


# Predictors of accelerated FEV<sub>1</sub> decline in adults with airflow limitation—Findings from the Health2006 cohort

Chronic Respiratory Disease  
Volume 16: 1–11  
© The Author(s) 2019  
Article reuse guidelines:  
sagepub.com/journals-permissions  
DOI: 10.1177/1479973119838278  
journals.sagepub.com/home/crd  


Camilla Boslev Baarnes<sup>1</sup>, Betina H Thuesen<sup>2</sup>, Allan Linneberg<sup>2,3</sup> ,  
Amalie S Ustrup<sup>1</sup>, Signe Knag Pedersen<sup>1</sup>  and Charlotte Suppli Ulrik<sup>1,3</sup> 

## Abstract

To investigate predictors of accelerated decline in forced expiratory volume in 1 s (FEV<sub>1</sub>) in individuals with preexisting airflow limitation (AL). Participants in the Health2006 baseline study aged  $\geq 35$  with FEV<sub>1</sub>/forced vital capacity (FVC) < lower limit of normal (LLN) were invited for a 10-year follow-up. At both examinations, data were obtained on demographics, spirometry, fitness level, allergy, and exhaled nitric oxide. We used multiple regression modeling to predict the annual decline in FEV<sub>1</sub>, reported as regression coefficients (*R*) and 95% confidence intervals (CIs). A total of 123 (43% of those invited) participated in the follow-up examination, where more had exercise-induced dyspnea but fewer had asthma symptoms. Being female (*R* = −29.8 ml, CI: −39.7 to −19.8), diagnosed with asthma (*R* = −13.7, CI: −20.4 to −7.0) or atopic dermatitis (*R* = −29.0, CI: −39.7 to −18.4), and having current asthma symptoms or nightly respiratory symptoms (*R* = −22.1, CI: −31.9 to −12.4 and *R* = −14.3, CI: −19.9 to −8.7, respectively) were significantly associated with a steeper decline in FEV<sub>1</sub>. Although to a smaller extent, a steeper decline was also predicted by age, baseline FEV<sub>1</sub>, waist/hip-ratio, and number of pack-years smoked. In individuals with preexisting AL, being female and having ever or current respiratory symptoms were associated with an accelerated annual decline in FEV<sub>1</sub>.

## Keywords

Airflow limitation, chronic obstructive pulmonary disease, asthma, respiratory symptoms, lung function decline

Date received: 12 August 2018; accepted: 16 January 2019

## Introduction

Since the study published in 1977 by Fletcher and Peto,<sup>1</sup> it has been widely accepted that forced expiratory volume in 1 s (FEV<sub>1</sub>) gradually declines throughout adulthood. Studies addressing annual decline of FEV<sub>1</sub> in both chronic obstructive pulmonary disease (COPD)<sup>2,3</sup> and asthma<sup>4,5</sup> have shown a greater decline than in individuals with no history of obstructive airway disease. However, a very high degree of variability in decline within both COPD and asthma has been reported,<sup>2–4</sup> making it hard to risk-stratify individuals based solely on their level of lung function, especially in early stages of airflow limitation (AL).

<sup>1</sup> Department of Respiratory Medicine, Hvidovre Hospital, Hvidovre, Denmark

<sup>2</sup> Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark

<sup>3</sup> Faculty of Health and Medical Sciences, Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

### Corresponding author:

Charlotte Suppli Ulrik, Respiratory Research Unit Hvidovre, Department of Respiratory Medicine, Hvidovre Hospital, DK-2650 Hvidovre, Denmark.  
Email: csulrik@dadlnet.dk



Most studies on the course of FEV<sub>1</sub> over the life span have been conducted in either large population cohorts<sup>5,6</sup> or in individuals with known asthma or COPD.<sup>2–4</sup> However, increasing focus on the heterogeneity of both asthma, not least in adults, and COPD, as well as recognition of the overlap between the two,<sup>7–11</sup> warrants studies where these airway diseases are deconstructed into traits that can be measured, with the overall aim of potentially identifying traits or factors that can be modified and lead to an improvement in outcome. AL is seen not only in patients labeled as having either asthma or COPD but also in asymptomatic individuals. Studying predictors of long-term outcome in individuals with AL in general, irrespective of a diagnostic label or not, may thus add knowledge useful for predicting future risk in individuals with this trait. Another potential gap in the available studies of FEV<sub>1</sub> decline is that most are solely based on spirometry data, smoking history, and self-reported symptoms. A more multifaceted approach, including more detailed information on symptoms and objective assessments, may therefore be of importance, as a wide variety of characteristics are likely to influence the rate of decline in lung function.

Therapeutic trials have so far been the most promising regarding asthma,<sup>12–15</sup> not showing desired results in COPD.<sup>16,17</sup> Prevention, mainly in the form of smoking cessation,<sup>18,19</sup> is preferable by far, and early initiation is crucial.<sup>20</sup> AL can be detected easily through spirometry. Although underdiagnosing of COPD is a known problem,<sup>21,22</sup> screening is not recommended in asymptomatic smokers.<sup>23</sup> In a large cohort study of individuals at high risk of COPD, Colak et al. found 78% of those meeting the spirometric criteria for COPD (pre-bronchodilator (BD) AL, plus a FEV<sub>1</sub> < 80% predicted) not to have been previously diagnosed, although only 29% of these individuals were asymptomatic.<sup>24</sup> Thus, waiting for individuals to recognize, and respond to, symptoms of a low lung function can result in an already extensive damage before receiving a diagnosis.

With this 10-year follow-up study, we aimed to identify predictors of decline in FEV<sub>1</sub> in individuals with AL at baseline, in hope of providing knowledge to assist in early detection of individuals at high risk of progressive AL.

## Methods

### Material

For this study, we focused on a subgroup ( $n = 313$ ) from the Danish Health2006 cohort.<sup>25</sup> We selected

participants who, at the baseline examination, were 35 years or older and had a FEV<sub>1</sub>/FVC ratio < lower limit of normal (LLN, 5% percentile).<sup>26</sup> Invitations were issued via post, with reminder letters sent after 3 and 9 months. A final reminder was sent after 12 months, including a copy of the questionnaires and a prepaid return envelope. Participants were deemed unresponsive if not having responded 3 months after the final letter.

### Examinations

All examinations were performed in all participants at both baseline (2006–2008) and follow-up (2016–2017) if not otherwise stated. A detailed description of the examinations has been published elsewhere.<sup>25</sup>

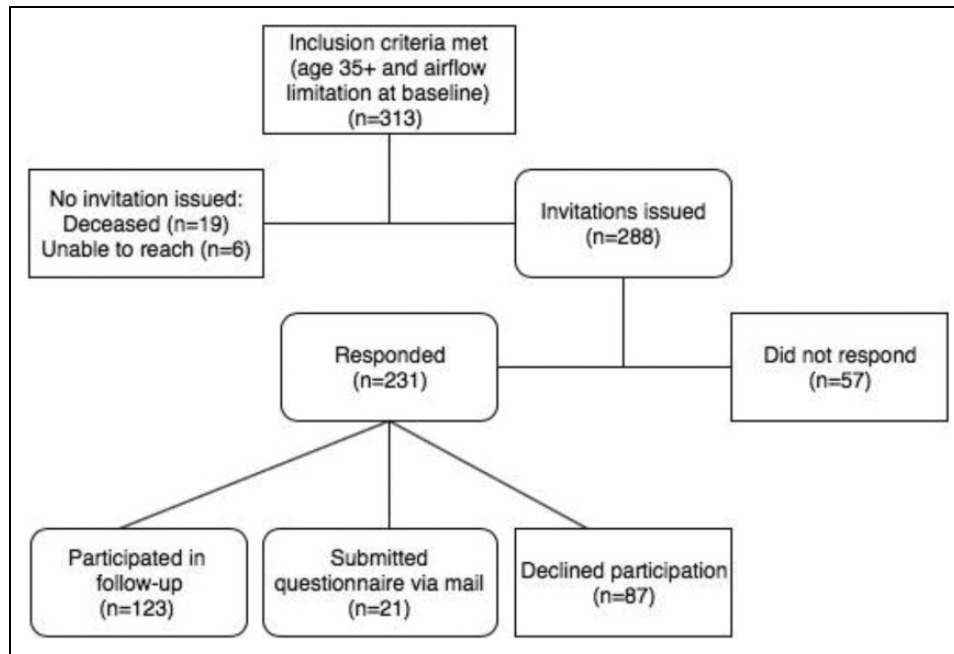
**Questionnaires.** All participants answered questionnaires on perceived health, known diseases (including, e.g. eczema, rhinitis, and asthma), physical activity level, dietary habits, alcohol, smoking habits, hormone replacement therapy, family and social relations, education, and work.

**Anthropometric measures and obesity.** Height, weight, and hip- and waist-circumference were measured. Body fat percentage was determined using impedance.

**Fitness level.** Fitness level was measured through the Danish Step Test:<sup>27</sup> a test with fixed step height but increasing pace up to a maximum of 6 min.

**Sensitization to specific aeroallergens.** At baseline, skin prick testing was only performed in a subgroup of participants, at follow-up in all participants. Skin prick testing for 10 aeroallergens (birch, grass, mugwort, horse dander, dog hair, cat hair, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria alternate*, and *Cladosporium herbarum*) was performed using the Soluprick (ALK-Abelló A/S, Hørsholm, Denmark). Participants were considered sensitized to allergens if developing a wheal with a diameter larger than 3 mm. Specific immunoglobulin E (IgE) to the most common aeroallergens, that is, birch, grass, cat, and *D. pteronyssinus*, was measured and considered positive if >0.35 kU/l.

**Lung function.** Lung function was measured according to the American Thoracic Society/European Respiratory Society (ATS/ERS) standards,<sup>28</sup> at baseline with a SpiroUSB (Micro-Medical Ltd, Rochester, UK), and at follow-up with a Vitalograph 6800 pneumotrac (Hamburg, Germany), primarily because the



**Figure 1.** Flowchart over inclusion process of participants from the Health2006 cohort.

SpiroUSB was not available at the time of the follow-up examination. Predicted FEV<sub>1</sub> was calculated based on height, age, and sex.<sup>29</sup>

**Fractional exhaled nitric oxide.** Fractional exhaled nitric oxide (FeNO) was measured with Niox-Mino (Aerocrine AB, Solna, Sweden) according to ATS standards.<sup>30</sup>

### Definitions

Participants were defined as never-smokers or ever-smokers (former or current) by answering the questionnaire item *Do you smoke?* with the options *Yes*, *No, but I have previously*, or *No, never*. Pack-years were calculated by multiplying the duration (years) with intensity (grams tobacco per day, with 1 cigarette equating to 1 g, a pipe or cheroot to 3 g, and a cigar to 5 g of tobacco). Regarding alcohol consumption, participants were defined as nondrinkers if they had a weekly consumption <1 international unit. Body mass index (BMI) was divided into the following groups: underweight (<18.5), normal weight (18.5–24.99), overweight (25–29.99), and obese (>30).<sup>31</sup>

### Statistical analysis

All analyses were done in IBM SPSS Statistics, V.24. For differences between baseline and follow-up, we

ran Paired *T*-test for continuous, McNemars test for dichotomous, and Wilcoxon signed rank test for ordinal variables. Missing data, primarily unanswered items from the questionnaires with different items in different cases and fitness tests not undertaken due to musculoskeletal problems were considered missing at random and were dealt with by multiple imputation in SPSS. Results are reported as either percentage of group or mean (SD).

A multiple linear regression analysis with backward stepwise deletion of nonsignificant variables was run to predict decline in FEV<sub>1</sub> from clinical and self-reported variables. All variables included in the final model added statistical significance ( $p < 0.05$ ). Results from the regression analysis are reported as unstandardized regression coefficient (*R*), unstandardized standard error (SE), and 95% confidence interval (CI).

## Results

### Follow-up cohort

Of the 313 eligible for invitation 19 were deceased since baseline, and we were unable to obtain valid contact information on six. Invitations were sent to the remaining 288 participants.

A total of 123 (42.7%) participants were examined, another 21 filled in and returned the questionnaires by mail (Figure 1).

The analyses in the present study are based on data from the 123 individuals who participated physically in both examinations. Compared to the 165 eligible, but not participating individuals, participants in the follow-up examination were at baseline more likely to be current smokers ( $p < 0.05$ ), have a positive skin prick test ( $p < 0.02$ ) and positive specific IgE ( $p < 0.01$ ), but less likely to have chronic bronchitis ( $p < 0.01$ ) and diabetes ( $p < 0.05$ ). The mean fitness level (NS) and weekly alcohol consumption (NS) were slightly higher in the 123 who participated at follow-up, otherwise the follow-up group was representative of the entire group eligible for invitation to participate in the present study.

During the 10 years from baseline to follow-up, 24 participants had quit smoking (and none started). At follow-up, a greater proportion of participants experienced exercise-induced dyspnea, while fewer had symptoms of rhinitis or asthma (Tables 1 and 2; Figure 2). Mean decline in FEV<sub>1</sub> was 28.2 ml/year (SD: 31.6 ml), with a broad range of annual change from a 128 ml decline to a 64 ml increase.

### Predictors of decline in FEV<sub>1</sub>

In the multiple regression analysis, we ended with a final model which statistically significantly predicted loss of FEV<sub>1</sub> ( $p < 0.001$ , adjusted  $R^2$ : 0.28). Independent variables did not show multicollinearity, assessed by both correlation coefficients and tolerance values. All variables included in the final model are given in Figure 3.

Variables predicting a greater decline in FEV<sub>1</sub> were heterogeneous in character. Women lost nearly 30 ml more in FEV<sub>1</sub> per year than men ( $R = -29.8$ , CI:  $-39.7$  to  $-19.8$ ,  $p < 0.001$ ), same as participants ever diagnosed with atopic dermatitis compared to those without ( $R = -29.0$ , CI:  $-39.7$  to  $-18.4$ ,  $p < 0.001$ ). Ever receiving a diagnosis of asthma also predicted a greater decline in FEV<sub>1</sub>, but to a smaller extent ( $R = -13.7$ , CI:  $-20.4$  to  $-7.0$ ,  $p < 0.001$ ). Both symptoms of asthma ( $R = -22.1$ , CI:  $-31.9$  to  $-12.4$ ,  $p < 0.001$ ) and nightly respiratory symptoms ( $R = -14.3$ , CI:  $-19.9$  to  $-8.7$ ,  $p < 0.001$ ) in the 12 months prior to the baseline examination predicted a greater decline in FEV<sub>1</sub>. In contrast, a higher fitness level was the most prominent predictor of a smaller annual decline of FEV<sub>1</sub> ( $R = 8.7$  ml per 10 units increase, CI: 5.0 to 12.4,  $p < 0.001$ ). All regression coefficients ( $R$ ), SEs, and CIs are given in Table 3.

**Table 1.** Self-reported characteristics of participants in the Health2006 follow-up study at baseline and follow-up ( $n = 123$ ).<sup>a</sup>

	Baseline	Follow-up	p-Value
Smoking			<0.001
Current smokers (%)	29.1	13.5	
Former smokers (%)	42.6	58.2	
Never-smokers (%)	28.4	28.4	
Pack years <sup>b</sup>	27.0 (16.9)	29.8 (27.5)	NS
Alcohol consumption			
Nondrinkers (%)	5.6	9.0	<0.001
Weekly consumption <sup>c</sup> (units)	11.5 (11.1)	8.8 (8.1)	0.01
Education			
10 years of school or less (%)	20.8	19.4	NS
Hormone replacement (women only)			
Yes (%)	22.2	21.7	NS
Number of years	6.3 (7.9)	8.3 (9.0)	<0.001
Symptoms last 12 months			
Rhinitis (%)	54.2	32.2	<0.001
Asthma symptoms <sup>d</sup> (%)	32.1	16.7	NS
Dyspnea during activity (%)	11.2	47.6	<0.001
Chronic bronchitis <sup>e</sup> (%)	16.0	15.3	NS
Nightly respiratory symptoms (%)	21.5	21.5	NS
Wheezing (%)	40.3	43.8	NS
Ever diagnosed with			
Rhinitis (%)	26.4	22.9	NS
Asthma (%)	20.1	20.8	NS
Hypertension (%)	26.4	36.8	0.02
Diabetes (%)	1.4	4.2	NS
Hypercholesterolemia (%)	22.6	31.8	<0.001
Self-reported <sup>f</sup>			
Overall health	2.6 (0.9)	2.6 (0.8)	NS
Physical shape	3.1 (0.9)	3.0 (0.9)	NS
Dietary habits	2.7 (0.6)	2.6 (0.6)	NS
Social position	2.7 (0.6)	2.38 (0.7)	<0.001

<sup>a</sup>Numbers reported as mean (SD).

<sup>b</sup>Calculated for participants with a current or former history of smoking.

<sup>c</sup>Calculated for participants who reported a current alcohol consumption only.

<sup>d</sup>Calculated for participants reporting a diagnosis of asthma only.

<sup>e</sup>Cough with sputum for at least 3 months/year for at least 2 consecutive years.

<sup>f</sup>Measured on a scale from 1 to 5, where 1 is best.

## Discussion

In this population-based, follow-up study of individuals with preexisting AL, we found that the decline in FEV<sub>1</sub> ranged considerably between participants. The

**Table 2.** Clinical characteristics of participants in the Health2006 follow-up study at baseline and follow-up ( $n = 123$ ).<sup>a</sup>

	Baseline	Follow-up	p-Value
Age (years)	51.0 (9.1)	60.5 (9.2)	<0.001
BMI <sup>b</sup>			0.002
Normal or underweight (%)	52.1	43.9	
Overweight (%)	34.7	36.6	
Obese (%)	13.2	19.5	
Body composition			
Fat percentage	30.7 (8.9)	29.6 (9.3)	0.04
Waist/hip ratio	0.87 (0.09)	0.89 (0.10)	<0.001
Spirometry and fitness			
FEV <sub>1</sub> (% predicted)	81.0 (15.9)	79.8 (19.8)	0.04
FVC (% predicted)	104.1 (18.4)	106.3 (18.0)	NS
FEV <sub>1</sub> /FVC (%)	64.7 (5.7)	61.2 (9.8)	<0.001
FeNO (ppb)	17.8 (15.1)	20.8 (20.5)	NS
Fitness level (mlO <sub>2</sub> /kg/min)	31.6 (8.8)	32.2 (13.0)	NS
Allergic sensitization			
Positive skin prick test <sup>c</sup> (%)	39.1	42.4	0.02
Positive specific IgE <sup>d</sup> (%)	24.4	30.9	<0.001

FEV<sub>1</sub>: forced expiratory volume in 1 s; BMI: body mass index; FeNO: fractional exhaled nitric oxide; FVC: forced vital capacity; IgE: immunoglobulin E.

<sup>a</sup>Numbers are reported as mean (SD).

<sup>b</sup>BMI grouped into following categories: normal or underweight ( $\leq 24.9$ ), overweight (25.0–29.9), and obese ( $\geq 30.0$ ).

<sup>c</sup>Positive reaction to at least 1 of 10 aeroallergens (birch, grass, mug wort, horse, dog, cat, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria alternata*, and *Cladosporium herbarum*).

<sup>d</sup>Positive reaction to at least one of the four tested allergens: cat, grass, house dust mites, and birch.

main predictors of accelerated decline in FEV<sub>1</sub> were being female, having respiratory symptoms and ever being diagnosed with asthma or atopic dermatitis.

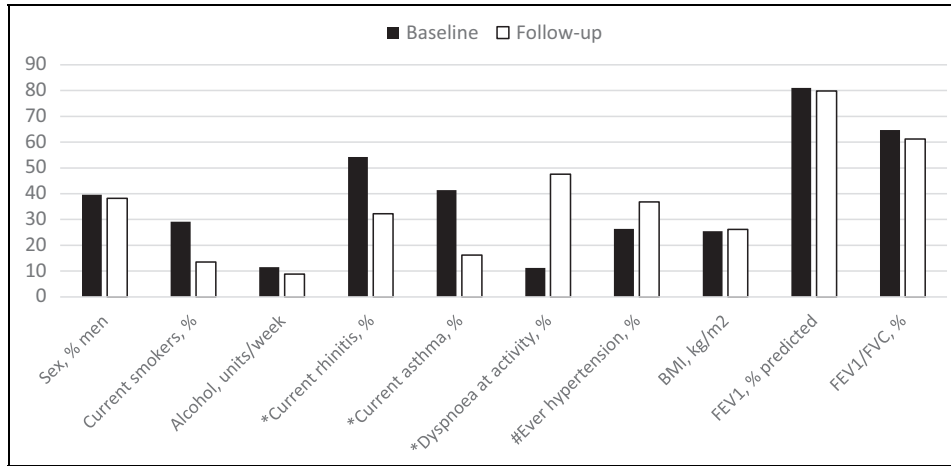
There is an ongoing debate over which definition of AL to use; FEV<sub>1</sub>/FVC < LLN, or the more straightforward FEV<sub>1</sub>/FVC < 0.70. Using the traditionally applied fixed ratio (FEV<sub>1</sub>/FVC < 0.70), there may be over diagnosing in the older population and underdiagnosing of the younger.<sup>32</sup> Underdiagnosing has also been a point of critique for using LLN, missing those with milder degrees of airflow obstruction.<sup>33</sup> In the tiotropium trial TIOSPIR, Calverley et al.<sup>34</sup> found that the participants who would have been excluded

using LLN had the same risk of death and cardiovascular events as the remaining participants in the trial, although a lower risk of exacerbations. On the other hand, Colak et al.<sup>35</sup> found increased cardiovascular morbidity and early death in those underdiagnosed using fixed ratio, compared to LLN. Recently, Miller et al. found that using fixed ratio only, a large group of individuals were diagnosed with COPD, who might simply have an age-related lower lung function, and symptoms due to cardiovascular problems, and not necessarily COPD.<sup>36</sup> Finally, Akkermans et al.<sup>37</sup> found that the decline in FEV<sub>1</sub> in those diagnosed with airflow obstruction based on a fixed ratio was close to those deemed non-obstructed, compared to those with obstruction based on LLN. Whichever definition of airflow obstruction is chosen, whether for interventional or explorative studies, researchers have to decide either to risk inclusion of individuals with age-related AL or exclusion of primarily younger individuals with negative normal FEV<sub>1</sub>/FVC ratio. For the present study, we decided, also based on the age distribution in our cohort, to define AL based on FEV<sub>1</sub>/FVC < LLN.

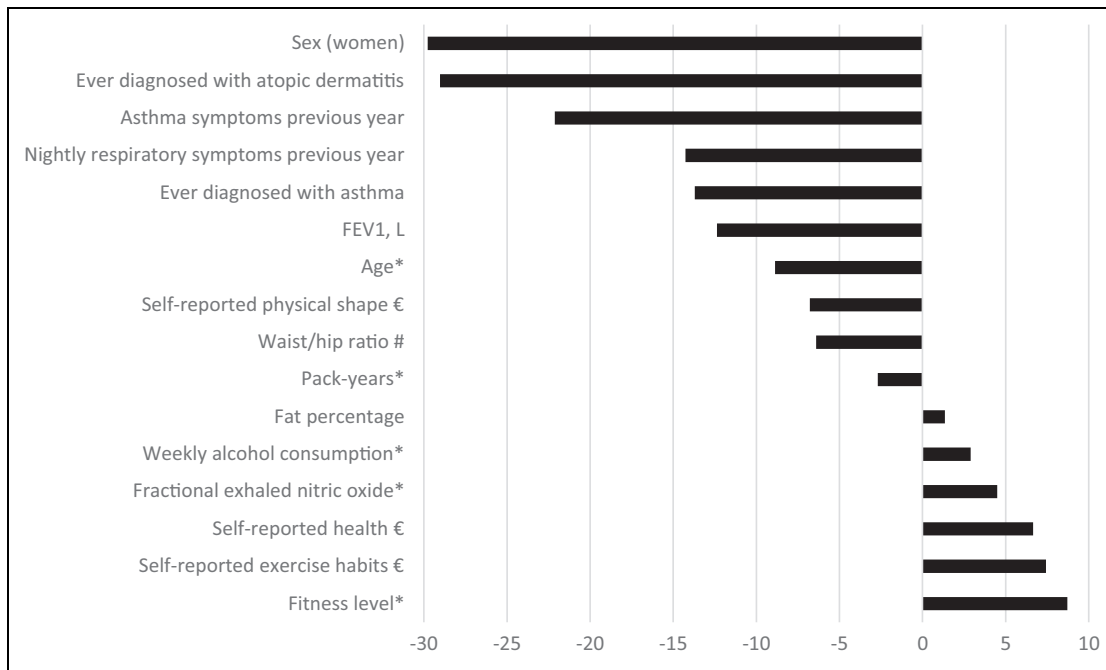
### Decline in FEV<sub>1</sub>

The mean decline observed in our study in FEV<sub>1</sub> is comparable to other observations—both in studies of individuals with asthma or COPD and in studies of the general population. van Oostrom et al.<sup>6</sup> found different trajectories of FEV<sub>1</sub> in a general population, where the decline in those with a normal course (trajectory in line with reference values) was 31.1 and 25.9 ml/year for men and women, respectively. Lange et al.<sup>4</sup> analyzed the changes in FEV<sub>1</sub> in a large cohort over 15 years and found that people who reported having asthma had both a lower FEV<sub>1</sub> at inclusion and a steeper decline in FEV<sub>1</sub> over time, compared to those without asthma (38 vs. 22 ml, respectively). In patients with known COPD, Vestbo et al.<sup>2</sup> found a mean decline in FEV<sub>1</sub> of 33 ml/year, the most prominent predictors of decline in FEV<sub>1</sub> being smoking, exacerbations, emphysema, and BD reversibility. The traditional view was that an accelerated decline in FEV<sub>1</sub> over time, due to tobacco smoking, leads to COPD.<sup>1</sup> However, FEV<sub>1</sub> at a given point of life is determined not only by rate of decline, but also by the peak level attained in early adulthood.<sup>5,38,39</sup>

More than 10% ( $n = 15$ ) of our cohort had an increase in FEV<sub>1</sub> over the 10 years between baseline and follow-up. They were more likely to be men and



**Figure 2.** Characteristics of participants from Health2006 ( $n = 123$ ) at baseline and follow-up. \*Self-reported symptoms during the previous 12 months. #Doctor diagnosed at any point in life.



**Figure 3.** Regression coefficients for prediction of decline in FEV<sub>1</sub> at follow-up for participants at the Health2006 cohort ( $n = 123$ ), change in ml per year per 1 unit increase in each variable, unless otherwise stated. \*Per 10 unit increase. €On a scale of 1-5, where 1 is best. #Per 0.1 unit increase. FEV<sub>1</sub>: forced expiratory volume in 1 s.

had a baseline FEV<sub>1</sub> nearly 12% lower than the remaining cohort. The large variation could be due to technical issues with spirometry, natural, spontaneous variation in participants with asthma or a result of regression toward the mean. Some participants might also have been unaware of their low lung function when entering the cohort, subsequently being examined and possibly started on treatment by their physician. This could have led to an initial increase in FEV<sub>1</sub>, resulting in the higher value at follow-up than

at baseline. Vestbo et al.<sup>2</sup> also found a considerable between-subject variation, from over 200 ml decline to over 100 ml increase per year. In patients with COPD, Zafari et al.<sup>3</sup> found a change in FEV<sub>1</sub> ranging from a 124 ml/year decline to a 15 ml/year increase.

### Predictors of decline in FEV<sub>1</sub>

**Smoking.** Several studies have shown that smoking is a determinant of decline of FEV<sub>1</sub>.<sup>2-6</sup> We didn't find an

**Table 3.** Multiple regression analysis for prediction of annual decline in FEV<sub>1</sub> over time in participants from the Health2006 cohort (n = 123) with airflow limitation at baseline.<sup>a</sup>

	Unstandardized coefficients		Significance p-Value	95% Confidence interval for R	
	R	SE		Lower limit	Upper limit
Constant	161.5	30.8	<0.001	101.1	221.9
Sex (women)	-29.8	5.1	<0.001	-39.7	-19.8
Ever diagnosed with atopic dermatitis	-29.0	5.4	<0.001	-39.7	-18.4
Asthma symptoms previous year	-22.1	5.0	<0.001	-31.9	-12.4
Nightly respiratory symptoms previous year	-14.3	2.9	<0.001	-19.9	-8.7
Ever diagnosed with asthma	-13.7	3.4	<0.001	-20.4	-7.0
FEV <sub>1</sub> (l)	-12.4	2.4	<0.001	-17.1	-7.7
Age <sup>b</sup>	-8.9	1.7	<0.001	-12.2	-5.5
Self-reported physical shape <sup>c</sup>	-6.8	1.9	<0.001	-10.6	-3.0
Waist/hip ratio <sup>d</sup>	-6.4	2.2	0.003	-10.6	-2.2
Pack-years <sup>b</sup>	-2.7	0.7	<0.001	-4.1	-1.3
Fat percentage	1.4	0.2	<0.001	0.9	1.8
Weekly alcohol consumption <sup>b</sup>	2.9	1.0	0.005	0.9	4.9
Fractional exhaled nitric oxide <sup>b</sup>	4.5	0.9	<0.001	2.8	6.1
Self-reported health <sup>c</sup>	6.7	1.6	<0.001	3.5	9.8
Self-reported exercise habits <sup>c</sup>	7.4	1.5	<0.001	4.4	10.5
Fitness level <sup>b</sup>	8.7	1.9	<0.001	5.0	12.4

FEV<sub>1</sub>: forced expiratory volume in l s; SE: standard error.

<sup>a</sup>Regression coefficients are reported as change in ml per year per l unit increase in each variable, unless otherwise stated.

<sup>b</sup>Per 10 unit increase.

<sup>c</sup>On a scale of 1–5, where 1 is best.

<sup>d</sup>Per 0.1 unit increase.

effect of smoking status, and the effect of pack-years was not of a substantial size, with barely 3 ml greater decline per year per 10 additional pack-years. The divergence in results could be due to the type of study population, as both Vestbo et al.<sup>2</sup> and Zafari et al.<sup>3</sup> studied populations with known COPD, and thus a smoking history. Participants with asthma have been shown to be more susceptible to the detrimental effect of smoking than non-asthmatics.<sup>4,5</sup> However, when performing linear regression for those with a smoking history only, the decline was only found to be 5 ml greater per 10 pack-years. The differences in effect of smoking may also simply just be a problem regarding power due to the size of our cohort.

**Sex.** As FEV<sub>1</sub> is affected by height, and men are usually taller than women, one would expect men to have a greater decline over time than women. Neither Lange et al.<sup>4</sup> nor Vestbo et al.<sup>2</sup> reported a marked between-sex difference, and Zafari et al.<sup>3</sup> only found a 8.9-ml greater decline in women than men. In contrast, we found women to have a much steeper decline in FEV<sub>1</sub> than men, more than twice the yearly decline. Analyzing only individuals with a low baseline FEV<sub>1</sub>

weakened the effect of sex. Although women had a higher mean FEV<sub>1</sub>% predicted, their mean absolute FEV<sub>1</sub> was, as expected, lower than in men (results not shown). Thus, it is not a case of a greater decline due to a greater volume at onset.

**Fractional exhaled nitric oxide.** We found a high FeNO to be associated with a slower decline in FEV<sub>1</sub>. In contrast to our findings, van Veen et al.<sup>40</sup> found that having a high FeNO (>20 ppb) predicted over 40 ml greater loss per year compared to having a low FeNO (<20 ppb). However, their study was on non-smoking, difficult-to-treat asthmatics. Smoking is known to lower FeNO.<sup>41</sup> With the number of smokers at baseline, FeNO was likely suppressed, and “high” FeNO might represent normal values, compared to the lower FeNO in smokers. FeNO is higher during rhinovirus infections, which may also result in a lower lung function. If having a common cold at baseline could result in both higher FeNO and lower FEV<sub>1</sub>, the resulting loss over time may be underestimated. Participants were asked to cancel their appointment in the case of illness, but some could have forgotten.

**Alcohol.** Our finding of a relationship between higher alcohol consumption and a slower decline in FEV<sub>1</sub> seems peculiar. Lange et al.<sup>42</sup> found that the effect on FEV<sub>1</sub> decline by a high alcohol consumption (350 g per week or more) was equivalent to 15 g of tobacco daily, while Schünemann et al.<sup>43</sup> found no correlation between total alcohol consumption and lung function decline, but on the other hand a positive relationship between wine drinking and change in FEV<sub>1</sub>, which is most likely due to confounding by a healthier lifestyle in wine drinkers. The mean weekly consumption in our cohort was around 130 g, and by that substantially lower than that in the cohort of Lange et al.,<sup>42</sup> which may explain some of the differences in observations. However, the coefficient for alcohol consumption in our study was not very large, only 2.9 ml per 10 units of alcohol or more per week, which is not likely to be clinically relevant.

**Body composition.** We found no statistically significant association between BMI and decline in FEV<sub>1</sub>. However, a high waist/hip ratio predicted a steeper decline in FEV<sub>1</sub>, whereas a higher bodyfat percentage predicted a slower decline. Other studies on the effect of obesity on lung function have shown inconsistent results, from no effect<sup>44</sup> to a significant effect.<sup>45</sup> In mild to moderate COPD, Landbo et al.<sup>46</sup> observed a U-shaped curve for mortality risk with the lowest risk in normal to overweight participants. On the other hand, for severe COPD, the association was more linear with increasing risk of mortality for decreasing BMI. Our results may reflect a similar relationship, with a higher fat percentage being advantageous for FEV<sub>1</sub> until a certain point.

### **Limitations and future perspectives**

With our study being epidemiologically based, it has an inherent set of potential biases. First, participants in the original Health2006 cohort may not be representative for all invited individuals or for the background population. Thuesen et al.<sup>25</sup> found nonparticipants to be younger, more often male, with a shorter education and lower income than participants in Health2006, as well as having more hospital admissions. Thus, the external validity of the baseline examination might be suboptimal. Second, we found differences between those who accepted our invitation to the follow-up examination and those who either declined, did not respond, or were deceased. Attrition bias, with the most affected participants at

baseline being more likely to not attend a follow-up examination, is very likely. Our participation rate was 43%, comparable to the rate in the baseline examination,<sup>25</sup> while some other Danish cohorts have had higher participation rates.<sup>4,47</sup> As participants in our cohort all had AL, it might explain our lower participation rate at follow-up, as nonparticipants might simply be too frail. Due to our closed cohort, we did not have the option of recruiting additional participants, as other long-term studies have done. We had originally calculated a sample size of 200 participants to be able to detect a 10 ml difference in annual decline of FEV<sub>1</sub>. With the 123 participants included, our minimal detectable difference was thus larger than 10 ml. Finally, recall bias is always a possibility in studies relying on self-reporting from participants, and with many of our data points being based on questionnaires, the internal validity might be affected.

As we found a diagnosis of asthma to be a predictor of decline in FEV<sub>1</sub>, and other studies have shown accelerated decline in participants with COPD, it seems legitimate to assume that we could have found similar results. Unfortunately, at baseline, the questionnaire did not include an item regarding previously diagnosed COPD. However, self-reported symptoms of chronic bronchitis were not associated with an accelerated decline in our analyses.

Another consideration is the lack of information between the baseline- and the follow-up examinations. Had we had more points of data over the years, it would have been a more accurate calculation of trajectories, as well as possibly explaining the few outlying cases, such as the participants experiencing an immense improvement in FEV<sub>1</sub>. Combined with more information, for example, on the use of inhaled medication over the years of follow-up and seasonal variations, more data points would probably have given us a better fitted model.

Our values of FEV<sub>1</sub> were all without BDs, as the baseline examinations had not included reversibility testing. Most studies use post-BD values. Participants with more asthma-like traits could have a higher post-BD FEV<sub>1</sub>, compared with a more COPD-like participant with a more fixed FEV<sub>1</sub>, thus potentially skewing the effect of variables such as number of pack-years.

Medication has been shown in observational studies to slow the decline in FEV<sub>1</sub> in patients with asthma,<sup>12,15</sup> and initially improve FEV<sub>1</sub> in COPD.<sup>48</sup> In future studies, it would be interesting to link our cohort to the prescription databases, to look for treatment patterns in participants, at baseline as well as



over time. It would also be of interest to see if the individuals declining participation in follow-up, as well as those deceased since baseline, had characteristics differing markedly from those participating in the follow-up.

In conclusion, in individuals with preexisting AL, we found the main predictors of a steeper decline in FEV<sub>1</sub> to be female, have respiratory symptoms, and ever being diagnosed with asthma or atopic dermatitis. Our results lay the foundation for future analyses, and, adjusted for the shortcomings of the present study, may potentially help clinicians targeting the high-risk individuals for a more personalized intervention strategy.



### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

### ORCID iD

Allan Linneberg  <https://orcid.org/0000-0002-0994-0184>  
Signe Knag Pedersen  <https://orcid.org/0000-0002-5237-6128>

Charlotte Suppli Ulrik  <https://orcid.org/0000-0001-8689-3695>

### References

- Fletcher C and Peto R. The natural history of chronic airflow obstruction. *Br Med J* 1977; 1(6077): 1645–1648.
- Vestbo J, Edwards LD, Scanlon PD, et al. Changes in forced expiratory volume in 1 second over time in COPD. *N Engl J Med* 2011; 365(13): 1184–1192.
- Zafari Z, Sin DD, Postma DS, et al. Individualized prediction of lung-function decline in chronic obstructive pulmonary disease. *CMAJ* 2016; 188(14): 1004–1011.
- Lange P, Parner J, Vestbo J, et al. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998; 339(17): 1194–1200.
- James AL, Palmer LJ, Kicic E, et al. Decline in lung function in the Busselton health study: the effects of asthma and cigarette smoking. *Am J Resp Crit Care* 2005; 171(2): 109–114.
- van Oostrom SH, Engelfriet PM, Verschuren WMM, et al. Aging-related trajectories of lung function in the general population—The Doetinchem cohort study. *PLoS One* 2018; 13(5): e0197250.
- Corren J. Asthma phenotypes and endotypes: an evolving paradigm for classification. *Discov Med* 2013; 15(83): 243–249.
- Gibson PG and McDonald VM. Asthma–COPD overlap 2015: now we are six. *Thorax* 2015; 70(7): 683–691.
- Han MK, Agusti A, Calverley PM, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. *Am J Resp Crit Care* 2010; 182(5): 598–604.
- Postma DS and Rabe KF. The asthma–COPD overlap syndrome. *N Engl J Med* 2015; 373(13): 1241–1249.
- Celli BR and Agusti A. COPD: time to improve its taxonomy? *ERJ Open Res* 2018; 4(1): 00132–2017.
- Dijkstra A, Vonk JM, Jongepier H, et al. Lung function decline in asthma: association with inhaled corticosteroids, smoking and sex. *Thorax* 2006; 61(2): 105–110.
- Haahtela T, Jarvinen M, Kava T, et al. Comparison of a  $\beta_2$ -agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *New Engl J Med* 1991; 325(6): 388–392.
- Haahtela T, Jarvinen M, Kava T, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994; 331(11): 700–705.
- Lange P, Scharling H, Ulrik CS, et al. Inhaled corticosteroids and decline of lung function in community residents with asthma. *Thorax* 2006; 61(2): 100–104.
- Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *New Engl J Med* 2007; 356(8): 775–789.
- Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *New Engl J Med* 2008; 359(15): 1543–1554.
- Anthonisen NR, Connett JE and Murray RP. Smoking and lung function of lung health study participants after 11 years. *Am J Resp Crit Care* 2002; 166(5): 675–679.
- Godtfredsen NS, Lam TH, Hansel TT, et al. COPD-related morbidity and mortality after smoking cessation: status of the evidence. *Eur Respir J* 2008; 32(4): 844–853.
- Welte T, Vogelmeier C and Papi A. COPD: early diagnosis and treatment to slow disease progression. *Int J Clin Pract* 2015; 69(3): 336–349.
- Ohar JA, Sadeghnejad A, Meyers DA, et al. Do symptoms predict COPD in smokers? *Chest* 2010; 137(6): 1345–1353.

22. Vandevorode J, Verbanck S, Gijssels L, et al. Early detection of COPD: a case finding study in general practice. *Respir Med* 2007; 101(3): 525–530.
23. Guirguis-Blake JM, Senger CA, Webber EM, et al. Screening for chronic obstructive pulmonary disease: evidence report and systematic review for the US preventive services task force. *JAMA* 2016; 315(13): 1378–1393.
24. Colak Y, Afzal S, Nordestgaard BG, et al. Prognosis of asymptomatic and symptomatic, undiagnosed COPD in the general population in Denmark: a prospective cohort study. *Lancet Respir Med* 2017; 5(5): 426–434.
25. Thuesen BH, Cerqueira C, Aadahl M, et al. Cohort profile: the Health2006 cohort, research centre for prevention and health. *Int J Epidemiol* 2014; 43(2): 568–575.
26. Hankinson JL, Odencrantz JR and Fedan KB. Spirometric reference values from a sample of the general US population. *Am J Resp Crit Care* 1999; 159(1): 179–187.
27. Aadahl M, Zacho M, Linneberg A, et al. Comparison of the Danish step test and the watt-max test for estimation of maximal oxygen uptake: the Health2008 study. *Eur J Prev Cardiol* 2013; 20(6): 1088–1094.
28. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005; 26(2): 319–338.
29. Quanjer PH, Tammeling GJ, Cotes JE, et al. Lung volumes and forced ventilatory flows. Report working party standardization of lung function tests, European community for steel and coal. Official statement of the European respiratory society. *Eur Respir J* 1993; 6(5): 40.
30. American Thoracic S and European Respiratory S. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005; 171(8): 912–930.
31. Organization WH. *The WHO global database on BMI*. Geneva: BMI Classification 2018, 2018.
32. Mohamed Hoesein FA, Zanen P and Lammers JW. Lower limit of normal or FEV<sub>1</sub>/FVC < 0.70 in diagnosing COPD: an evidence-based review. *Respir Med* 2011; 105(6): 907–915.
33. Vollmer WM, Gislason T, Burney P, et al. Comparison of spirometry criteria for the diagnosis of COPD: results from the BOLD study. *Eur Respir J* 2009; 34(3): 588–597.
34. Calverley PMA, Mueller A, Fowler A, et al. The effect of defining chronic obstructive pulmonary disease by the lower limit of normal of FEV<sub>1</sub>/FVC ratio in tiotropium safety and performance in respimat participants. *Ann Am Thorac Soc* 2018; 15(2): 200–208.
35. Colak Y, Afzal S, Nordestgaard BG, et al. Young and middle-aged adults with airflow limitation according to lower limit of normal but not fixed ratio have high morbidity and poor survival: a population-based prospective cohort study. *Eur Respir J* 2018; 51(3): pii: 1702681.
36. Miller MR, Haroon S, Jordan RE, et al. Clinical characteristics of patients newly diagnosed with COPD by the fixed ratio and lower limit of normal criteria: a cross-sectional analysis of the TargetCOPD trial. *Int J Chron Obstruct Pulmon Dis* 2018; 13: 1979–1986.
37. Akkermans RP, Biermans M, Robberts B, et al. COPD prognosis in relation to diagnostic criteria for airflow obstruction in smokers. *Eur Respir J* 2014; 43(1): 54–63.
38. Bui DS, Lodge CJ, Burgess JA, et al. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir Med* 2018; 6(7): 535–544.
39. Lange P, Celli B, Agusti A, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med* 2015; 373(2): 111–122.
40. van Veen IH, Ten Brinke A, Sterk PJ, et al. Exhaled nitric oxide predicts lung function decline in difficult-to-treat asthma. *Eur Respir J* 2008; 32(2): 344–349.
41. Kharitonov SA, Robbins RA, Yates D, et al. Acute and chronic effects of cigarette smoking on exhaled nitric oxide. *Am J Resp Crit Care* 1995; 152(2): 609–612.
42. Lange P, Groth S, Mortensen J, et al. Pulmonary function is influenced by heavy alcohol consumption. *Am Rev Respir Dis* 1988; 137(5): 1119–1123.
43. Schünemann HJ, Grant BJ, Freudenheim JL, et al. Evidence for a positive association between pulmonary function and wine intake in a population-based study. *Sleep Breath* 2002; 6(4): 161–173.
44. Al Ghobain M. The effect of obesity on spirometry tests among healthy non-smoking adults. *BMC Pulm Med* 2012; 12(1): 10.
45. Salome CM, King GG and Berend N. Physiology of obesity and effects on lung function. *J Appl Physiol (1985)* 2010; 108(1): 206–211.
46. Landbo C, Prescott E, Lange P, et al. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Resp Crit Care* 1999; 160(6): 1856–1861.

- 
47. Olsen MH, Hansen TW, Christensen MK, et al. N-terminal pro-brain natriuretic peptide, but not high sensitivity C-reactive protein, improves cardiovascular risk prediction in the general population. *Eur Heart J* 2007; 28(11): 1374–1381.
48. Rodrigo GJ, Price D, Anzueto A, et al. LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2017; 12: 907–922.