	0.03
Weight change categories						
Lost , n (%)	329 (16.3)	81 (13.5)		357 (16.8)	100 (13.5)	
Gained ≤5%, n (%)	499 (24.7)	145 (24.2)		414 (19.5)	155 (20.9)	
Gained ≤9%, n (%)	437 (21.7)	119 (19.8)	0.165	445 (21.0)	133 (17.9)	0.02
Gained ≤14%, n (%)	397 (19.7)	133 (22.2)		412 (19.4)	148 (20.0)	
Gained >14%, n (%)	354 (17.6)	122 (20.3)		493 (23.2)	206 (27.8)	
BMI, kg/m^2 (SD)	26.2 (3.6)	27.5 (4.0)	<0.001	24.6 (4.4)	25.8 (5.0)	<0.001
Associated conditions (2002) §						
Diabetes, %	3.3	6.0	0.003	1.6	1.6	0.979
Hypertension, %	16.2	24.2	<0.001	12.6	18.9	<0.001
Cardiac disease, %	6.1	13.5	<0.001	4.0	5.1	0.198
Hormonal therapy, n (%)	-	-		350 (16.5)	168 (22.6)	<0.001
Low education, %	2.7	5.0	<0.001	7.0	11.9	<0.001

Smoking status (2002) §						
Current smoker, %	26.1	30.2	<0.001	21.5	25.5	0.030
Never smoker, %	38.5	28.3		51.9	46.8	
Lifetime smoking for ever smokers (pack-year), mean (SD), [n]	20 (21) [1240]	28 (28) [430]	<0.001	14 (15) [1021]	20 (20) [395]	<0.001
Physical activity (2002) §						
Adequately active*, %	697 (34.6)	187 (31.2)	0.301	524 (24.7)	171 (23.1)	0.651
Pulmonary function tests						
Baseline (1991)						
FEV_1, (% predicted), mean (SD) (1991)	106 (14)	107 (16)	0.053	107 (14)	113 (17)	<0.001
FEV_1/FVC ratio, mean % (SD)	79 (7)	76 (8)	<0.001	81 (7)	78 (7)	<0.001
Follow up (2002)						
FEV_1, (% predicted), mean (SD) (2002)	107 (14)	91 (16)	<0.001	111 (14)	99 (17)	<0.001
FEV_1/FVC ratio, mean % (SD)	75 (7)	69 (9)	<0.001	77 (6)	72 (8)	<0.001
FEV_1/FVC ratio <0.7, %	17.4	46.0	<0.001	12.8	36.1	<0.001
Modified GOLD 2-4†, n (%)	28 (1.4)	97 (16.6)	<0.001	14 (0.7)	57 (7.9)	<0.001
Restricted ‡, n (%)	8 (0.5)	13 (2.2)	<0.001	2 (0.1)	9 (1.2)	<0.001
FEV_1 decline (ml/yr), mean (SD)	27 (24)	82 (24)	<0.001	21 (18)	61 (20)	<0.001

*= Exercise 2-3 times per week or more and get sweat or breathless 1 hour a week or more BMI: Body-mass Index; FEV_1: Forced Expiratory Volume in 1 sec; FVC: Forced Vital Capacity; †=FEV_1/FVC ratio <0.7 & FEV_1 <80% predicted (without bronchodilators); ‡= FEV_1/FVC ratio ≥0.7 and FVC <80% predicted;§= based on self report.

Associations between weight change categories, FEV_1 decline and hs-CRP

Overall, age-adjusted (age=52 years) geometric means of hs-CRP concentrations were 1.15 mg/L (CI 95% 1.11 – 1.20) for women and 1.06 (CI 95% 1.01 – 1.11) for men (Wilcoxon rank sum test: p=0.002). In both genders, before stratification by body weight change categories, subjects with fast FEV_1 decline had higher age-adjusted hs-CRP compared to subjects without fast FEV_1 decline (**table 2**). A positive association between body weight change categories and hs-CRP was observed. This relation was however more pronounced in women. Overall, men and women with fast FEV_1 decline had higher hs-CRP in all categories of body weight changes. No statistically significant interactions between fast FEV_1 decline and weight change categories were found. **Table 2** further shows that current smoking, lack of physical activity and hormone replacement therapy were all associated with higher hs-CRP. Interaction between current smoking and fast FEV_1 decline was found in women, not in men. Baseline BMI (1991), which was weakly correlated with weight change in men (R^2 =0.0124; P<0.001) and not correlated in women (R^2 =0.0007; P=0.120) was not a predictor of systemic inflammation at SAPALDIA 2 (2002).

Table 2: Age-adjusted hs-CRP concentration (geometric means with CI95%) for non fast and fast FEV_1 decliners†

Hs-CRP, mean	Men n=2616			Women n= 2863		
n=5479	Non fast FEV_1 decliners n=2016	Fast FEV_1 decliners n=600	*P*-value†	Non fast FEV_1 decliners n=2121	Fast FEV_1 decliners n=742	*P*-value†
Unstratified by body weight change categories	0.91 [0.87 , 0.95]	1.22 [1.13,1.31]	<0.001	1.00 [0.96, 1.04]	1.24 [1.15, 1.33]	<0.001
Weight change categories						
Lost	0.77 [0.69,0.85]	1.02 [0.83,1.27]	0.017	0.68 [0.61,0.76]	0.83 [0.67,1.02]	0.121
Gained ≤5%	0.78 [0.72,0.85]	1.07 [0.92,1.25]	<0.001	0.79 [0.73,0.87]	0.90 [0.77,1.04]	0.174
Gained ≤9%	0.82 [0.75,0.89]	1.10 [0.93,1.31]	0.002	0.87 [0.80,0.96]	1.00 [0.84,1.20]	0.169
Gained ≤14%	1.08 [0.98,1.18]	1.16 [1.00,1.35]	0.423	1.14 [1.04,1.26]	1.30 [1.12,1.52]	0.161
Gained >14%	1.25 [1.12,1.40]	1.60 [1.36,1.87]	0.015	1.59 [1.46,1.73]	1.98 [1.74,2.26]	0.005
P value for interaction between weight change categories & fast FEV_1 decline category (Wald test)		0.362			0.989	
Smoking status						
Current smoker (2002)	1.12 [1.03,1.22]	1.55 [1.35,1.79]	<0.001	0.96 [0.87,1.06]	1.36 [1.18,1.58]	<0.001
Never smoker (2002)	0.78 [0.73,0.83]	1.05 [0.92,1.20]	<0.001	1.01 [0.96,1.07]	1.06 [0.96,1.19]	0.435
P value for interaction between smoking status & fast FEV_1 decline category (Wald test)		0.710			<0.001	
Physical activity (2002)						
Adequately active*	0.82 [0.77,0.88]	1.10 [1.01,1.21]	<0.001	0.90 [0.84,0.98]	1.12 [1.01,1.23]	<0.001
Inadequately active	0.95 [0.91,1.00]	1.27 [1.17,1.38]	<0.001	1.03 [0.98,1.08]	1.28 [1.18,1.38]	<0.001
P value for interaction between physical activity categories & fast FEV_1 decline category (Wald test)		0.486			0.427	
Hormonal replacement therapy	-	-	-	0.95 [0.90,1.00]	1.17 [1.08,1.26]	<0.001

No hormonal replacement therapy	-	-	-	1.23 [1.12,1.35]	1.52 [1.35,1.70]	<0.001
P value for interaction hormonal therapy & fast FEV_1 decline category (Wald test)	-				0.301	

†: from linear regression models adjusting for age.

Figure 2 shows the probability of elevated hs-CRP (>3mg/L) in men and women with or without fast FEV_1 decline as a function of weight change. Subjects with fast FEV_1 decline had higher probability of elevated hs-CRP compared to controls. Body weight increase was also associated with higher probability of elevated hs-CRP. **Figure 2** also indicates that the effect of weight gain was much more pronounced in women than in men. Subjects with GOLD stage 2-4 COPD were more likely to be in the fast decliner categories of both sexes. Hosmer and Lemeshow test was non significant meaning adequate model fit.

Figure 2: Probability of elevated hs-CRP as a function of weight change in men and women

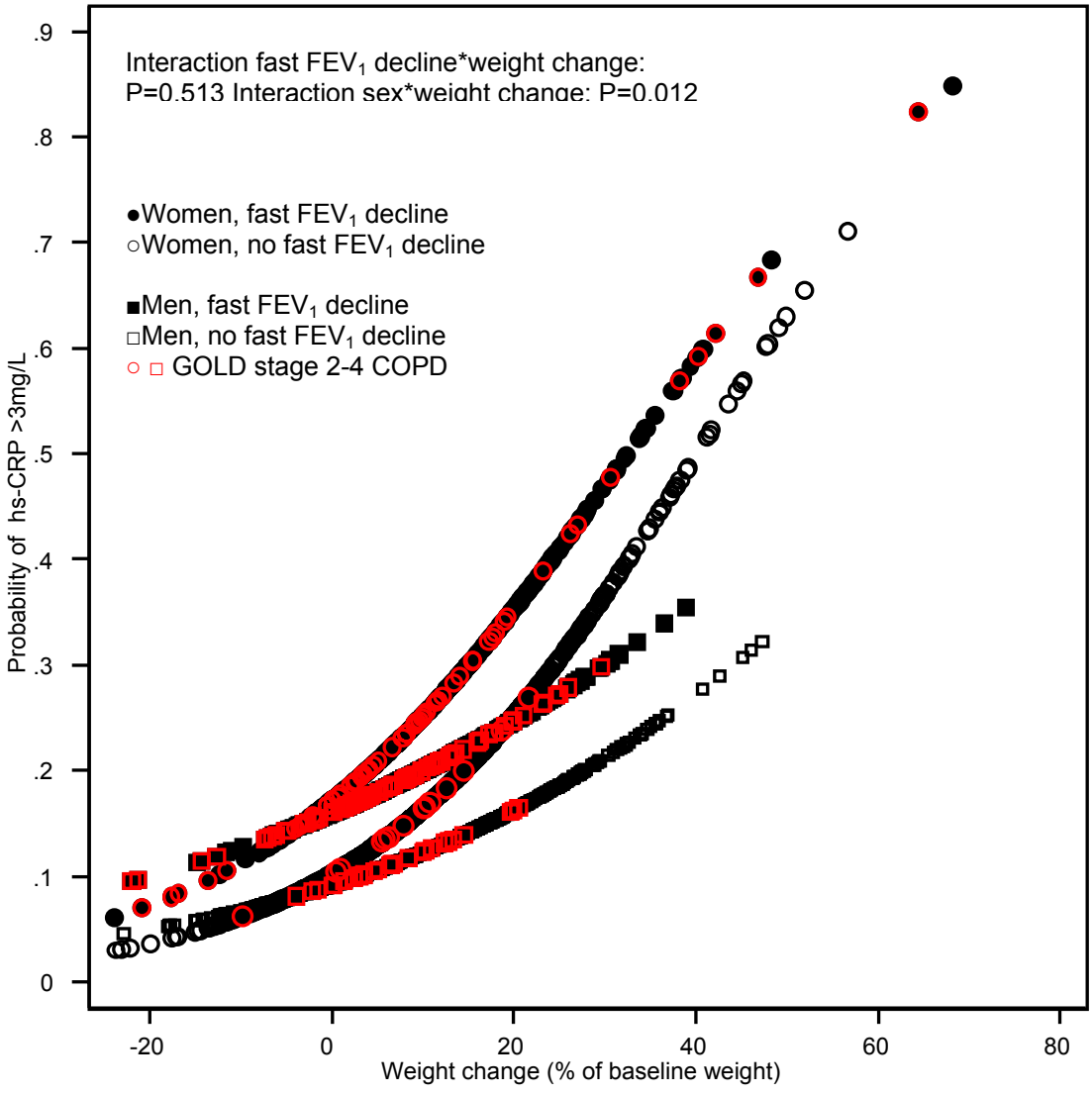


Table 3 shows the unadjusted and adjusted odds ratio of high hs-CRP for men and women. For both sexes, fast FEV_1 decline and weight gain were associated with high hs-CRP. Weight loss was negatively associated with high hs-CRP in men but not in women. Overall, the relationship between high hs-CRP and weight gain or fast FEV_1 decline was stronger and more significant in women than in men. For example, women with fast FEV_1 decline and weight gain >14% were 4.5 times more likely to have hs-CRP above 3 mg/L than women with stable weight. Men with fast FEV_1 decline and similar weight gain were only twice as likely to have elevated hs-CRP. When controlling for weight change categories and other covariates, women with fast FEV_1 decline had a 31% increase in probability of elevated hs-CRP, whereas men had a smaller (25%) and not statistically significant increase. Sensitivity analyses with different definition of COPD are displayed in the online supplement.

Table 3: Odds ratio of high hs-CRP (≥3mg) in SAPALDIA subjects

	Men				Women			
	total n, (% with high CRP)	**Unadjusted n=2616**	**Model 1† n=2595**	**Model 2†* n=2595**	**total n, (% with high CRP)**	**Unadjusted n=2863**	**Model 1‡ n= 2582**	**Model 2‡* n= 2582**
FEV_1 decline category								
Non fast	2016/235 (11.7)	ref	ref	Ref	2121/348 (16.4)	ref	ref	ref
Fast	600/117 (19.5)	1.83 (1.44 2.34)	1.25 (0.96 1.63)	1.38 (1.05 1.79)*	742/192 (25.9)	1.78 (1.44 2.34)	1.31 (1.05 1.65)	1.42 (1.13 1.77)*
Weight change categories								
Lost	410 (9.3)	0.73 (0.48 1.10)	0.62 (0.41 0.96)		457 (12.7)	1.28 (0.87 1.89)	1.22 (0.81 1.84)	
Gained ≤5%	644 (12.3)	ref	ref		569 (10.2)	ref	ref	
Gained ≤9%	556 (13.3)	1.10 (0.78 1.54)	1.20 (0.85 1.72)		578 (16.8)	1.78 (1.25 2.51)	1.74 (1.20 2.52)	
Gained ≤14%	530 (14.2)	1.18 (0.84 1.65)	1.44 (1.01 2.06)		560 (19.3)	2.11 (1.49 2.97)	2.24 (1.56 3.23)	
Gained >14%	476 (18.1)	1.58 (1.13 2.19)	2.04 (1.42 2.93)		699 (31.3)	4.02 (2.93 5.51)	4.51 (3.21 6.34)	

†: adjusted for age, age squared, fast FEV_1 decline, categories of weight change, smoking status, lifetime smoking (pack*yr), physical activity, diabetes and study area (random effect)
‡ adjusted for age, age squared, fast FEV_1 decline, categories of weight change, smoking status, lifetime smoking (pack*yr), physical activity, diabetes, hormone replacement therapy and study area (random effect)
*no adjustment for weight change categories

Sensitivity analyses

The relation between weight change and hs-CRP was not modified by inclusion of subjects with hs-CRP ≥10mg/L (women, n=96, men, n=91). It was neither modified when subjects with restrictive physiology (n=33) were excluded nor when covariates such as diabetes, hypertension, cardiac disease, physician-diagnosed asthma or education level were added. Association between hs-CRP and weight change and FEV_1 decline categories were amplified when absolute values of FEV_1 decline and weight change were used. Interpretations of the data were unchanged when definition of COPD was restricted as shown in the online supplement tables (5^{th} to 7^{th} sensitivity analysis).

DISCUSSION

In this 11-year cohort study, we found that the associated effect of weight gain and fast FEV_1 decline predicted a greater systemic inflammation, as measured by hs-CRP, in women compared to men. This association persisted after controlling for common predictors of systemic inflammation, such as age, smoking, hormonal replacement therapy or physical activity. We hypothesized that fast FEV_1 decline and weight gain would interact to increase systemic inflammation. We found that fast FEV_1 decline and weight increase are independent predictors of systemic inflammation and more so in women. This finding is robust and insensitive to COPD definition or to exclusion of subjects with restrictive physiology.

The rate of FEV_1 decline among fast FEV_1 decliners appears larger in our cohort compared to recent clinical trials on COPD, whereas it is similar to other population studies among non fast FEV_1 decliners [28-30]. Several factors may explain this. First, our definition captured subjects in the upper quartile of FEV_1 decline where the distribution of FEV_1 decline is skewed. This provides a first explanation for the high mean value in this group. Second, the generally high FEV_1 values at baseline in our population sample allow for larger absolute

values of decline. Given the large differences in rate of decline between non fast and fast FEV_1 decliners and the considerable length of follow-up, misclassification of fast FEV_1 decline is unlikely.

The level of hs-CRP in our subjects with fast FEV_1 decline is concordant with recent articles reporting various biomarkers of inflammation including CRP, despite a different definition of COPD (GOLD stage 2 criteria versus fast FEV_1 decline) [31]. Sin et al showed that moderate and severe COPD were associated with high CRP in a population study. They also found that signs of myocardial ischemia on electro-cardiographic studies correlated with systemic inflammation[32]. Others found that raised CRP was a marker of disease severity in patients with COPD[33]. Our study complements these findings and shows that level of hs-CRP in subjects with accelerated FEV1 decline is sex-specific and dependent on weight gain. At the other end of the spectrum of weight change, we found a trend toward higher systemic inflammation in women with fast FEV_1 decline and weight loss (table 3). Weight loss in women, but not in men was associated with lower health status and higher health care utilization (data not shown). This suggests that the effect of weight loss in women with COPD is a consistent marker of poor outcome, whereas the heterogeneity of causes leading to weight loss in men precludes further conclusion.

Similar association was previously described by Fogarty et al, who found that subjects with low BMI (<20 kg/m2) and low FEV_1 had higher level of systemic inflammation [34].

There are multiple factors that could explain the different levels of systemic inflammation in men and women with COPD. Higher systemic inflammation in women with COPD and weight gain may be due to a higher release of pro-inflammatory factors, such as interleukin-6, from adipose tissue or from damaged lung. This first explanation would be in line with a large population study, showing that the association between CRP and obesity was stronger in women than in men [35]. Oestrogen or progesterone substitutive therapies have also been

described as factors stimulating hs-CRP [36]. Also possible is a higher pro-inflammatory cytokines production by the lung exposed to cigarette smoking in women, (assuming similar level of exposure in men). This suggests an increased susceptibility to the effects of smoking in women. Other plausible explanations for the higher level of systemic inflammation in women with COPD and weight gain, are i) relative lower level of physical activity or ii) lower use of alcohol. For example, a study showing that moderate intake of alcohol was associated with lower level of systemic inflammation found less frequent drinking of alcohol in women than in men [37]. In our study we were able to control for cigarette smoking and level of physical activity, which suggests that these factors do not fully explain the observed sex differences in levels of systemic inflammation.

From a patho-physiological point, the higher systemic inflammation measured in women with weight gain and COPD is relevant because it may partly explain why women with COPD seem to fare worse than men in terms of mortality [5]. Systemic inflammation may play an independent role in the pathogenesis of cardiovascular disease or diabetes, as shown in large population studies of women [38, 39]. In a study, hs-CRP was a stronger predictor of incident cardiovascular events than traditional risk factors in women [38]. Future epidemiological studies measuring systemic inflammation, weight gain and incident cardiovascular events in subjects with mild or moderate COPD are needed to bring evidence that women with COPD experience worse outcomes because of higher level of systemic inflammation and not because of other factors. These studies would also allow the determination of comorbid conditions which are amenable to therapy. For example, inhaled cortico-steroids or statins decreased CRP[40, 41], whereas tiotropium had no effect on systemic inflammation [42]. Through diminution of systemic inflammation, statins may reduce FEV_1 decline [43]. Also, statin therapy reduces cardiovascular mortality in men and women with abnormal CRP but low

cholesterol level[44]. We show that the subgroup of women with weight gain and fast FEV_1 decline have particularly high level of hs-CRP. Because of the high probability of elevated CRP value in this subgroup of women, the measure of hs-CRP in this target population might help to better predict incident cardiovascular events.

Strengths of our analysis include size of the population, which is an unbiased sample of the Swiss population and standardized assessment of FEV_1 and other covariates such as hormonal therapy or physical activity.

Potential limitations are related to the absence of repeated measures of hs-CRP and body weight during the follow-up period. Because of potential confounding by respiratory infections, we excluded subjects with high hs-CRP. Residual confounding is however possible. Inclusion of these subjects (n=187) in the analyses did not modify our estimates. Reverse causation (systemic inflammation causing FEV_1 decline or weight change) can not be formally excluded by our study design. Longitudinal studies with repeated measures of weight, FEV_1, hs-CRP and incident cardiovascular or respiratory events, may bring a more definite answer.

In summary, our results show that COPD, approximated by fast FEV_1 decline, and weight gain are independent predictors of systemic inflammation with a exposure response relationship. Notably, the relation is sex-specific: weight gain in subjects with COPD is more strongly associated with high hs-CRP in women than in men. These results may stimulate interventional studies specifically aimed at weight control among women with COPD.

Funding: The SAPALDIA cohort study is supported by the Swiss National Science Foundation (grants no 4026-28099, 3347CO-108796, 3247BO-104283, 3247BO-104288, 3247BO-104284, 32-65896.01, 32-59302.99, 32-52720.97, 32-4253.94), the Federal Office for Forest, Environment and Landscape, the Federal Office of Public Health, the Federal Office of Roads and Transport, the canton's government of Aargau, Basel-Stadt, Basel-Land, Geneva, Luzern, Ticino, Zurich, the Swiss

Lung League, the canton's Lung League of Basel Stadt/ Basel Landschaft, Geneva, Ticino and Zurich.

Competing interest: None declared

Acknowledgments:

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We are indebted to the study participants, the technical and administrative support at coordinating centres, and the medical teams and field workers at the local study sites.

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