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ORIGINAL RESEARCH

Determinants of airflow limitation in Danish adults – findings from the Health2006 cohort

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Background and aim: Airflow limitation may be found in patients with both asthma and COPD and is often associated with more symptoms and poorer outcome. We aimed to identify factors associated with airflow limitation in a well-characterized, population-based sample of adults.

Methods: From the Health2006 cohort, we selected participants aged ≥35 years at enrolment (n=2,959). Airflow limitation was defined as $FEV_1/FVC <$ lower limit of normal. Participants with (cases) and without (controls) airflow limitation were compared with regard to self-reported symptoms, medical history, atopy, lung function and exhaled nitric oxide. Between-group differences were analyzed using Chi-square and Mann–Whitney U tests, and effect size was estimated by logistic regression (reported as OR and 95% CI).

Results: We identified 313 cases, majority of which were female, reported poor overall health, physically inactivity and experienced respiratory symptoms within the previous year. The presence of airflow limitation was associated with BMI (OR 3.1 for overweight, $P<0.001$, CI 1.97–4.78), age (OR 2.3, $P<0.001$ for age 55+, CI 1.7–3.2), tobacco exposure (OR 1.6, $P=0.01$, CI 1.1–2.32, and OR 1.76, $P=0.019$, CI 1.2–2.3 for former and current smokers, respectively), sex (OR 1.6 for being female, $P=0.002$, CI 1.2–2.2), presence of specific IgE to common aeroallergen(s) (OR 1.4, $P=0.041$, CI 1.2–2.0), and ever being diagnosed with asthma (OR 1.6, $P=0.003$, CI 1.3–2.0).

Conclusion: Apart from tobacco exposure and age, the presence of airflow limitation was associated with being overweight, female, sensitized to common aeroallergens or ever having a diagnosis of asthma.

Keywords: epidemiology, cohort study, asthma, COPD, risk factors

Introduction

Chronic airways diseases are common, especially in the western world. In Denmark, the prevalence of COPD is 12%[1] among adults ≥45 years of age, likewise up to 10% of the Danish population is prescribed medication for asthma.[2] Despite traditionally being considered two very distinct diseases, asthma and COPD have several overlapping features, including the presence of airflow limitation.

In patients with asthma, more severe airflow limitation, as well as more pronounced bronchodilator reversibility, has been associated with higher mortality.[3,4] Although Santibanez et al[5] did not report the same association between airflow limitation and mortality in COPD patients, they did find an increasing risk of hospital admission for COPD exacerbation with higher degree of airflow limitation. Furthermore, Huang et al[6] found that airflow limitation ($FEV_1/FVC <0.70$) was independently associated with a higher mortality risk compared to individuals without either an asthma diagnosis or airflow limitation, and this risk was considerably higher in patients with both doctor-diagnosed asthma and airflow limitation.

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Provided that airflow limitation is an indicator of poorer outcome, interventions that preserve current level of lung function and slow down the rate of deterioration could possibly lead to a better prognosis. The most effective intervention to reduce decline of lung function is smoking cessation.[7,8] In COPD, inhaled corticosteroids (ICS) and bronchodilators may initially improve FEV_1, but the effect on long-term decline in lung function is at best not remarkable.[9–11] Treatment with ICS has been shown to reduce the annual decline in FEV_1,[12,13] and the earlier the initiation, the better the outcome and the lesser the amount of ICS and additional asthma treatment needed to achieve asthma control.[14–16]

Since time to initial treatment seems crucial for the long-term outcome, including decline of lung function, it is of outmost importance to intervene as early as possible in those individuals at risk of developing airflow limitation. The aim of the present study was, therefore, to identify, especially modifiable, factors, associated with airflow limitation in a well-characterized population-based cohort of adults and by that, potentially facilitate future interventions, which aim at reducing decline in lung function in individuals at high risk.

Methods

Cohort

The Health2006 cohort comprises a sample of Danish adults aged 18–69 years at inclusion, at the time living in the south-western part of the greater the Copenhagen area. A total of 7,770 individuals, all Danish citizens and born in Denmark, were invited to participate in a general health examination. Of these, 3,471 (44.7%) accepted the invitation and were examined between June 2006 and June 2008. The cohort has been described in detail elsewhere.[17] Participants <35 years of age at enrolment (n=512) were excluded from the present analysis, as the Danish National Board of Health recommends screening with spirometry in current or former smokers, ≥35 years of age, with a minimum of one respiratory symptom.[18] This resulted in a cohort of 2,959 participants (Figure 1).

Questionnaire

All participants answered an extensive questionnaire on self-perceived health, current and previous diseases (including eczema, rhinitis and asthma), intolerance reactions (food, alcohol, perfume and chemical substances), physical activity level, dietary habits, alcohol consumption, smoking habits, use of hormone replacement therapy after menopause, family and social relations, education and work and mental health.

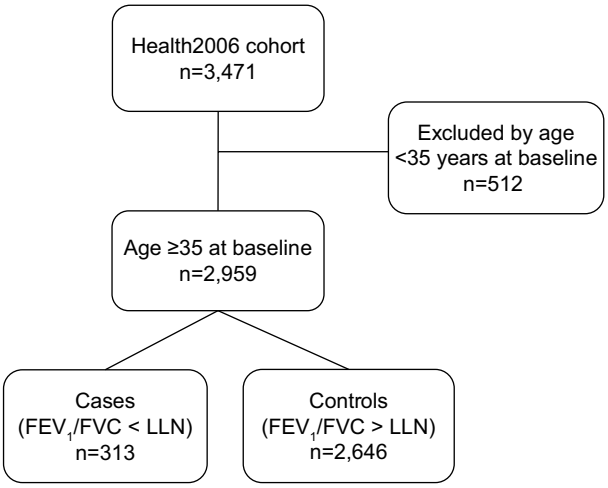

Figure 1 Selection and categorization of participants in the Health2006 cohort for present analyses.
Abbreviation: LLN, lower limit of normal.

Anthropometric measures and obesity

Height and weight were measured with light clothing and without shoes, BMI calculated as weight divided by height squared. Hip circumference was measured over the clothing on the widest part of the body. Waist circumference was measured directly on the skin, between the lower ribs and the iliac crest. Body fat percentage was measured using impedance.

Fitness and cardiovascular function

Fitness level was measured through the Danish Step Test,[19] a test with fixed step height but increasing pace through a maximum of six minutes. Pulse rate and systolic and diastolic blood pressures were measured at rest.

Sensitization to aeroallergens

Serum-specific IgE was measured for the four most common aeroallergens (birch, grass, cat and *Dermatophagoides pteronyssinus*), and classified as positive if >0.35 kU/L.[20] Skin prick testing for ten aeroallergens (birch, grass, mugwort, horse, dog, cat, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria alternate* and *Cladosporium herbarum*) was performed using the Soluprick system (ALK-Abelló A/S, Hørsholm, Denmark). Skin prick test reactivity was defined as a mean wheal diameter ≥3 mm.[21]

Lung function

Lung function was measured according to American Thoracic Society's and European Respiratory Society's (ATS/ERS) standards[22] with a SpiroUSB (Micro-Medical Ltd, Rochester, UK). Predicted FEV_1 was calculated based on height, age

and sex.[23] FEV_1 and FVC are expressed as percentage of predicted values, FEV_1/FVC as total percentage.

Fractional exhaled nitric oxide (FeNO)

FeNO, was measured with Niox-Mino (Aerocrine AB) according to ATS standards.[24]

Definitions

The smoking status of the participants was assessed through the questionnaire item "Do you smoke?", with the possible answers of "Yes", "No, but I have previously smoked" and "No, never". Pack-years were calculated by multiplying the duration (years) with intensity (grams tobacco per day, with one 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 non-drinkers if they had a weekly consumption <1 IU. BMI was divided into the following groups: underweight (<18.50), normal weight (18.5–24.99), overweight (25–29.99) and obese (>30).[25] Airflow limitation was defined as FEV_1/FVC below the Lower Limit of Normal (LLN).[26]

Statistical analyses

All analyses were done in IBM SPSS Statistics V.24 (IBM Corporation, Armonk, NY, USA), using 0.05 as the level of significance. Descriptive statistics are reported as median (IQ-range) for non-normally distributed data. Between-group testing was performed using the Mann–Whitney U test for numerical variables and chi-squared test for ordinal and categorical variables. Univariate logistic regression was used to identify factors associated with airflow limitation. Multiple regression models, adjusted for FEV_1 % predicted, with backward stepwise elimination was run for self-reported variables, clinical and paraclinical variables. All variables significant in the preliminary analyses were combined in a final logistic regression model, and findings were reported as OR with 95% CI.

Ethics statement

The Health2006 cohort was approved by the Ethical Committee of Copenhagen County (ID KA20060011). All participants provided written informed consent.

Results

Due to limitation of space, not all results are reported. Non-reported results were non-significant, including, but not limited to, waist and hip circumference and blood pressure (these results are available upon request).

Cohort characteristics

Present analysis included 2,959 participants (46% men and mean age 54 years at inclusion). A total of 61% were ex- or current smokers, and mean FEV_1 97.8% of predicted. (Tables 1 and 2)

Comparison of cases and controls

Airflow limitation was found in 313 individuals (10.6%), mean age 52.0 years, 37.4% men. Participants with airflow limitation were, as expected, more likely to be ever smokers (80.2%) and have a lower mean FEV_1 (83.0% of predicted) compared to controls, ie, participants without airflow limitation. Further details are given in Tables 1 and 2.

Factors associated with airflow limitation

The variables associated with the highest odds ratio for airflow limitation were increasing age (OR 2.08 [CI 1.29–3.37] and OR 2.29 [CI 1.66–3.15] for age 41–55 and >55 years, respectively), being overweight (OR 3.07 [CI 1.97–4.78]) and a history of tobacco smoking (OR 1.76 [CI 1.18-2-25] and OR 1.62 [CI 1.12–2.34] for current and former smokers, respectively). Further results are given in Table 3.

Discussion

The current study provides details on self-reported and clinical characteristics of participants with or without airflow limitation and identifies a number of variables associated with an increased risk of presenting with airflow limitation.

One reason no association between FeNO and airflow limitation was found could be the lower FeNO in our case group due to the larger number of current smokers, as smoking is associated with lower levelse of FeNO.[27] Ten Brinke et al[28] found a small, but significant, association between airflow limitation and FeNO (OR 1.7 for FeNO >10 ppb), but their cut-off value was low, compared to the 95th percentile value of 39 ppb found in healthy subjects in National Health and Nutrition Examination Survey (NHANES).[29] Bommarito et al[30] reported that a high FeNO was significantly associated with a high risk of asthma as well as a negative association between smoking and FeNO. Matsunaga et al[31] found FeNO to be a specific, though not very sensitive, marker for rapid decline of lung function. They also observed that a suppression of FeNO was associated with an improvement in airflow limitation.[32] In contrast, Tay et al[33] found no association between FeNO and chronic airflow limitation in patients with asthma.

Tobacco smoking is the most important risk factor for COPD development.[34] Thus, the higher risk of airflow limitation associated with smoking was not an unexpected finding in

Table 1 Self-reported characteristics of participants in the Health2006 study according to presence (cases) or absence (controls) of airflow limitation

	Controls n=2,646	Cases n=313	*P*-value
Smoking habits			
Current smokers, %	22.4	41.9	<0.001
Never-smokers, %	41.3	19.8	<0.001
Pack years	19.5 (19.0)	26.0 (25.7)	<0.001
Alcohol consumption			
Non-drinkers, %	5.6	6.7	NS
Weekly consumption, units[a]	8.0 (11.0)	8.0 (11.0)	NS
10 years of school or less, %	10.1	13.7	NS
Hormone replacement treatment (women only)			
Yes, %	34.9	35.8	NS
Number of years	7.0 (8.0)	5.0 (8.0)	NS
Symptoms last 12 months			
Rhinitis, %	51.9	56.1	NS
Asthma symptoms, %	2.5	17.0	<0.001
Dyspnoea at rest, %	26.9	48.5	<0.001
Dyspnoea during activity, %	6.5	10.0	0.021
Chronic bronchitis,[b] %	8.3	22.3	<0.001
Nightly respiratory symptoms, %	16.0	23.1	0.002
Wheezing, %	19.6	43.4	<0.001
Ever diagnosed with			
Rhinitis, %	17.4	22.3	0.034
Asthma, %	8.8	20.9	<0.001
Eczema, %	4.5	7.0	NS
Hypertension, %	31.4	30.1	NS
Diabetes, %	4.4	4.5	NS
Hyper-cholesterolaemia, %	34.7	30.5	NS
Self-rated[c]			
Overall health (1–5), mean (SD)	2.5 (0.8)	2.7 (0.9)	<0.001
Exercise habits (1–5), mean (SD)	3.2 (1.0)	3.4 (1.0)	0.013
Dietary habits (1–5), mean (SD)	2.7 (0.6)	2.7 (0.6)	NS
Social position (1–5), mean (SD)	2.7 (0.6)	2.7 (0.6)	NS

Notes: Using Chi-square and Mann-Whitney U-test. Unless otherwise stated, numbers are reported as median (IQ-range). [a]Calculated for people who reported a current alcohol consumption only. [b]Self-reported cough with sputum for at least 3 months/year for at least two consecutive years. [c]Measured on a scale from 1 to 5, where 1 is best.
Abbreviation: NS, not significant.

this study. Nakao et al[35] found OR of 1.91 for current smokers compared to never smokers, but no increased risk for former smokers, contrasting with our findings. However, the number of former smokers in their study was quite small, 9%, compared to our 36% of controls and 38% of cases, making it more difficult to show smaller differences between groups. Both active and passive tobacco smoking is associated with more symptoms, lower lung function, lower quality of life and a worse outcome for patients with asthma.[36] Though it could be argued that our finding of increased risk of airflow limitation with increasing tobacco consumption is a risk for developing COPD only, the fact that we also found an increased risk with both atopy and ever having had asthma, indicates that the higher OR related to smoking habits is for airflow limitation in general, not only for COPD in its traditional definition.[34]

Previous cluster analyses have described two obesity-related phenotypes of asthma, early- and late onset.[37] While early-onset asthma is often allergic, and made worse by obesity, late-onset is predominantly non-atopic, most often seen in women, and could be due to both local and systemic inflammatory effects of obesity.[38] In line with our findings, Nakao et al[35] found high BMI to be an independent predictor of airflow limitation (adjusted OR 2.05 for BMI >25). In contrast, Colak et al[39] found that a high BMI reduced the

Table 2 Clinical characteristics of participants in the Health2006 study according to presence (cases) or absence (controls) of airflow limitation

	Controls n=2,646	Cases n=313	*P*-value
Sex, % men	46.5	37.4	0.002
Age, years	52.0 (17.0)	52.0 (15.0)	NS
BMI[a] (kg/m^2)	25.3 (5.0)	24.6 (5.0)	<0.001
Normal or underweight, %	43.3	54.5	<0.001
Overweight, %	39.1	33.0	0.035
Obese, %	17.6	12.5	0.021
Fat percentage, %	29.2 (13.0)	30.0 (14.0)	NS
FEV_1, % predicted	101.0 (18.0)	83.0 (19.0)	<0.001
FVC, % predicted	105.0 (19.0)	106.0 (25.0)	NS
FEV_1/FVC, %	79.5 (7.0)	65.8 (7.0)	<0.001
FeNO, ppb	16.0 (13.0)	14.0 (14.0)	<0.001
Fitness level, mlO_2/kg/min	30.0 (11.0)	28.0 (12.0)	NS
Positive skin prick test, %	27.9	27.9	NS
Positive IgE,[b] %	21.8	19.3	NS
Systolic blood pressure, mmHg	124.0 (21.0)	128.5 (22.0)	NS

Notes: Using Chi-square and Mann-Whitney U-test. Unless otherwise stated, numbers are reported as median (IQ-range). Values in parentheses are IQ-range for the mean values. [a]BMI: Body mass index, using following categories: Normal or underweight (≤24.9), overweight (25.0–29.9), obese (≥30.0). FEV_1: Forced expiratory volume in 1 second. FVC: Forced vital capacity. FeNO: Fractional exhaled nitric oxide. [b]IgE: mmunoglobulin E. Positive for at least one of the four tested allergens: cat, grass, house dust mites and birch.
Abbreviation: NS, not significant.

probability of airflow limitation, defined as FEV_1/FVC <0.70 (adjusted OR 0.63 for BMI 25–29.9, adjusted OR 0.50 for BMI >35), the results remaining the same when defining airflow limitation as FEV_1/FVC < LLN. Others found that for a given BMI quartile, lung function was negatively associated with increasing waist to hip ratio, but less clearly directly associated with increasing BMI.[40] The effect was stronger in men than in women, possibly due to differences in distribution of adipose tissue between sexes. Obese women often have a smaller waist to hip ratio as the adipose tissue accumulates on the hip and thighs,[41] while men tend to develop abdominal obesity, which has an extra-thoracic restrictive effect on lung volumes.[42] Boulet & Des Cormiers[43] found self-reported asthma to increase linearly with BMI, though mostly evident in women with BMI of ≥30, and for men only with BMI of ≥40. The difference might be due to the heterogeneity of our participants, as Boulet and Des Cormiers[43] focused on asthma, not airflow limitation in general.

Overall, the number of women with respiratory disease, including COPD and lung cancer, has increased. The higher risk of airflow limitation for women may be due to women having caught up on the habit of smoking in the last decades, or it may simply be that women's lungs, being smaller than men's, are more vulnerable to damage.

Table 3 Factors associated with airflow limitation in the Health2006 cohort reported as odds ratios

	OR	95% CI	*P*-value
Sex[a]	1.61	1.20–2.16	0.002
BMI[b]			
Overweight	3.07	1.97–4.78	<0.001
Obese	1.70	1.08–2.68	0.023
Age[c]			
41–55 years	2.08	1.29–3.37	0.003
>55 years	2.29	1.66–3.15	<0.001
Positive specific IgE to aeroallergens[d]	1.44	1.18–1.98	0.041
Ever asthma	1.57	1.32–2.02	0.003
Smoking habits[e]			
Current smoker	1.76	1.18–2.25	0.019
Former smoker	1.62	1.12–2.34	0.010

Notes: Adjusted for FEV_1. [a]OR for women, compared to men. [b]BMI: Body mass index. Reference group normal/underweight. [c]Compared to age <41 years. [d]IgE: Immunoglobulin E. Positive for at least one of the four tested allergens: cat, grass, house dust mites and birch. [e]Compared to never-smokers.

Conclusion

The present study showed that being females, being overweight, a history of ever having received a diagnosis of asthma and sensitization to common aeroallergens, together with tobacco exposure and increasing age, were associated with the presence of airflow limitation. Longitudinal studies are required to determine causality and to identify risk factors most suited for intervention to prevent loss of lung function over time.

Disclosure

The authors report no conflicts of interest in this work.

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