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BMI increase – A risk factor for FEV_1 decline for overweight and obese adults with asthma

Nicolás Bermúdez Barón[1], Hannu Kankaanranta[2,3,4], Linnea Hedman[1], Martin Andersson[1], Caroline Stridsman[5], Anne Lindberg[5], Eva Rönmark[1], Helena Backman[1]

[1]Dept of Public Health and Clinical Medicine, Section of Sustainable Health, OLIN unit, Umeå University, Umeå, Sweden.
[2]Krefting Research Centre, Dept of Internal Medicine and Clinical Nutrition, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden
[3]Tampere University Respiratory Research Group, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland.
[4]Dept of Respiratory Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland.
[5]Dept of Public Health and Clinical Medicine, Section of Medicine, OLIN unit, Umeå University, Umeå, Sweden

Correspondence

Nicolás Bermúdez Barón
E-mail address: nicolas.bermudez@umu.se
Postal address: OLIN studies, Robertsviksgatan 7, 971 89 Luleå, Sweden

Take home message: BMI increase is associated with faster FEV_1 and FVC decline in adults with asthma, and this association is stronger among overweight and obese adults with asthma than among their normal weight counterparts.

ABSTRACT

Background: With increasing prevalence of overweight and obesity, it is important to study how BMI change may affect lung function among subjects with asthma. There are few prospective studies on this topic, especially with separate analyses of those with normal and high BMI.

Aim: To prospectively study the association between annual BMI change and annual lung function decline, separately among those with normal initial BMI and overweight/obesity, in an adult asthma cohort.

Methods: A population-based adult asthma cohort was examined at study entry between 1986-2001 and at follow-up between 2012-2014 (n=945). Annual BMI change was analyzed in association to annual decline in FEV_1, FVC and FEV_1/FVC separately in those with normal weight (BMI=18.5-24.9) and overweight/obesity (BMI≥25) at study entry. Regression models were used to adjust for sex, age, smoking, ICS use and occupational exposure to gas, dust, or fumes.

Results: Subjects with overweight/obesity had lower FEV_1 and FVC but slower annual FEV_1 and FVC decline compared to those with normal weight. After adjustment through regression modelling, the association between BMI change with FEV_1 and FVC decline remained significant for both BMI groups, but with stronger associations among the overweight/obese (FEV_1 $B_{[Overweight/obese]}$=-25ml vs. $B_{[normal\ weight]}$=-15ml). However, when including only those with BMI increase during follow-up, the associations remained significant among those with overweight/obesity, but not in the normal weight group. No associations were seen for FEV_1/FVC.

Conclusions: BMI increase is associated with faster FEV_1 and FVC decline among overweight and obese adults with asthma in comparison with their normal weight counterparts.

INTRODUCTION

Asthma is characterized by a variable expiratory airflow limitation which may become persistent[1] and lead to a more accelerated FEV_1 decline[2]. Impaired lung function in asthma is known to be associated with multiple factors such as current smoking[3], smoking pack-years[4] but also obesity[5]. Consequently, these factors relate to a worse asthma control[6] and severity[7], which in turn associate with lower quality of life[8–10].

Overweight and obesity are becoming more common worldwide[11] and increased body mass index (BMI≥25)[12,13] is known to be related to lower FEV_1. There are cross-sectional studies that have shown that obese adults with asthma have lower FEV_1 than adults with asthma having normal weight[5]. However, there are few population-based longitudinal studies on this topic[14], and specifically those focusing on adults with asthma have been lacking. One prospective study[15] showed that BMI increase indeed was related to FEV_1 decline among young adults with non-obstructive asthma, but this study did not separate overweight and obese subjects from those with normal weight, and thus it is not known if the association differs depending on initial BMI.

Asthma treatment response has been shown to vary depending on the underlying asthma phenotypes and should ideally be tailored based on clinical and molecular traits[1,16]. Despite the available pharmacological therapies, obese asthma patients often remain symptomatic, with more exacerbations and hospitalizations, although these results are less clear regarding overweight asthma patients[17–19]. Overweight and obese subjects with asthma are more commonly resistant to the standard treatment with inhaled corticosteroids (ICS), likely related to frequent lack of the eosinophilic airway inflammation and also to dysregulation of some metabolic signaling pathways[20–22]. Thus, non-pharmacological interventions such as weight loss and smoking cessation may be particularly important for this group[1,3,23,24].

In summary, prospective studies focusing on the association between longitudinal changes in BMI and lung function in asthma are important but scarce[15], especially with sample sizes allowing for stratification by baseline BMI[25]. Thus, our aim is to study the association between annual BMI change and annual lung function decline, separately among those with normal weight and overweight/obesity, in a 10–28-year follow-up of a population-based adult asthma cohort.

METHODS

Study design

This study is part of the Obstructive Lung Disease in Northern Sweden (OLIN) research program. A population-based cohort of adults with asthma living in the northernmost county of Sweden, Norrbotten, (n=2055, 55% women, aged 19-72 years), was identified from five original population-based cohorts during 1986-2001. The inclusion criteria were strictly predefined based on data from clinical examinations and detailed structured interviews.

Participants from cohorts I-IV with at least one of the following criteria were included:

a) Physician-diagnosed asthma or report of ever having asthma.
b) Asthmatic wheeze without a cold last 12 months in combination with attacks of shortness of breath/wheeze or use of asthma medication.
c) Attacks of shortness of breath last 12 months with FEV_1 reversibility of both ≥12% and ≥200ml.
d) Attacks of shortness of breath or wheeze last 12 months with methacholine bronchial hyperresponsiveness.

All participants from cohort V were included as they were physician-diagnosed with adult-onset asthma from primary care and had a medical history of asthma together with methacholine bronchial hyperresponsiveness[26].

At study entry in 1986-2001, a detailed structured interview was performed including questions regarding asthma diagnosis, potential risk factors, treatment of obstructive respiratory diseases and occupation. Clinical examinations included spirometry and assessment of height and weight.

The follow-up was performed during 2012-2014 in which those still alive and living in the county (n=1425) were invited. In total, n=1006 (71%) participated in similar clinical examinations that included structured interviews, spirometry and measurement of height and weight[26].

Participants with BMI≥18.5 at study entry and not missing FEV_1 or BMI measurements both at study entry and at follow-up were included in the study sample (n=945) (Supplemental figure 1).

Lung function

At study entry, spirometry was performed with a Mijnhardt Vicatest 5 dry volume spirometer following the 1987/1994 ATS guidelines with a repeatability criterion of the two best measurements of ≤5%, and ≤100 milliliters (ml) when the best FEV_1 was ≤1 liter[27,28].

Spirometry at follow-up was performed with a Jaeger Masterscope pneumotach spirometer following the 2005 ERS/ATS guidelines with a repeatability criterion of ≤150 ml[29].

FEV_1 and FVC were measured (before bronchodilatation), expressed both in ml and as percent of predicted (pp) using the OLIN reference values[30]. The ratio between FEV_1 and FVC was also calculated. Post-bronchodilatory values were not included in the current study as they were available only in certain subsamples.

Changes in FEV_1, FVC and FEV_1/FVC were calculated as the value at follow-up minus the value at study entry. The annual decline was calculated as the change divided by the numbers of years between examinations (10-28 follow-up years), expressed in terms of pp/year and ml/year, respectively, as ΔFEV_1pp/y, ΔFVCpp/y, ΔFEV_1ml/y, ΔFVCml/y and ΔFEV_1/FVC/y.

BMI

At study entry, participants were categorized based on BMI (kg/m^2) as normal weight (18.5≤BMI<25) and overweight/obese (BMI≥25). Additional analyses were also performed by dividing overweight/obese into the categories overweight (25≤BMI<30) and obese (BMI≥30), these results are presented in the supplemental material.

BMI change was calculated as the value at follow up minus the value at study entry. The annual BMI change was calculated by dividing the BMI change with the number of years between examinations (ΔBMI/y). The sample was also divided by quartiles for ΔBMI/y with cutoffs of Q1<0.042 (n=236), 0.042≤Q2<0.142 (n=237), 0.142≤Q3<0.274 (n=236) and Q4≥0.274 (n=236).

Other definitions

Data at study entry included sex, age, inhaled corticosteroids (ICS) use in the last 12 months, smoking habits (categorized as non-smoker, ex-smoker and current smoker) and original cohort (I-V).

Follow-up data included smoking pack-years which was calculated by multiplying the number of packs of cigarettes smoked per day by the number of years of smoking, as well as ICS use in the last 12 months. Occupational exposure to gas, dust or fumes (GDF) at follow-up was defined by the question "Have you been heavily exposed to dust, gases or fumes at your work (not including tobacco)?".

Changes in smoking habits from study entry to follow-up were defined as: never smokers (non-smokers on both occasions), ex-smokers (from non-smokers or ex-smokers to ex-smokers), quitters (from current smokers to ex-smokers), current smokers (from non-smokers or ex-smokers or current smokers to current smokers) and inconsistent (from ex-smokers or current smokers to non-smokers).

Statistical analyses

The analyses were made with IBM Statistical Package for the Social Sciences (SPSS) software version 26. Results were stratified by BMI categories (normal and overweight/obese) at study entry. The assumption of normal distributions for annual changes in BMI and lung function were assessed by histograms. Spearman correlation coefficients (rho) were used to evaluate correlations between annual changes in BMI and lung function. Comparisons of proportions of female sex, smoking categories and ICS use across BMI categories were done by Chi-squared test. Comparisons of means of BMI and lung function variables between BMI categories were done by independent T-test, and across quartiles of ΔBMI/y by ANOVA. P-values<0.05 were considered statistically significant. Separate linear regression models with each lung function value as dependent variable were constructed including ΔBMI/y, sex, age, changes in smoking habits, pack-years, ICS use, occupational GDF exposure at follow-up and original cohort as independent variables. Subgroup analyses were performed by additionally separating overweight from obese, by stratifying for sex and also by including only those gaining BMI during follow-up (ΔBMI/y>0).

RESULTS

Basic characteristics

In total, 62.5% were women among those with normal weight, compared to 48,5% of the overweight/obese. The overweight/obese were older, while non-smoking was more common in the normal weight group. Mean pack-years was similar in both BMI groups. ICS use at study entry was uncommon, 11.1% (normal weight) and 13.3% (overweight/obese), while at follow-up it increased to 42.1% and 45.9%, respectively (Table 1). Basic characteristics are presented separately for overweight and obese subgroups in Supplemental table 1.

BMI and lung function

The overweight/obese had lower FEV_1 at study entry (pp and ml) and follow-up (pp) than the normal weight group (Table 2). However, subjects with normal weight had a larger ΔBMI/y and tended to have faster (i. e. worse) ΔFEV_1pp/y than the overweight/obese, while there was no difference in ΔFEV_1ml/y. When studying the overweight and obese separately, the obese presented the lowest FEV_1 (pp and ml) at study entry but slower ΔBMI/y and ΔFEV_1/y (pp and ml) than both the overweight and the normal weight groups. Similar results were seen regarding FVC at study entry and follow-up, while no significant differences between BMI groups were seen regarding ΔFVC/y (pp or ml) and ΔFEV1/FVC/y (Table 2, Supplemental table 2). Distributions of changes in BMI, FEV_1, FVC and FEV_1/FVC among subjects with normal weight and overweight/obesity, respectively, are shown in Supplemental figure 2.

Associations between changes in BMI and lung function

Correlation analysis between annual changes in BMI and FEV_1 were performed separately among those with normal weight and overweight/obesity. These analyses yielded a rho in the overweight/obese of -0.246 ($p<0.001$) for ΔFEV_1pp/y and -0.196 ($p<0.001$) for ΔFEV_1ml/y, compared to -0.093 ($p=0.040$) for ΔFEV_1pp/y and -0.030 ($p=0.516$) for ΔFEV_1ml/y in the normal weight group (Figure 1). Correlation analysis of ΔBMI/y with ΔFVCpp/y, ΔFVCml/y and ΔFEV_1/FVC/y showed the same pattern as for FEV_1 with significant stronger negative correlations for FVC (pp and ml) in the overweight/obese. In contrast, ΔFEV_1/FVC/y had a significant but weak negative correlation with ΔBMI/y among those with normal weight (rho=-0.104 $p=0.022$) but not among the overweight/obese (rho=-0.026, $p=0.572$) (Supplemental figure 2).

To compare those who gained most BMI and those who gained the least or even decreased their BMI, the sample was divided by quartiles of ΔBMI/y. Among the overweight/obese, a linear trend was seen where the larger ΔBMI/y (from Q1 to Q4), the faster ΔFEV_1/y (pp and ml). No linear trend was seen among those with normal weight (Table 3). Similar results were seen for ΔFVC/y (pp and ml), while no linear trends in ΔFEV1/FVC/y or pack-years were observed (Supplemental table 3).

Adjusted associations between changes in BMI and lung function

To further analyze the relationship between ΔBMI/y and annual lung function decline, adjusted regression models were constructed. The associations between ΔBMI/y and respectively ΔFEV_1pp/y and ΔFEV_1ml/y remained significant after adjustment, but were about twice as strong among the overweight/obese compared to those with normal weight. Regarding associations between ΔBMI/y with ΔFVCpp/y and ΔFVCml/y, significance remained only in the overweight/obese, while no associations were found with ΔFEV_1/FVC/y (Table 4). Adjusted regression curves for associations between ΔBMI/y and lung function outcomes are illustrated in figure 2 (regression coefficients are shown in Supplemental table 4).

Regression analyses in subgroups

As BMI increase was of particular interest, analyses including only subjects with a BMI increase between study entry and follow-up (n=782) were performed. The overweight/obese had strong associations between ΔBMI/y with ΔFEV_1/y and ΔFVC/y (pp and ml) while no significance was seen in their normal weight counterparts. No significant associations were seen regarding ΔFEV_1/FVC/y (Table 5).

Stratified analyses were also performed to see if the observed associations were present in both sexes. All lung function values, now also with the addition of ΔFEV1/FVC/y, were associated to ΔBMI/y among both women and men with overweight/obesity (Supplemental table 5).

Additionally overweight and obese were studied separately. Here, the adjusted associations between ΔBMI/y with ΔFEV_1/y and ΔFVC/y (pp and ml) remained significant and stronger compared to the normal weight group for both subgroups. No associations were seen for ΔFEV_1/FVC/y (Supplemental table 6).

DISCUSSION

This long-term prospective asthma cohort study highlights BMI increase as a risk factor for a worse decline in both FEV_1 and FVC particularly among those who are overweight or obese at study entry, independently of ICS use and several other factors. BMI increase associated weakly with the decline in FEV_1, but not FVC, also in those with normal weight, while BMI change (increase or decrease) did not associate with the decline in FEV_1/FVC regardless of having normal weight, overweight or obesity at study entry.

A BMI ≥25 is associated with higher incidence and prevalence of asthma[31,32] and often a more severe clinical presentation among adults with asthma[7,10,18]. Lower lung function levels in overweight/obese than in normal weight adults have been observed, however with a greater difference among those without asthma than among those with asthma[33], probably related to the fact that adults with asthma generally have lower lung function and thus are less likely to have a large further reduction. In our study, overweight and obese subjects were grouped together in the main analyses both to maintain equal sample size as those with normal weight, and also as it is known that features of silent systemic inflammation as well as other morbidities associated to obesity can be present not only in obese but also in overweight subjects[34]. Whether BMI change affects lung function decline in the long-term among adults with asthma, and whether this association differs between those with overweight/obesity and those with normal weight, has however not been studied before[25]. Our study enabled such analyses and revealed that BMI increase associates stronger with faster decline in both FEV_1 and FVC among those who were overweight or obese than among those who were normal weight at study entry, which are novel results. Interestingly, when overweight and obese were studied separately, the association between BMI change and lung function decline tended to be equally strong or even stronger for the overweight subgroup compared to the obese. Thus, although there is emerging evidence that overweight may associate with a more favorable asthma prognosis in terms of less mortality compared to normal weight[35], this was not observed in our study which assessed prognosis in terms of lung function.

The effect of BMI increase on lung function has been studied prospectively among healthy adults using the 10-year follow-up of the US CARDIA study[14] and the 6-year follow-up of the Humboldt cohort recruited from the general population[36]. These two studies showed that both BMI level at study entry as well as weight gain during follow-up related to changes in lung function. In the CARDIA study, obesity at study entry associated strongly with excess decline in FVC but not

FEV_1, while the Humboldt study showed such associations for decline in both FVC and FEV_1. Although not stratifying for baseline BMI group, both studies showed that large weight gain during follow-up associated with excess decline in FEV_1 as well as FVC[14,36], which is well in line with our results for adults with asthma with an even longer follow-up period.

Regarding the association between changes in BMI and lung function among adults with asthma, there are utmost few prospective studies. Within the ECRHS[15], 638 asthmatics were followed from 1998 to 2002 and were stratified by having airflow obstruction or not at study entry. In line with our results, they showed that those with normal weight had faster FEV_1 decline during follow-up than the obese. Further, they also showed that those with largest BMI increase also had the fastest FEV_1 decline. In contrast to our study, they did not stratify for BMI at study entry and did not perform analysis of association between BMI change and decline in FEV_1, and further they did not analyze changes in FVC or FEV_1/FVC[15]. Our study confirmed a strong association between BMI increase and FEV_1 decline in adults with asthma, but also revealed that this association was twice as strong among the overweight/obese at study entry compared to normal weight subjects. In addition, regarding FVC the corresponding associations in our study were only seen in those with overweight and obesity at study entry. As no associations between BMI change and FEV_1/FVC were seen in our study this implies that BMI increase may mostly relate to the development of a restrictive rather than obstructive lung function pattern.

Asthma is a heterogeneous condition with different phenotypes, including the non-Th2-related (obesity-related and neutrophilic)[16]. The obesity-related asthma phenotype is often complicated with the presence of several obesity-related comorbidities such as diabetes or ischemic heart disease[17,18]. It is also known that e. g. obstructive sleep apnea syndrome and gastro-esophageal reflux, which are common comorbidities particularly in severe asthma[37] may impact the association between BMI and lung function. Smoking has also adverse effects on lung function among adults with asthma[4], and was more common among the overweight/obese than those with normal weight in our study. Further, obesity-related asthma is known more often to be therapy-resistant with regard to corticosteroid use due to less eosinophilic inflammation[19–21]. Obesity have also physiological effects on lung mechanics as the increase of the thoracic and abdominal fat tissue increases the compression of the lungs and therefore reduces lung volumes[12,38]. These premises remark the potential of weight loss as one of the non-pharmacological treatment alternatives for asthma due to the potential positive long-term effect on lung function in overweight and obese subjects[23,39].

Limitations of our study include that BMI may not be the most accurate indicator for determining overweight and obesity as it may account poorly for the amount and distribution of fat tissue[40]. However, BMI is widely used and results are directly applicable to clinical practice. Further, different guidelines and types of spirometers were used at study entry and follow-up resulting in potential systematic differences in lung function measurements between examinations[41]. One example is the implementation of 6 seconds of forced expiratory time during FVC measuring at follow-up, which can be a possible explanation why some subjects presented with a higher FVC at follow-up. Still, as this applies for all subjects, the association with change in BMI and the comparability between BMI groups should not be affected.

The long follow-up time may yield a healthy survivor effect both regarding lung function and BMI. This was addressed in previous publications that implied that non-participants at follow-up were more frequently overweight or obese and had lower lung function at study entry than participants. Therefore subjects with lower lung function and overweight/obesity may be underrepresented at follow-up[26,42]. This means that the observed associations between changes in BMI and lung function, which in our study seem to be moderate, in fact might be stronger if the healthy survivor effect would not be present.

That study entry was between 1986 and 2001 from five different cohorts can be another potential weakness as treatment guidelines changed during the recruitment period. A cohort effect of successively improved lung function in the general population may be present as large scale studies have presented such evidence[43]. In order to account for this, the regression analyses were adjusted for original cohorts. Further, the exclusion of 61 subjects from the study as they had underweight (BMI<18.5) or lacked valid measurements of BMI or FEV_1pp at follow-up may reduce the statistical power and could affect the results. However, we prioritized using a complete case method as we could use real measurements and exclusively focus on the normal weight and overweight/obese categories.

Strengths of our study include high participation rate and large sample size which allows for stratification while maintaining similar number of subjects in both BMI groups. The long follow-up can also be regarded as a strength as there are few prospective studies allowing for 10–28-year follow-ups. The large amount of data collected enabled us to adjust for several factors that could act as potential confounders or mediators, e.g. smoking habits which is known to be strongly associated

with decreased lung function. Finally, validation studies regarding self-reported physician diagnosed asthma within OLIN have shown that the positive predictive value is >90% among adults[44]

In conclusion, BMI increase associates with a faster decline in FEV_1 and FVC but not in FEV_1/FVC in adults with asthma. The association between BMI change and decline in FEV_1 and FVC is stronger among those with overweight or obesity in comparison with their normal weight counterparts. Maintaining or achieving a normal weight should be considered as an important cornerstone in asthma management to avoid excess lung function decline in the long run.

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LEGENDS TO FIGURES

Figure 1. Correlations of ΔBMI/y with ΔFEV1pp/y and FEV1ml/y by BMI group presented as scatterplots with rho coefficients and p-values. ● Normal weight (BMI=18.5-24.9) n=485. ● Overweight/obese (BMI≥25) n=460.

Figure 2. Adjusted regression curves of ΔBMI/y with ΔFEV1pp/y, ΔFEV1ml/y, ΔFVCpp/y and ΔFVCml/y by BMI groups. ▒ Normal weight (BMI=18.5-24.9) n=485. ▉ Overweight/obese (BMI≥25) n=460. Regression curves are presented along with 95% confidence intervals. Only significant factors were included in the models for each BMI group (Supplemental table 2).

TABLES

Table 1. Basic characteristics at study entry and follow-up by BMI groups at study entry

		Normal weight n=485		Overweight/obese n=460		p-value
Sex	Women	303	(62.5)	223	(48.5)	**<0.001**
Mean age at study entry (SD)		37.7	(11.4)	43.3	(11.2)	**<0.001**
Mean age at follow-up (SD)		56.6	(12.3)	61.4	(11.9)	**<0.001**
Overweight/obese at follow-up		283	(58.4)	442	(96.1)	**<0.001**
Smoking habits at study entry	Non-smoker	238	(49.1)	186	(40.4)	
	Ex-smoker	113	(23.3)	158	(34.3)	
	Smoker	134	(27.6)	116	(25.2)	**0.001**
Smoking habits at follow-up	Non-smoker	251	(51.8)	202	(43.9)	
	Ex-smoker	177	(36.5)	209	(45.4)	
	Smoker	57	(11.8)	49	(10.7)	**0.019**
Mean packyears at follow-up (SD)*		16.5	(14.9)	17.6	(16.6)	0.436
ICS use at study entry		54	(11.1)	61	(13.3)	0.318
ICS use at follow-up		204	(42.1)	211	(45.9)	0.238

Frequencies presented as n(%) unless otherwise stated. SD=Standard deviation. Bold values indicate p<0.05.
BMI=Body mass index. Normal weight (BMI=18.5-24.9). Overweight/obese (BMI≥25). ICS=Inhaled corticosteroids.
*Among ever smokers with: Normal weight n=234. Overweight/obese n=258.

Table 2. BMI and lung function by BMI groups at study entry

	Normal weight n=485		Overweight/obese n=460		p-value
Years between examinations	18.8	(4.4)	18.1	(4.3)	**0.011**
BMI at study entry	22.6	(1.7)	28.9	(3.3)	**<0.001**
BMI at follow-up	25.9	(3.3)	31.5	(4.9)	**<0.001**
ΔBMI/y	0.179	(0.165)	0.149	(0.242)	**0.025**
FEV1pp at study entry	90.4	(13.7)	86.6	(13.7)	**<0.001**
FEV1pp at follow-up	88.4	(16.6)	85.8	(15.7)	**0.015**
ΔFEV1pp/y	-0.099	(0.571)	-0.023	(0.678)	0.062
FEV1ml at study entry	3 272	(818)	3 163	(804)	**0.040**
FEV1ml at follow-up	2 749	(824)	2 651	(797)	0.061
ΔFEV1ml/y	-27.3	(20.0)	-27.7	(23.1)	0.788
FVCpp at study entry	89.0	(11.5)	85.3	(11.8)	**<0.001**
FVCpp at follow-up	95.5	(15.1)	91.7	(14.9)	**<0.001**
ΔFVCpp/y	0.377	(0.603)	0.386	(0.785)	0.847
FVCml at study entry	4 032	(953)	3 939	(957)	0.133
FVCml at follow-up	3 849	(1057)	3 706	(1060)	**0.038**
ΔFVCml/y	-8.3	(27.0)	-11.5	(36.0)	0.119
FEV1/FVC at study entry	0.812	(0.076)	0.805	(0.074)	0.143
FEV1/FVC at follow-up	0.714	(0.093)	0.717	(0.082)	0.643
ΔFEV1/FVC/y	-0.005	(0.004)	-0.005	(0.004)	0.122

Results presented as Mean (SD). SD=Standard deviation. Bold values indicate p<0.05.
ΔBMI/y=Annual BMI change. BMI=Body mass index. Normal weight (BMI=18.5-24.9). Overweight/obese (BMI≥25).
ΔFEV1pp/y=Annual FEV1pp decline. ΔFVCpp/y= Annual FVCpp decline. pp=% of predicted.
ΔFEV1ml/y=Annual FEV1ml decline. ΔFVCml/y= Annual FVCml decline. ml=milliliters.
ΔFEV1/FVC/y= Annual FEV1/FVC decline.

Table 3. Mean changes in BMI and changes in lung function within quartiles based on ΔBMI/y, by BMI groups at study entry

		Quartiles of ΔBMI/y				p-value
Normal weight		Q1 (n=90)	Q2 (n=140)	Q3 (n=134)	Q4 (n=121)	
	ΔBMI/y	-0.024 (0.055)	0.091 (0.029)	0.206 (0.037)	0.402 (0.119)	**<0.001**
	ΔFEV1pp/y	-0.003 (0.577)	-0.132 (0.535)	-0.096 (0.589)	-0.136 (0.584)	0.322
	ΔFEV1ml/y	-23.6 (20.2)	-29.8 (18.9)	-27.9 (18.7)	-26.6 (21.9)	0.127
Overweight/ obese		Q1 (n=146)	Q2 (n=97)	Q3 (n=102)	Q4 (n=115)	
	ΔBMI/y	-0.091 (0.137)	0.095 (0.029)	0.195 (0.036)	0.457 (0.193)	**<0.001**
	ΔFEV1pp/y	0.125 (0.695)	0.030 (.625)	-0.036 (0.674)	-0.244 (0.651)	**<0.001**
	ΔFEV1ml/y	-24.4 (21.2)	-26.8 (20.2)	-27.6 (26.2)	-32.8 (24.0)	**0.032**

Results presented as mean (SD). SD=Standard deviation. Bold values indicate p<0.05.

P-values are used to test differences in mean values across quartiles of ΔBMI/y by ANOVA.

Quartile 1: ΔBMI/y < 0.042, Quartile 2: 0.042 <= ΔBMI/y < 0.142, Quartile 3: 0.142 <= ΔBMI/y < 0.274, Quartile 4: ΔBMI/y => 0.274.

ΔBMI/y=Annual BMI change. BMI=Body mass index. Normal weight (BMI=18.5-24.9). Overweight/obese (BMI≥25).

ΔFEV1pp/y=Annual FEV1pp decline. ΔFEV1ml/y=Annual FEV1ml decline. pp=% of predicted. ml=milliliters.

Table 4. Association between ΔBMI/y and annual decline in lung function after adjusting for other factors among BMI groups

	ΔBMI/y			
	Normal weight		Overweight/obese	
	B	95% Confidence Interval	B	95% Confidence Interval
ΔFEV1pp/y	-0.356	**(-0.663 - -0.049)**	-0.747	**(-1.003 - -0.491)**
ΔFEV1ml/y	-14.662	**(-24.903 - -4.420)**	-24.809	**(-33.608 - -16.010)**
ΔFVCpp/y	-0.102	(-0.436 - 0.232)	-0.719	**(-1.026 - -0.413)**
ΔFVCml/y	-10.091	(-23.509 - 3.328)	-34.422	**(-48.073 - -20.772)**
ΔFEV1/FVC/y	-0.002	(-0.004 - 0.000)	-0.000	(-0.002 - 0.002)

B=Beta-coefficient from linear regression models. Significant values in bold

ΔBMI/y=Annual BMI change. BMI=Body mass index. Normal weight (BMI=18.5-24.9). Overweight/obese (BMI≥25).

ΔFEV1pp/y=Annual FEV1pp decline. ΔFVCpp/y= Annual FVCpp decline. pp=% of predicted.

ΔFEV1ml/y=Annual FEV1ml decline. ΔFVCml/y= Annual FVCml decline. ml=milliliters.

ΔFEV1/FVC/y= Annual FEV1/FVC decline.

Adjusting factors: Sex, age, changes in smoking habits, pack-years, ICS use, occupational GDF exposure at follow-up and original cohort.

Table 5. Association between ΔBMI/y and annual decline in lung function after adjusting for other factors among only BMI gainers by BMI groups

	ΔBMI/y			
	Normal weight n=432		Overweight/obese n=350	
	B	95% Confidence Interval	B	95% Confidence Interval
ΔFEV1pp/y	-0.287	(-0.642 - 0.069)	-0.731	**(-1.098 - -0.364)**
ΔFEV1ml/y	-10.745	(-22.882 - 1.392)	-22.437	**(-35.813 - -9.062)**
ΔFVCpp/y	-0.043	(-0.430 - 0.343)	-0.718	**(-1.164 - -0.271)**
ΔFVCml/y	-4.857	(-20.482 - 10.767)	-35.251	**(-55.969 - -14.533)**
ΔFEV1/FVC/y	-0.002	(-0.005 - 0.001)	0.000	(-0.002 - 0.003)

B=Beta-coefficient from linear regression models. Significant values in bold.

ΔBMI/y=Annual BMI change. BMI=Body mass index. Normal weight (BMI=18.5-24.9). Overweight/obese (BMI≥25). BMI gainer (ΔBMI/y>0).

ΔFEV1pp/y=Annual FEV1pp decline. ΔFVCpp/y= Annual FVCpp decline. pp=% of predicted.

ΔFEV1ml/y=Annual FEV1ml decline. ΔFVCml/y= Annual FVCml decline. ml=milliliters.

ΔFEV1/FVC/y= Annual FEV1/FVC decline.

Adjusting factors: Sex, age, changes in smoking habits, pack-years, ICS use, occupational GDF exposure at follow-up and original cohort.

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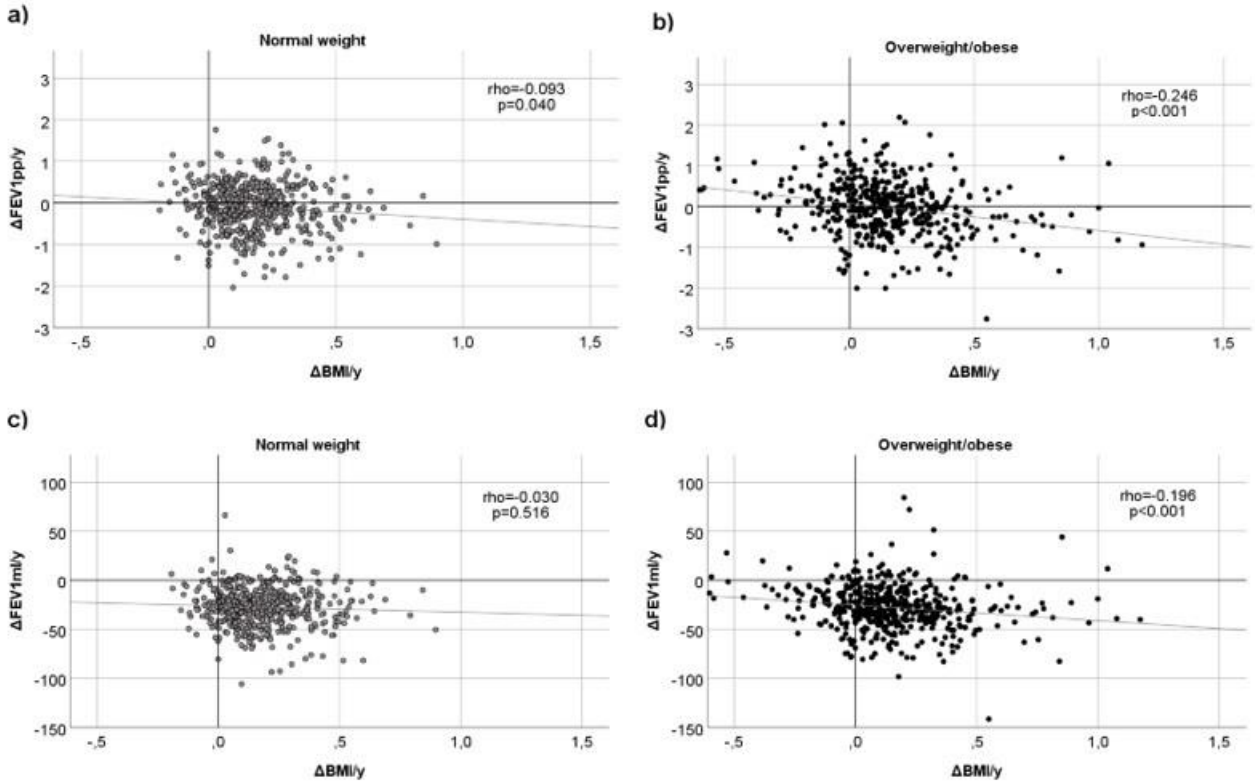


Figure 1. Correlations of ΔBMI/y with ΔFEV1pp/y and FEV1ml/y by BMI group presented as scatterplots with rho coefficients and p-values. ● Normal weight (BMI=18.5-24.9) n=485. ● Overweight/obese (BMI≥25) n=460.

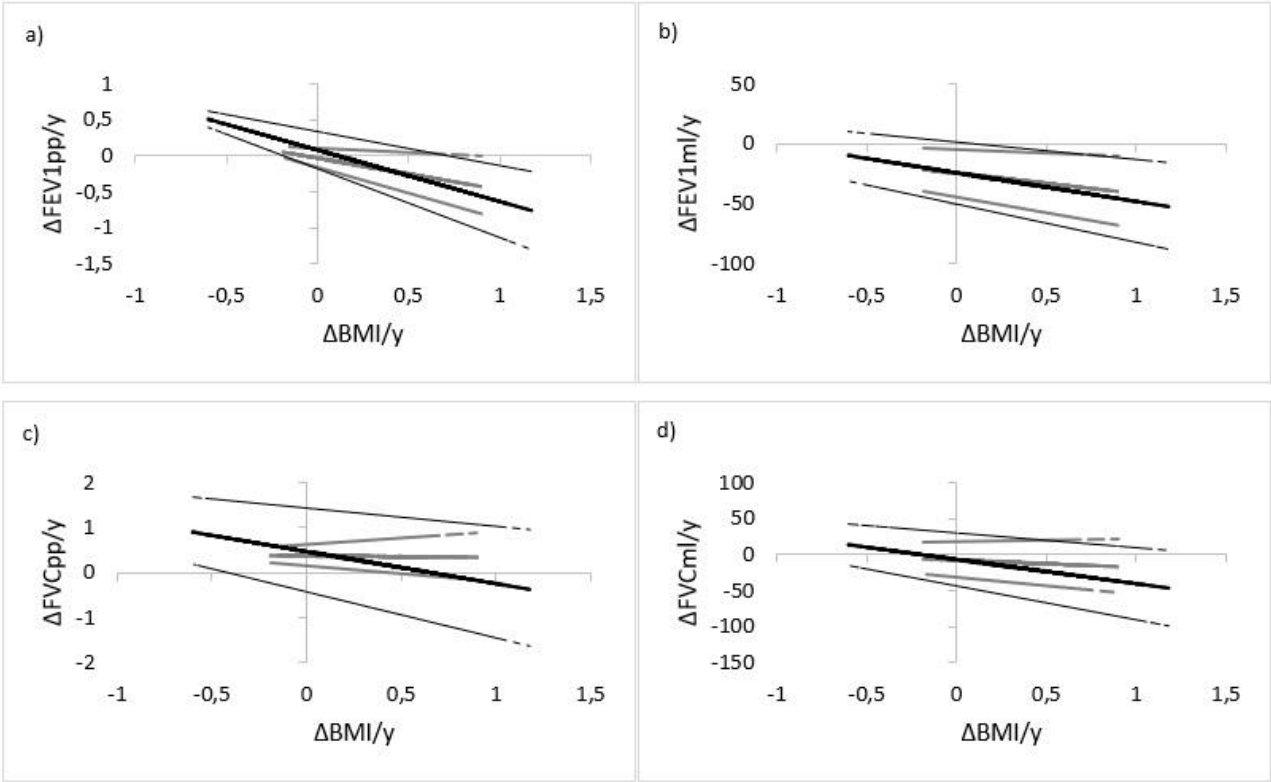
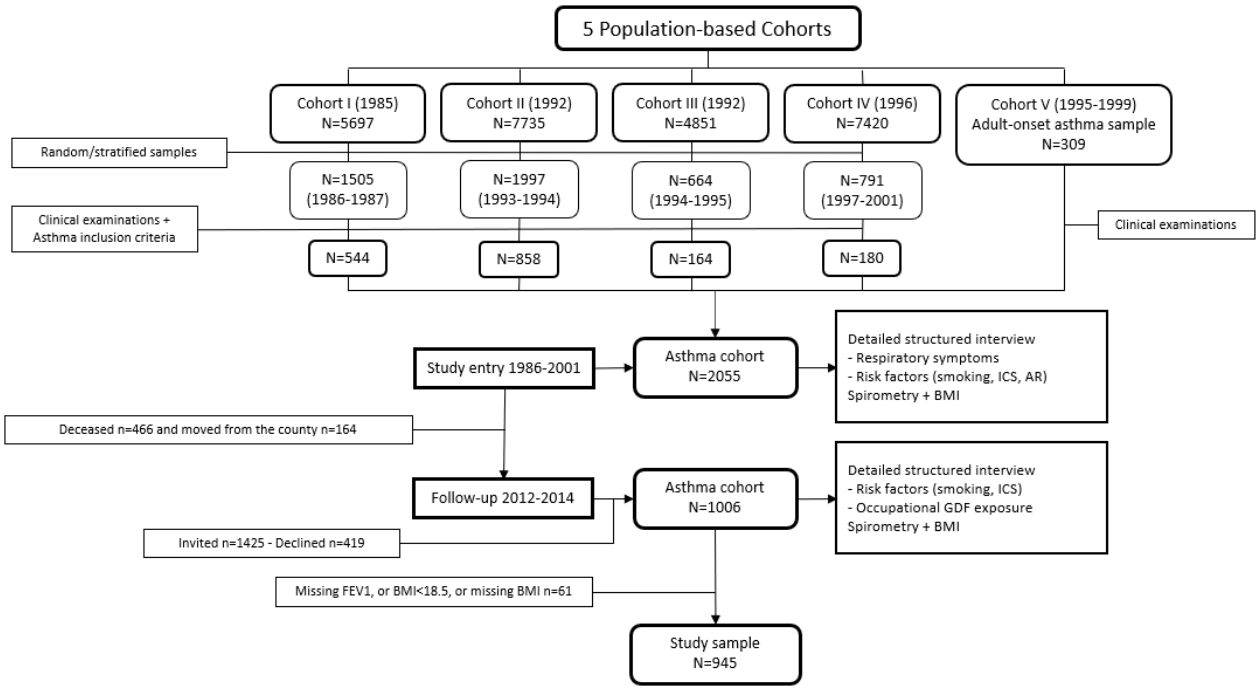


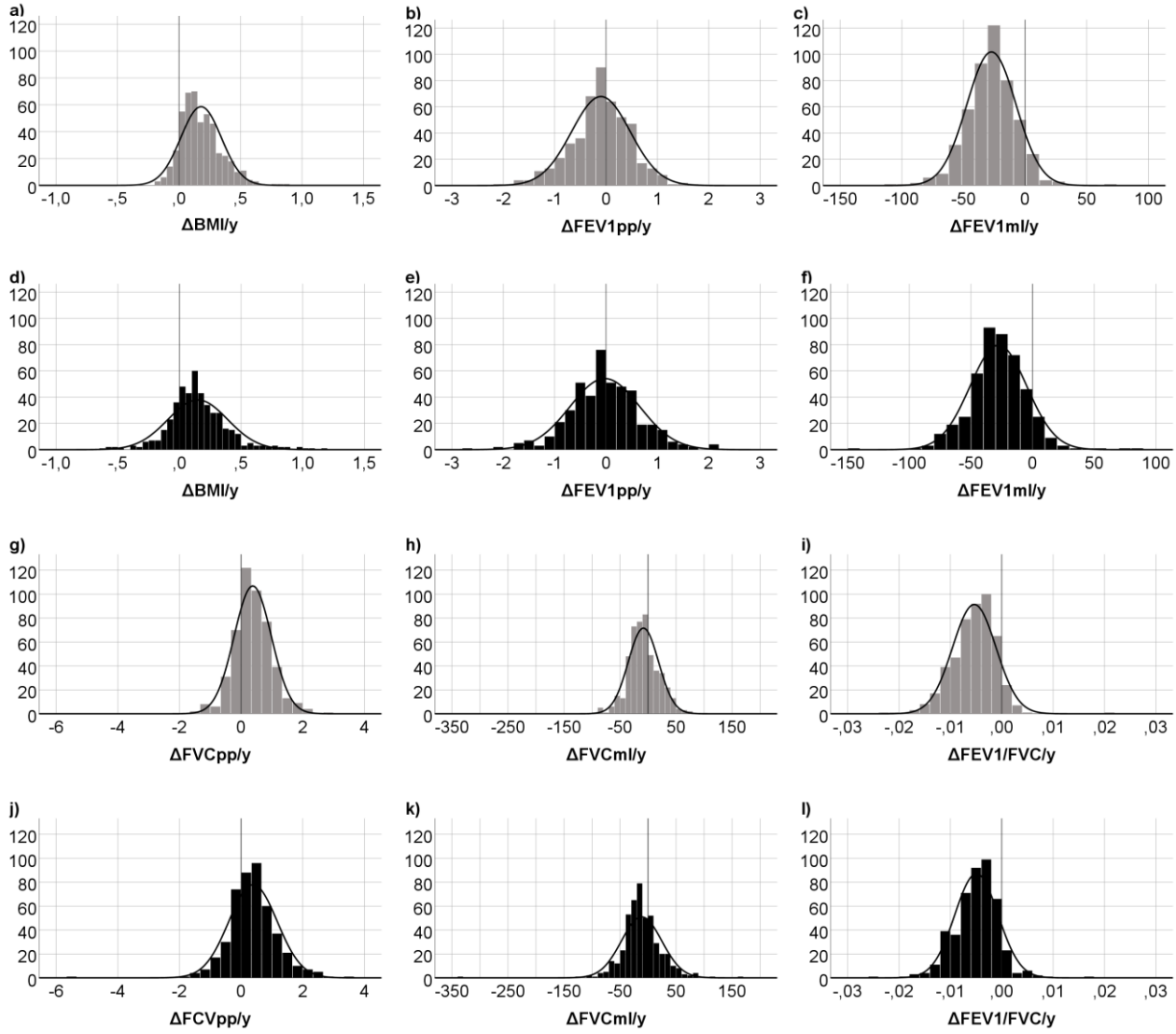
Figure 2. Adjusted regression curves of ΔBMI/y with ΔFEV1pp/y, ΔFEV1ml/y, ΔFVCpp/y and ΔFVCml/y by BMI groups. ▒ Normal weight (BMI=18.5-24.9) n=485. ▉ Overweight/obese (BMI≥25) n=460. Regression curves are presented along with 95% confidence intervals. Only significant factors were included in the models for each BMI group (Supplemental table 2).

SUPPLEMENTAL MATERIAL

Supplemental figures

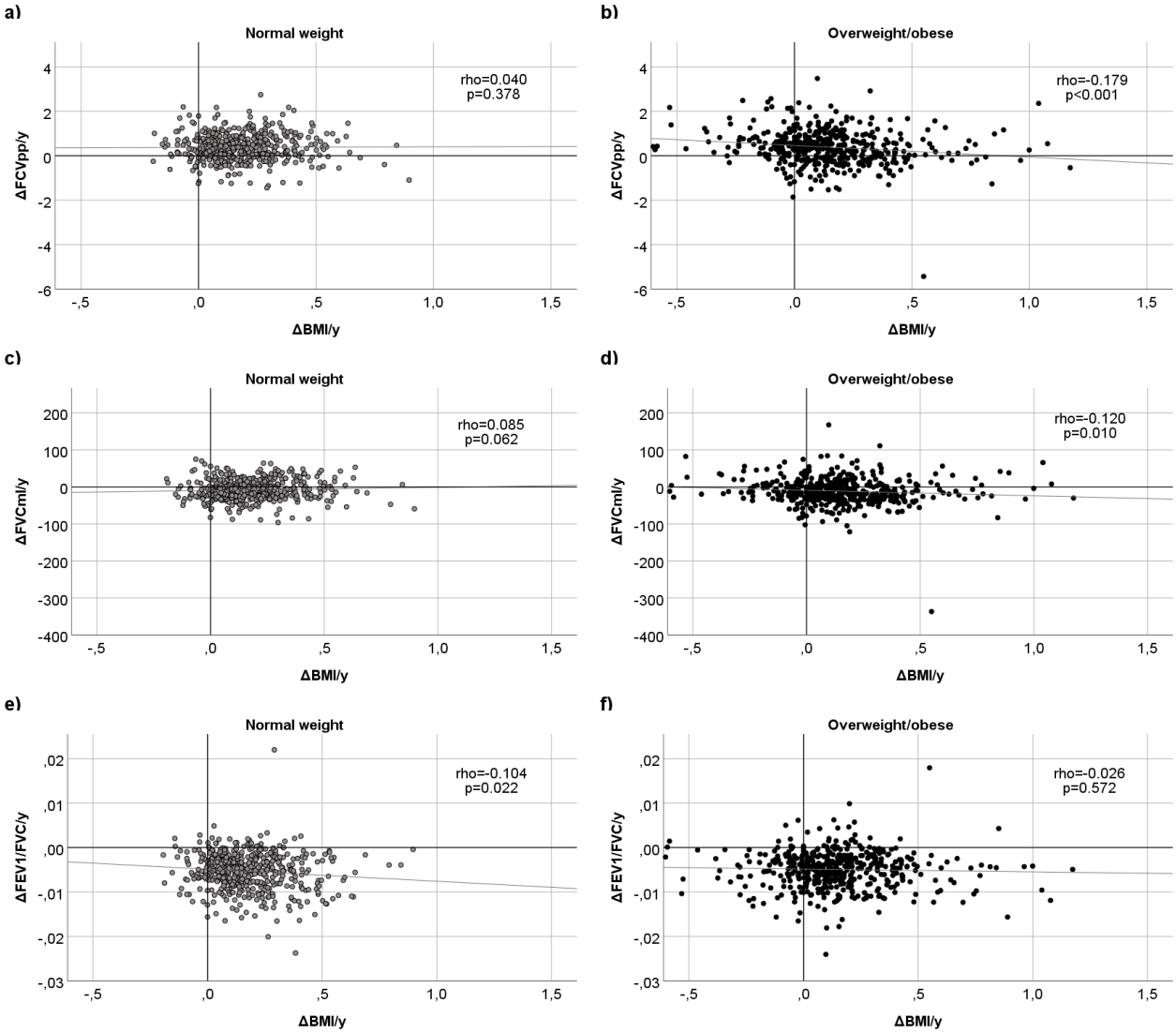


Supplemental figure 1. Study flow chart.

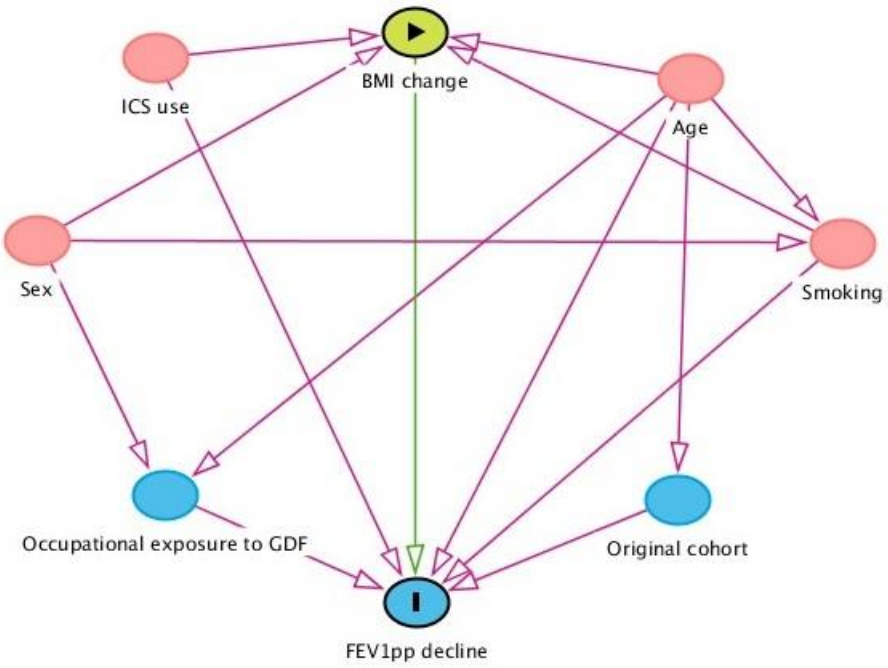


Supplemental figure 2. Distributions of ΔBMI/y, ΔFEV1pp/y, ΔFEV1ml/y, ΔFVCpp/y, ΔFVCml/y and ΔFEV1/FVC/y by BMI group.

Normal weight (BMI=18.5-24.9) n=485. Overweight/obese (BMI≥25) n=460.



Supplemental figure 3. Correlations of ΔBMI/y with ΔFVCpp/y, ΔFVCml/y and ΔFEV1/FVC/y by BMI group presented as scatterplots with rho coefficients and p-values. ● Normal weight (BMI=18.5-24.9) n=485. ● Overweight/obese (BMI≥25) n=460.



Supplemental figure 4. Directed acyclic graph showing interaction rationale between changes of BMI and lung function with their corresponding related factors.

Supplemental tables

Supplemental table 1. Basic characteristics at study entry and follow-up among overweight and obese groups, with p-values representing comparisons to the normal weight group at study entry

		Overweight/obese n=460			
		Overweight n=327	p-value	Obese n=133	p-value
Sex	Women	145 (44.3)	**<0.001**	78 (58.6)	0.421
Mean age at study entry (SD)		43.3 (11.2)	**<0.001**	43.3 (11.2)	**<0.001**
Mean age at follow-up (SD)		61.6 (11.9)	**<0.001**	61.1 (11.9)	**<0.001**
Smoking habits at study entry	Non-smoker	133 (40.7)		53 (39.8)	
	Ex-smoker	109 (33.3)		49 (36.8)	
	Smoker	85 (26.0)	**0.006**	31 (23.3)	**0.007**
Smoking habits at follow-up	Non-smoker	142 (43.4)		60 (45.1)	
	Ex-smoker	153 (46.8)		56 (42.1)	
	Smoker	32 (9.8)	**0.014**	17 (12.8)	0.391
Mean packyears at follow-up (SD)*		16.6 (14.0)	0.970	20.3 (21.8)	0.170
ICS use at study entry		38 (11.6)	0.830	23 (17.3)	0.057
ICS use at follow-up		145 (44.3)	0.520	66 (49.6)	0.119

Frequencies presented as n(%) unless otherwise stated. SD=Standard deviation.

BMI=Body mass index. Overweight (BMI=25-29.9). Obese (BMI≥30). ICS=Inhaled corticosteroids.

P-values refer to comparison with the normal weight group. Bold values indicate p<0.05.

*Among ever smokers: Overweight n=185. Obese n=73.

Supplemental table 2. BMI and lung function change of overweight and obese groups, with p-values representing comparisons to the normal weight group at study entry

	Elevated BMI n=460					
	Overweight n=327		p-value	Obese n=133		p-value
Years between examinations	18.2	(4.3)	0.064	17.7	(4.2)	**0.011**
BMI at study entry	27.2	(1.4)	**<0.001**	33.0	(3.0)	**<0.001**
BMI at follow-up	30.0	(3.9)	**<0.001**	35.0	(5.4)	**<0.001**
ΔBMI/y	0.161	(0.216)	0.194	0.119	(0.296)	**0.026**
FEV1pp at study entry	87.2	(13.7)	**0.001**	85.1	(13.6)	**<0.001**
FEV1pp at follow-up	85.7	(15.7)	**0.022**	86.0	(15.7)	0.123
ΔFEV1pp/y	-0.055	(0.659)	0.322	0.056	(0.718)	**0.023**
FEV1ml at study entry	3 230	(806)	0.467	3 000	(778)	**0.001**
FEV1ml at follow-up	2 691	(802)	0.314	2 552	(780)	**0.011**
ΔFEV1ml/y	-28.8	(22.4)	0.335	-25.0	(24.5)	0.316
FVCpp at study entry	86.3	(11.7)	**0.002**	82.6	(11.7)	**<0.001**
FVCpp at follow-up	92.1	(14.9)	**0.001**	90.9	(14.7)	**0.001**
ΔFVCpp/y	0.347	(0.797)	0.558	0.482	(0.748)	0.136
FVCml at study entry	4 046	(965)	0.838	3 674	(887)	**<0.001**
FVCml at follow-up	3 783	(1082)	0.387	3 518	(981)	**0.001**
ΔFVCml/y	-13.0	(37.2)	**0.050**	-7.9	(32.7)	0.904
FEV1/FVC at study entry	0.800	(0.077)	**0.035**	0.816	(0.064)	0.568
FEV1/FVC at follow-up	0.714	(0.084)	0.985	0.723	(0.078)	0.235
ΔFEV1/FVC/y	-0.005	(0.004)	0.068	-0.005	(0.004)	0.797

Results presented as Mean (SD). SD=Standard deviation.

P-values refer to comparison with the normal weight group. Bold values indicate p<0.05.

ΔBMI/y=Annual BMI change. BMI=Body mass index. Overweight (BMI=25-29.9). Obese (BMI≥30).

ΔFEV1pp/y=Annual FEV1pp decline. ΔFVCpp/y= Annual FVCpp decline. pp=% of predicted.

ΔFEV1ml/y=Annual FEV1ml decline. ΔFVCml/y= Annual FVCml decline. ml=milliliters.

ΔFEV1/FVC/y= Annual FEV1/FVC decline.

Supplemental table 3. Changes in FVC, FEV_1/FVC and pack-years at follow-up within quartiles based on ΔBMI/y, by BMI groups at study entry

		Quartiles of ΔBMI/y								p-value
Normal weight		Q1 (n=90)		Q2 (n=140)		Q3 (n=134)		Q4 (n=121)		
	ΔFCVpp/y	0.351	(0.616)	0.350	(0.547)	0.391	(0.586)	0.413	(0.677)	0.815
	ΔFVCml/y	-8.5	(29.4)	-11.4	(24.1)	-8.2	(24.7)	-4.5	(30.5)	0.245
	ΔFEV1/FVC/y	-0.005	(0.004)	-0.005	(0.003)	-0.006	(0.004)	-0.006	(0.005)	0.188
	Pack-years*	8.3	(14.9)	7.2	(12.7)	7.6	(13.0)	9.0	(12.8)	0.729
	Pack-years**	19.1	(17.4)	16.3	(14.8)	15.0	(14.9)	16.8	(13.3)	0.597
Overweight/ obese		Q1 (n=146)		Q2 (n=97)		Q3 (n=102)		Q4 (n=115)		
	ΔFCVpp/y	0.515	(0.764)	0.431	(0.734)	0.354	(0.718)	0.213	(0.880)	**0.018**
	ΔFVCml/y	-8.4	(31.5)	-8.6	(35.3)	-13.2	(33.3)	-16.3	(43.3)	0.264
	ΔFEV1/FVC/y	-0.005	(0.004)	-0.005	(0.004)	-0.005	(0.005)	-0.005	(0.004)	0.801
	Pack-years*	12.0	(19.2)	9.9	(13.4)	9.2	(12.3)	7.9	(13.0)	0.171
	Pack-years**	21.1	(21.3)	16.0	(14.0)	16.4	(12.4)	15.6	(14.7)	0.152

Results presented as mean (SD). SD=Standard deviation. Bold values indicate p<0.05.

P-values are used to test differences in mean values across quartiles of ΔBMI/y by ANOVA.

Quartile 1: ΔBMI/y < 0.042, Quartile 2: 0.042 <= ΔBMI/y < 0.142, Quartile 3: 0.142 <= ΔBMI/y < 0.274, Quartile 4: ΔBMI/y => 0.274.

ΔBMI/y=Annual BMI change. BMI=Body mass index. Normal weight (BMI=18.5-24.9). Overweight/obese (BMI≥25).

ΔFVCpp/y= Annual FVCpp decline. ΔFVCml/y= Annual FVCml decline. ΔFEV1/FVC/y= Annual FEV1/FVC decline.

pp=% of predicted. ml=milliliters.

*Among all. **Among ever smokers with: Normal weight n=234. Overweight/obesity n=258.

Supplemental table 4. Regression estimates for ΔBMI/y and other factors significantly associated with lung function outcomes, by BMI groups

		Factor	B	95% Confidence Interval
Normal weight	ΔFEV1pp/y	ΔBMI/y	-0.425	**(-0.719 - -0.131)**
		Sex	-0.259	**(-0.359 - -0.159)**
		Current smokers	-0.389	**(-0.539 - -0.238)**
	ΔFEV1ml/y	ΔBMI/y	-16.451	**(-26.509 - -6.393)**
		Age at follow-up	-0.497	**(-0.635 - -0.359)**
		Sex	-9.622	**(-12.994 - -6.251)**
		Current smokers	-10.549	**(-15.572 - -5.525)**
		Cohort II	-4.866	**(-8.212 - -1.520)**
	ΔFVCpp/y	ΔBMI/y	-0.033	(-0.352 - 0.286)
		Sex	-0.181	**(-0.292 - -0.070)**
		ICS use at follow-up	-0.138	**(-0.247 - -0.030)**
		Cohort IV	0.237	**(0.062 - 0.411)**
		Cohort V	0.194	**(0.056 - 0.333)**
	ΔFVCml/y	ΔBMI/y	-10.089	(-23.315 - 3.136)
		Age at follow-up	-1.006	**(-1.186 - -0.827)**
		Sex	-6.462	**(-10.887 - -2.038)**
		ICS use at follow-up	-4.438	**(-8.779 - -0.097)**
	ΔFEV1/FVC/y	ΔBMI/y	-0.003	**(-0.005 - 0.000)**
		Pack-years	-0.000	**(0.000 - 0.000)**
		Cohort IV	-0.001	(-0.002 - 0.000)
Overweight/obese	ΔFEV1pp/y	ΔBMI/y	-0.708	**(-0.948 - -0.467)**
		Sex	-0.253	**(-0.369 - -0.137)**
		Current smokers	-0.351	**(-0.539 - -0.163)**
		Cohort III	0.191	(-0.002 - 0.383)
		Cohort IV	0.334	**(0.149 - 0.518)**
		Cohort V	0.213	**(0.069 - 0.357)**
	ΔFEV1ml/y	ΔBMI/y	-23.440	**(-32.252 - -14.628)**
		Age at follow-up	-0.482	**(-0.663 - -0.301)**
		Sex	-6.832	**(-10.883 - -2.781)**
	ΔFVCpp/y	ΔBMI/y	-0.714	**(-1.021 - -0.407)**
		Age at follow-up	-0.009	**(-0.015 - -0.002)**
		Current smokers	-0.310	**(-0.540 - -0.080)**
		Cohort IV	0.229	**(0.009 - 0.448)**
		Cohort V	0.171	(-0.002 - 0.345)
	ΔFVCml/y	ΔBMI/y	-34.312	**(-47.825 - -20.800)**
		Age at follow-up	-1.151	**(-1.430 - -0.872)**
		Current smoker	-14.539	**(-24.656 - -4.421)**
	ΔFEV1/FVC/y	ΔBMI/y	-0.001	(-0.002 - 0.001)

B = Beta-coefficient from linear regression models. Significant values in bold.

ΔBMI/y=Annual BMI change. BMI=Body mass index. Normal weight (BMI=18.5-24.9). Overweight/obese (BMI≥25).

ΔFEV1pp/y=Annual FEV1pp decline. ΔFVCpp/y= Annual FVCpp decline. pp=% of predicted.

ΔFEV1ml/y=Annual FEV1ml decline. ΔFVCml/y= Annual FVCml decline. ml=milliliters.

ΔFEV1/FVC/y= Annual FEV1/FVC decline.

Supplemental table 5. Association of lung function and ΔBMI/y after adjusting for other factors among BMI groups at study entry and categorized by sex

		ΔBMI/y			
Women		Normal weight n=303		Overweight/obese n=223	
		B	95% Confidence Interval	B	95% Confidence Interval
	ΔFEV1pp/y	-0.307	(-0.665 - 0.050)	-0.742	**(-1.053 - -0.430)**
	ΔFEV1ml/y	-11.144	**(-21.220 - -1.068)**	-23.923	**(-32.101 - -15.746)**
	ΔFCVpp/y	-0.057	(-0.462 - 0.349)	-0.485	**(-0.837 - -0.133)**
	ΔFVCml/y	-6.899	(-20.987 - 7.189)	-22.008	**(-33.777 - -10.238)**
	ΔFEV1/FVC/y	-0.002	(-0.005 - 0.001)	-0.002	**(-0.004 - 0.000)**
Men		Normal weight n=182		Overweight/obese n=223	
		B	95% Confidence Interval	B	95% Confidence Interval
	ΔFEV1pp/y	-0.606	(-1.226 - 0.013)	-0.726	**(-1.182 - -0.271)**
	ΔFEV1ml/y	-26.504	**(-51.499 - -1.509)**	-25.318	**(-43.844 - -6.792)**
	ΔFCVpp/y	-0.349	(-0.967 - 0.269)	-1.151	**(-1.716 - -0.586)**
	ΔFVCml/y	-21.846	(-52.417 - 8.725)	-56.669	**(-85.790 - -27.549)**
	ΔFEV1/FVC/y	-0.002	(-0.006 - 0.002)	0.003	**(0.000 - 0.007)**

B=Beta-coefficient from linear regression models. Significant values in bold.

ΔBMI/y=Annual BMI change. BMI=Body mass index. Normal weight (BMI=18.5-24.9). Overweight/obese (BMI≥25).

ΔFEV1pp/y=Annual FEV1pp decline. ΔFVCpp/y= Annual FVCpp decline. pp=% of predicted.

ΔFEV1ml/y=Annual FEV1ml decline. ΔFVCml/y= Annual FVCml decline. ml=milliliters.

ΔFEV1/FVC/y= Annual FEV1/FVC decline.

Adjusting factors: Sex, age, changes in smoking habits, pack-years, ICS use, occupational GDF exposure at follow-up and original cohort.

Supplemental table 6. Association between ΔBMI/y and annual decline in lung function after adjusting for other factors of overweight and obese groups

	ΔBMI/y			
	Overweight/obese			
	Overweight n=327		Obese n=133	
	B	95% Confidence Interval	B	95% Confidence Interval
ΔFEV1pp/y	-0.852	**(-1.201 - -0.503)**	-0.670	**(-1.106 - -0.235)**
ΔFEV1ml/y	-25.395	**(-37.506 - -13.283)**	-24.860	**(-39.682 - -10.037)**
ΔFVCpp/y	-0.901	**(-1.338 - -0.464)**	-0.491	**(-0.946 - -0.035)**
ΔFVCml/y	-39.844	**(-59.812 - -19.876)**	-27.047	**(-46.083 - -8.012)**
ΔFEV1/FVC/y	0.000	(-0.002 - 0.003)	-0.001	(-0.004 - 0.001)

B=Beta-coefficient from linear regression models. Significant values in bold.

ΔBMI/y=Annual BMI change. BMI=Body mass index. Overweight (BMI=25-29.9). Obese (BMI≥30).

ΔFEV1pp/y=Annual FEV1pp decline. ΔFVCpp/y= Annual FVCpp decline. pp=% of predicted.

ΔFEV1ml/y=Annual FEV1ml decline. ΔFVCml/y= Annual FVCml decline. ml=milliliters.

ΔFEV1/FVC/y= Annual FEV1/FVC decline.

Adjusting factors: Sex, age, changes in smoking habits, pack-years, ICS use, occupational GDF exposure at follow-up and original cohort.