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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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ABSTRACT: Systemic inflammation may mediate the association between chronic obstructive pulmonary disease (COPD) and extrapulmonary comorbidities. We measured high-sensitivity C-reactive protein (hs-CRP) in COPD and quantified the effect modification by body weight change and sex.

Using data from the Swiss study on Air Pollution and Lung Diseases in Adults (SAPALDIA; n=5,479) with measurements of forced expiratory volume in 1 s (FEV_1), body weight and hs-CRP, we examined the association of hs-CRP and categories of body weight change (lost weight and weight gained 0–5%, 5–9%, 9–14% and >14%) with 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 $mg \cdot L^{-1}$ for females *versus* 1.6 $mg \cdot L^{-1}$ for males). After adjustment for age, smoking, physical activity, hormonal therapy and diabetes, elevated hs-CRP (>3 mg) was found to be more likely in subjects with fast FEV_1 decline (OR_{males} 1.38, $OR_{females}$ 1.42) and in those with weight gain >14% (OR_{males} 2.04, $OR_{females}$ 4.51).

The association of weight gain and fast FEV_1 decline predicts a higher level of systemic inflammation. Since the effect of weight gain on systemic inflammation is larger in females than in males, weight gain may be a risk factor for extrapulmonary comorbidities in females with COPD.

KEYWORDS: Chronic obstructive pulmonary disease, forced expiratory volume in 1 s decline, obesity, sex differences, systemic inflammation

Worldwide, chronic obstructive pulmonary disease (COPD) is a prevalent disease which is projected to become the fourth leading cause of death by 2020 [1], although 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 females: in 2000, females dying with COPD outnumbered males dying with the condition in the USA [4]. Females 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 s (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, tumour necrosis factor-α, leukocytes, and interleukin-6 or -8 [7]. In fact, systemic inflammation may contribute to the diverse extrapulmonary comorbidities 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

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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]. Conversely, physical activity, smoking cessation or dietary interventions may reduce hs-CRP and have been associated with slower lung function decline [14–16]. Elevated CRP (>3 mg·L^{-1}) is strongly associated with cardiovascular morbidity and mortality, and it has been hypothesised that systemic inflammation mediates the relationship between mild COPD and cardiovascular mortality [9, 17, 18]. Thus, reducing systemic inflammation and, hence, cardiovascular morbidity and mortality would be a major objective of COPD management. Observational studies suggest 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 (*e.g.* obesity, smoking or lung inflammation) need to be better understood in order to propose efficient therapeutic interventions. As the prevalence of obesity is growing, a cumulative effect of COPD and obesity on systemic inflammation is possible.

It is unknown whether the excess of death related to COPD in females, as described in previous studies, could be related to higher levels of systemic inflammation compared with males [4]. The aim of the present study was to examine the complex relationship between weight gain and systemic inflammation in subjects with COPD, as defined by fast FEV1 decline. Specifically, we sought to determine whether body weight gain modifies systemic inflammation in COPD and, if so, whether this effect is different in males and females.

METHODS

Study population

The Swiss study on Air Pollution and Lung Diseases in Adults (SAPALDIA) 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, 9,651 randomly selected adults in eight geographically and culturally diverse areas (Basel, Aarau, Geneva, Montana, Davos, Wald, Payerne and Lugano) were included and followed for, on average, 10.9 yrs. Of those subjects, 8,876 had pulmonary function tests (PFTs). In 2002, the follow-up study enrolled 8,047 (83.4%) subjects from the 1991 sample. For the present study, we included subjects who had PFTs at both surveys (SAPALDIA 1 in 1991 and SAPALDIA 2 in 2002), and who provided blood for hs-CRP measurements in 2002. We excluded 187 subjects in whom elevated hs-CRP (>10 mg·L^{-1}) could be related to a current infection (fig. 1).

Pulmonary function tests

PFTs were performed according to the American Thoracic Society standards, using the same spirometers (SensorMedics 2200 SP; Yorba Linda, CA, USA) at both surveys. This was done in order to limit systematic bias error in volume measurement [23]. FEV1 and forced vital capacity (FVC) were obtained without bronchodilators. We used the European Respiratory Society equation to calculate the predicted values of FEV1 and FVC [24]. FEV1 decline was calculated as the difference between the two measurements divided by the baseline (1991) FEV1. Each subject was classified into a quartile of FEV1 decline and those in the highest quartile were defined as fast decliners. This definition of COPD was chosen because the rate of FEV1 decline is a key marker of COPD [25].

Weight change

Weight and height were recorded immediately before PFTs. Body weight change was calculated as the difference in weight between the two surveys divided by baseline (1991) weight. Body weight change was divided into five groups: 1) the ''weight loss'' group included subjects who lost $\geqslant 0.1\%$ of their baseline weight between the two surveys; 2) the ''gained $\leqslant 5\%$'' group encompassed subjects whose weight change was between 0% and $\leqslant 5\%$; 3) the ''gained $\leqslant 9\%$'' group had weight change between $>5\%$ and $\leqslant 9\%$; and 4) the ''gained $\leqslant 14\%$'' and 5) ''gained $>14\%$'' groups corresponded to a weight gain of $>9\%$ to $\leqslant 14\%$ and $>14\%$, 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 per day $\times$ smoking duration (yrs)) were recorded at both surveys.

The level of physical activity was assessed at SAPALDIA 2 with questions addressing the frequency and the intensity of

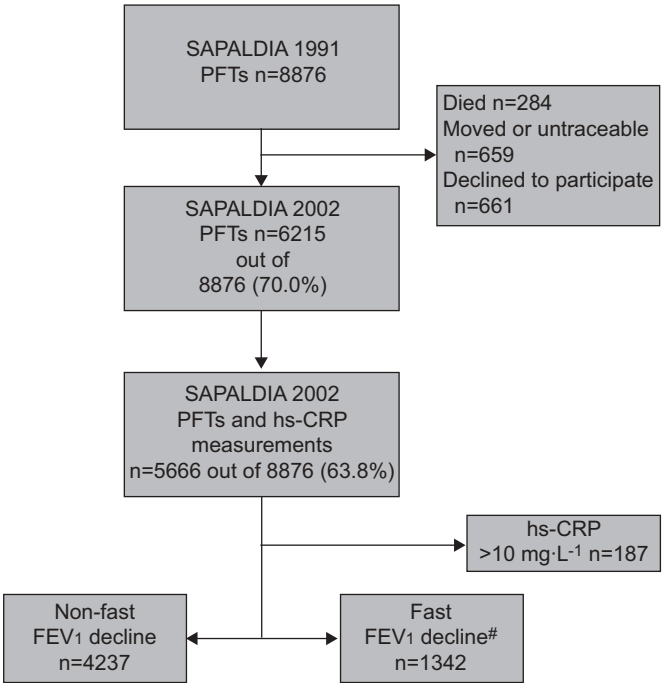

FIGURE 1. Flow chart of participants included in the present Swiss study on Air Pollution and Lung Diseases in Adults (SAPALDIA; 1991–2002). PFTs: pulmonary function tests; hs-CRP: high-sensitivity C-reactive protein; FEV1: forced expiratory volume in 1 s. #: upper quartile of FEV1 decline (% baseline FEV1).

physical activity. Results of these questions were combined into a single variable that defined subjects as ''physically active'' if they fulfilled the following criteria: 1) exercise for $\geqslant 1$ h·week^{-1} and 2) twice or more times per week. Categorisation of physical activity into two broad groups is in accordance with published literature [26, 27]. For detailed questions and subjects' classification, see the online supplementary material. Highest education reached, use of hormone replacement therapy and comorbid conditions were self-reported and extracted from the questionnaire administered by trained interviewers.

hs-CRP

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

Statistical analyses

Statistical analyses were carried out with Stata version 10 (StataCorp, College Station, TX, 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 FEV1 decline. Linear regression models were used to investigate the relationship between body weight change categories and log-transformed hs-CRP in subjects with or without fast FEV1 decline.

We tested the interactions between fast FEV1 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 dichotomised hs-CRP into a low and high hs-CRP level (>3 mg·L^{-1}). Logistic regression was applied to measure the association between fast FEV1 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-yrs), physical activity, diabetes and study area as a random effect variable. In females, hormone replacement therapy was also included in the models.

Sensitivity analysis

All analyses were repeated with the following changes. First, subjects with hs-CRP $\geqslant 10$ mg·L^{-1} were included. Secondly, subjects with a restrictive pattern (FEV1/FVC ratio $\geqslant 0.7$ and FVC $<80\%$ predicted) were excluded. Thirdly, the following potential confounders were included in the models: physician-diagnosed asthma, hypertension, cardiac disease or education level. Fourthly, absolute body weight change and absolute FEV1 decline were used as predictors of hs-CRP instead of relative changes. Fifthly, we restricted the definition of COPD further by adding the mandatory presence of respiratory symptoms (chronic cough, phlegm or shortness of breath by walking) to the group of subjects with fast FEV1 decline. Sixthly, we also tested our models using the modified (without bronchodilation) Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2–4 category to define COPD and, seventhly, using modified GOLD 1–4 definition and fast FEV1 decline as predictor.

RESULTS

Of the 6,215 adult participants who had PFTs at both SAPALDIA 1 and 2, 5,666 (91.1%) had determination of hs-CRP. Characteristics of the subjects by sex and FEV1 decline are shown in table 1 and in the online supplementary material. Fast FEV1 decline was associated with older age, lower education, higher smoking exposure, higher FEV1 at baseline, more symptoms and lower health-related quality of life. Males with fast FEV1 decline reported hypertension and cardiac disease more frequently. At follow-up, weight gain was larger for fast FEV1 decliners. The mean yearly FEV1 losses were three times larger among fast FEV1 decliners compared with non-fast decliners. Abnormal FEV1/FVC ratio (*i.e.* <0.7) according to the GOLD criterion was met in 46.0% of males and 36.1% of females with fast FEV1 decline *versus* 17.4% and 12.8%, respectively, in non-fast FEV1 decliners.

Associations between weight change categories, FEV1 decline and hs-CRP

Overall, age-adjusted (age 52 yrs) geometric means of hs-CRP concentrations were 1.15 mg·L^{-1} (95% CI 1.11–1.20) for females and 1.06 mg·L^{-1} (95% CI 1.01–1.11) for males (Wilcoxon rank-sum test: $p=0.002$). In both sexes, before stratification by body weight change categories, subjects with fast FEV1 decline had higher age-adjusted hs-CRP compared with subjects without fast FEV1 decline (table 2). A positive association between body weight change categories and hs-CRP was observed. However, this relationship was more pronounced in females. Overall, males and females with fast FEV1 decline had higher hs-CRP in all categories of body weight change. No statistically significant interactions between fast FEV1 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 FEV1 decline was found in females, but not in males.

Baseline body mass index (1991), which was weakly correlated with weight change in males ($R^2=0.0124$; $p<0.001$) and not correlated in females ($R^2=0.0007$; $p=0.120$), was not a predictor of systemic inflammation at SAPALDIA 2 (2002).

Figure 2 shows the probability of elevated hs-CRP (>3 mg·L^{-1}) in males and females with or without fast FEV1 decline as a function of weight change. Subjects with fast FEV1 decline had higher probability of elevated hs-CRP compared with controls. Body weight increase was also associated with a higher probability of elevated hs-CRP. Figure 2 also indicates that the effect of weight gain was much more pronounced in females than in males. Subjects with GOLD stage 2–4 COPD were more likely to be in the fast decliner categories of both sexes. The Hosmer and Lemeshow test was nonsignificant, indicating adequate model fit.

Table 3 shows the unadjusted and adjusted odds ratios of high hs-CRP for males and females. For both sexes, fast FEV1 decline and weight gain were associated with high hs-CRP. Weight loss was negatively associated with high hs-CRP in males but not in females. Overall, the relationship between

TABLE 1 Subject characteristics by categories of forced expiratory volume in 1 s (FEV_1) decline in the Swiss study on Air Pollution and Lung Diseases in Adults (SAPALDIA)

	Males			Females		
	Non-fast FEV_1 decliners	Fast FEV_1 decliners	p-value[#]	Non-fast FEV_1 decliners	Fast FEV_1 decliners	p-value[#]
Subjects n	2016	600		2121	742	
Age yrs	50±11	56±10	<0.001	50±11	57±10	<0.001
Weight kg	81.0±12.1	83.3±13.1	<0.001	65.8±12.1	67.8±13.2	<0.001
Weight change kg	+5.5±6.1	+6.3±6.59	0.003	+5.1±5.9	+6.0±6.4	<0.001
Weight change % baseline	+7.3±8.1	+8.2±8.2	0.026	+8.4±9.1	+9.6±9.9	0.03
Weight change categories						
Lost	329 (16.3)	81 (13.5)	0.165	357 (16.8)	100 (13.5)	0.02
Gained ⩽5%	499 (24.7)	145 (24.2)		414 (19.5)	155 (20.9)	
Gained ⩽9%	437 (21.7)	119 (19.8)		445 (21.0)	133 (17.9)	
Gained ⩽14%	397 (19.7)	133 (22.2)		412 (19.4)	148 (20.0)	
Gained >14%	354 (17.6)	122 (20.3)		493 (23.2)	206 (27.8)	
BMI $kg \cdot m^{-2}$	26.2±3.6	27.5±4.0	<0.001	24.6±4.4	25.8±5.0	<0.001
Associated conditions[¶]						
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				350 (16.5)	168 (22.6)	<0.001
Low education	2.7	5.0	<0.001	7.0	11.9	<0.001
Smoking status[¶]						
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-yrs	1240, 20±21	430, 28±28	<0.001	1021, 14±15	395, 20±20	<0.001
Physical activity[¶]						
Adequately active %[+]	697 (34.6)	187 (31.2)	0.301	524 (24.7)	171 (23.1)	0.651
PFTs						
Baseline[§]						
FEV_1 % pred	106±14	107±16	0.053	107±14	113±17	<0.001
FEV_1/FVC ratio %	79±7	76±8	<0.001	81±7	78±7	<0.001
Follow-up						
FEV_1 % pred	107±14	91±16	<0.001	111±14	99±17	<0.001
FEV_1/FVC ratio	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[f]	28 (1.4)	97 (16.6)	<0.001	14 (0.7)	57 (7.9)	<0.001
Restricted[##]	8 (0.5)	13 (2.2)	<0.001	2 (0.1)	9 (1.2)	<0.001
FEV_1 decline $mL \cdot yr^{-1}$	27±24	82±24	<0.001	21±18	61±20	<0.001

Unless otherwise indicated, data are presented as: mean±SD; n (%); %; or n, mean±SD. Characteristics are those at SAPALDIA 2 (2002), unless otherwise stated; n=5,479. BMI: body mass index; PFTs: pulmonary function tests; % pred: % predicted; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease. [#]: unpaired t-test or Chi-squared test; [¶]: based on self-reporting; [+]: exercise ⩾2–3 times per week and sweaty or breathless for ⩾1 $h \cdot week^{-1}$; [§]: 1991 data; [f]: FEV_1/FVC ratio <0.7 and FEV_1 <80% pred (without bronchodilators); [##]: FEV_1/FVC ratio ⩾0.7 and FVC <80% pred.

high hs-CRP and weight gain or fast FEV_1 decline was stronger and more significant in females than in males. For example, females with fast FEV_1 decline and weight gain >14% were 4.5 times more likely to have hs-CRP >3 $mg \cdot L^{-1}$ than females with stable weight. Males 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, females with fast FEV_1 decline had a 31% increase in probability of elevated hs-CRP, whereas males had a smaller (25%) and not statistically significant increase. Sensitivity analyses with different definitions of COPD are displayed in the online supplementary material.

Sensitivity analyses

The relationship between weight change and hs-CRP was not modified by inclusion of subjects with hs-CRP ⩾10 $mg \cdot L^{-1}$ (females, n=96; males, n=91). It was modified neither when subjects with restrictive physiology (n=33) were excluded nor

TABLE 2 Age-adjusted high-sensitivity C-reactive protein (hs-CRP) concentration ($mg \cdot L^{-1}$) for non-fast and fast forced expiratory volume in 1 s (FEV_1) decliners

	Males			Females		
	Non-fast FEV_1 decliners	Fast FEV_1 decliners	p-value#	Non-fast FEV_1 decliners	Fast FEV_1 decliners	p-value#
Subjects n	2016	600		2121	742	
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
Interaction			0.362§			0.989§
Smoking status¶						
Current smoker	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	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
Interaction			0.710§			<0.001§
Physical activity ¶						
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
Interaction			0.486§			0.427§
Hormonal replacement therapy				0.95 (0.90–1.00)	1.17 (1.08–1.26)	<0.001
No therapy				1.23 (1.12–1.35)	1.52 (1.35–1.70)	<0.001
Interaction						0.301§

Data are presented as geometric mean (95% CI), unless otherwise indicated. #: from linear regression models adjusting for age, unless otherwise stated; ¶: 2002 data; +: exercise ⩾2–3 times per week and sweaty or breathless for ⩾1 $h \cdot week^{-1}$; §: p-value for interaction with fast FEV_1 decline category (Wald test).

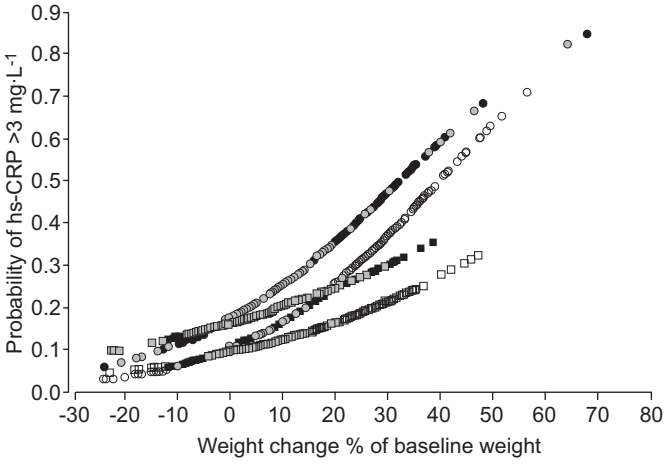

FIGURE 2. Probability of elevated high-sensitivity C-reactive protein (hs-CRP) as a function of weight change in males and females. ●: females, fast forced expiratory volume in 1 s (FEV_1) decline; ○: females, non-fast FEV_1 decline; ■: males, fast FEV_1 decline; □: males, non-fast FEV_1 decline; grey symbols: fast FEV_1 decline, Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 2–4 chronic obstructive pulmonary disease. For interaction between fast FEV_1 decline and weight change, p=0.513; for interaction between sex and weight change, p=0.012.

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 the definition of COPD was restricted as shown in the online supplementary material (fifth to seventh sensitivity analysis).

DISCUSSION

In this 11-yr cohort study, we found that the associated effects of weight gain and fast FEV_1 decline predicted a greater systemic inflammation, as measured by hs-CRP, in females compared with males. This association persisted after controlling for common predictors of systemic inflammation, such as age, smoking, hormonal replacement therapy or physical activity. We hypothesised 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 females. 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 with 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

TABLE 3 ORs and 95% CIs of high level of high-sensitivity C-reactive protein (hs-CRP; >3 mg) in subjects of the Swiss study on Air Pollution and Lung Diseases in Adults (SAPALDIA)

	Males				Females			
	Total subjects	Unadjusted	Model 1[#]	Model 2[#,¶]	Total subjects	Unadjusted	Model 1[+]	Model 2[¶,+]
Subjects n		2616	2595	2595		2863	2582	2582
FEV1 decline								
Non-fast	2016 (11.7)	Ref.	Ref.	Ref.	2121 (16.4)	Ref.	Ref.	Ref.
Fast	600 (19.5)	1.83 (1.44–2.34)	1.25 (0.96–1.63)	1.38 (1.05–1.79)[¶]	742 (25.9)	1.78 (1.44–2.34)	1.31 (1.05–1.65)	1.42 (1.13–1.77)[¶]
Weight change								
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)	

Data are presented as n (% with high CRP) or OR (95% CI), unless otherwise indicated. FEV1: forced expiratory volume in 1 s; Ref.: reference category. [#]: adjusted for age, age squared, fast FEV1 decline, categories of weight change, smoking status, lifetime smoking (pack-yrs), physical activity, diabetes and study area (random effect); [¶]: no adjustment for weight change categories; [+]: adjusted for age, age squared, fast FEV1 decline, categories of weight change, smoking status, lifetime smoking (pack-yrs), physical activity, diabetes, hormone replacement therapy and study area (random effect).

this. First, our definition captured subjects in the upper quartile of FEV1 decline where the distribution of FEV1 decline is skewed. This provides a first explanation for the high mean value in this group. Secondly, the generally high FEV1 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 FEV1 decliners and the considerable length of follow-up, misclassification of fast FEV1 decline is unlikely.

The level of hs-CRP in our subjects with fast FEV1 decline is concordant with recent studies reporting various biomarkers of inflammation including CRP, despite a different definition of COPD (GOLD stage 2 criteria *versus* fast FEV1 decline) [31]. In a population study, SIN and MAN [32] showed that moderate and severe COPD were associated with high CRP. They also found that signs of myocardial ischaemia on electrocardiographic 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 towards higher systemic inflammation in females with fast FEV1 decline and weight loss (table 3). Weight loss in females, but not in males, was associated with lower health status and higher healthcare utilisation (data not shown). This suggests that the effect of weight loss in females with COPD is a consistent marker of poor outcome, whereas the heterogeneity of causes leading to weight loss in males precludes further conclusion.

A similar association was previously described by FOGARTY *et al.* [34], who found that subjects with low body mass index (<20 kg·m^{-2}) and low FEV1 had a higher level of systemic inflammation.

There are multiple factors that could explain the different levels of systemic inflammation in males and females with COPD. Higher systemic inflammation in females 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 females than in males [35]. Oestrogen or progesterone substitutive therapies have also been described as factors stimulating hs-CRP [36]. Also possible is a higher rate of production of pro-inflammatory cytokines by the lung exposed to cigarette smoking in females (assuming a similar level of exposure in males). This suggests an increased susceptibility to the effects of smoking in females. Other plausible explanations for the higher level of systemic inflammation in females with COPD and weight gain are: 1) a relatively lower level of physical activity or 2) a 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 females than in males [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 pathophysiological point of view, the higher systemic inflammation measured in females with weight gain and COPD is relevant because it may partly explain why females with COPD seem to fare worse than males 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 females [38, 39]. In one study, hs-CRP was a stronger predictor of incident cardiovascular events than traditional risk factors in females [38]. Future

epidemiological studies measuring systemic inflammation, weight gain and incident cardiovascular events in subjects with mild or moderate COPD are needed to provide evidence that females with COPD experience worse outcomes because of higher levels of systemic inflammation and not because of other factors. These studies would also allow the determination of comorbid conditions that are amenable to therapy. For example, inhaled corticosteroids 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 males and females with abnormal CRP but low cholesterol levels [44]. We show herein that the subgroup of females with weight gain and fast FEV_1 decline have particularly high levels of hs-CRP. Due to the high probability of an elevated CRP value in this subgroup of females, the measurement of hs-CRP in this target population might help to better predict incident cardiovascular events.

Strengths of our analysis include the size of the population, which is an unbiased sample of the Swiss population, and standardised 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. Due to potential confounding by respiratory infections, we excluded subjects with high hs-CRP; however, residual confounding is 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) cannot 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 an exposure–response relationship. Notably, the relationship is sex specific: weight gain in subjects with COPD is more strongly associated with high hs-CRP in females than in males. These results may stimulate interventional studies specifically aimed at weight control among females with COPD.

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STATEMENT OF INTEREST

None declared.

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