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Predictors of new airway obstruction - an 11 year´s population based follow-up study

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Abstract

In the present study we aimed to investigate the incidence and predictors of spirometry based airway obstruction in a representative population-based sample.

Altogether 3863 subjects, 1651 males and 2212 females aged $\geq$ 30 years had normal spirometry in year 2000. 53% of them were never and 23% current smokers. A re-spirometry was performed 11 years later. Several characteristics, such as level of education, use of alcohol, physical activity, diet using AHEI index, BMI, circumwaist, sensitive CRP and cotinine of the laboratory values and co-morbidities including asthma, allergic rhinitis, sleep apnoea and chronic bronchitis, as potential risk factors for airway obstruction were evaluated.

Using FEV_1/FVC below the lower limit of normal, we observed 124 new cases of airway obstruction showing a cumulative 11-year incidence of 3.2% and corresponding to an incidence rate of 5.6/1000 PY. The incidence rate was higher in men than in women (6.3/1000PY vs. 5.0/1000PY, respectively). The strongest risk factors were current smoking (OR 2.5) and previously diagnosed asthma (OR 2.1). Sensitive CRP associated with the increased risk and high AHEI index with the decreased risk of airway obstruction.

Using the similar study approach our findings on the incidence of airway obstruction are in line with the previously published figures in Europe. We were able to confirm the recent findings on the protective effect of healthy diet.

Keywords: COPD, airway obstruction, spirometry, incidence, healthy diet

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity, disability and death worldwide [1, 2]. Based on a global estimate in 2010 the prevalence of COPD in adults over 30 years of age was 11.4% being more prevalent among males (14.3%) than females (7.6%) [3].

In studies on COPD incidence, two main approaches have been used. First, diagnosis based studies have attempted to define COPD based on clinical outcomes such as outpatient contacts, hospital visits for exacerbations, or self-reported physician diagnosed COPD. These studies have reported incidence rates around 2.6–2.9 cases / 1.000 patient years (PY) with higher incidence rates found in males and among older age categories [5,6]. The second approach is based on by showing irreversible airway obstruction in spirometry. Furthermore, the definition of airway obstruction varies. Many epidemiological studies have used the Global Initiative on Obstructive Lung Disease (GOLD) definition of a fixed ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) below 0.70. Fixed ratio has the benefit of easy comparability between populations, but is known to give false positives in subjects over 50 years of age. One example of this is the Rotterdam study, the incidence was almost 50% lower when population based reference values were used instead of the fixed ratio (5.5/1.000 PY vs. 8.9/1.000 PY), respectively [7].There is a large number of population based epidemiological studies that have evaluated the incidence of airway obstruction based on fixed ratio with widely varying incidence rates, 2.8–16.0 /1.000 PY [7-

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12]. Population age distribution, smoking habits and sampling differences can partially explain these widely varying incidence estimates.

Smoking is the main causative factor for COPD [2], but also other -causative and predisposing - factors have been recognised. Many of them are linked to low socioeconomic status [13], occupational exposures [14] and old age [15]. Of studied biomarkers, sensitive C-reactive protein shows the most constant association to low lung function and COPD [16]. Recently the diet has become of great interest, especially the association between low vitamin D levels and declined lung function [17], even though no causality to the incidence of COPD could be observed [18]. Also an association has been observed between high consumption of processed meat and lower lung function [19], whereas high fruit and vegetable consumption lowered the risk of COPD among current and ex-smokers [20]. Lately, high Alternate healthy eating index (AHEI 2010) has been associated with a lower risk of COPD [21].

The primary objective of this study was to investigate the incidence of airway obstruction in a population with high standard of living and smoking steadily decreasing [22, 23]. Spirometry based incidence on airway obstruction have never been published in Finland. The secondary objective was to find out associative factors of development of airway obstruction.

Methods

A sample of 9922 subjects aged 18 years or over was drawn from the population register (two-stage stratified, random sample) and invited to a comprehensive health survey (Health 2000 survey) in

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2000-2001. Of these subjects, 8028 (3637 males and 4391 females) were aged 30 years or over, and of whom altogether 6354 (79%) subjects completed the health examination, donated blood samples, and performed spirometry.

All study subjects of Health 2000 survey who lived in Finland were invited to participate Health 2011 survey (n=8135 subjects), and 58.2% (4736/8135) of them completed the health examination. The study population in the present study comprised of those 3863 subjects who were aged 30 years or over in Health 2000, participated and performed spirometry in both Health 2000 and Health 2011 surveys and had normal spirometry in Health 2000 survey.

Our aim was to analyse how baseline data collected in Health 2000 survey predicted airway obstruction in follow-up until Health 2011 survey. In Health 2000 survey information on age and gender (female/male) were obtained from population register. Height, weight and circumwaist were measured. Body mass index (BMI) (weight (kg)/height^2 (m^2)) was determined. The use of alcohol during previous 12 months was determined and categorised as: no, seldom (use of alcohol twice in a month or less) and often (use of alcohol once in a week or more often).

Smoking history was obtained through a standard interview and classified into three categories: never-smokers (those who had smoked daily less than 1 year during their life-time and quit smoking at least one month earlier), former smokers (those who had smoked daily over a year and quit smoking at least one month earlier) and current smokers (those who had smoked daily over a year and at least one cigarette, cigar or pipe for less than a month ago at any time preceding the survey). Educational level was categorised into three groups (basic, secondary, or higher). Leisure physical

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activity was classified into three groups: low (little physical exercise), moderate (exercise in connection with some hobbies or irregularly), or high (regular exercise).

Subjects were considered asthmatic if they reported that they had been diagnosed with asthma by a physician, that they were currently in a physician's control and received medication for asthma. The history, symptoms and possible findings of allergic rhinitis, sleep apnoea and chronic bronchitis were inquired about in the basic questionnaire and categorised as having these or not.

Participants' habitual dietary intake over preceding 12 months was collected with a validated 128-item semi quantitative food frequency questionnaire (FFQ) [25, 26]. Adherence to the healthy diet was measured using the Alternate Healthy Eating Index (AHEI) developed by McCullough et al. (2002) [27]. The AHEI in our data included the intake of seven components (vegetables; fresh fruits and berries; nuts and legumes; rye; the ratio of white to red meat; the ratio of polyunsaturated to saturated fat; trans fat), which were divided into sex-specific quintiles. The first six components received scores in an ascending order, so that one point was assigned for intakes in the lowest quintile and five points for intakes in the highest quintile. The trans fats component received scores in the descending order, with the lowest quintile gaining a value of five points and the highest quintile a value of one point. The total score ranged from 7 (worst) to 35 (best), with higher score values representing greater adherence to a healthy diet. Total energy in take was measured in kilocalories (kcal) according to the FFQ.

Serum samples used to characterise the participants were collected and frozen at -20 °C and stored at -70 °C. Cotinine concentrations were determined by a modified method of the Nicotine Metabolite RIA kit (Diagnostic Products Corporation, LA, USA). For cotinine a cut-off point of

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100 µg/L or over was used to separate smokers from non-smokers. The level of sensitive C reactive protein (sCRP) was determined using a chemiluminescent immunometric assay (Immulite, Diagnostic Products Corporation, Los Angeles, CA, USA).

In Health 2000, Vitalograph bellow spirometers (Vitalograph Ltd., Buckingham, England) were used, while in Health 2011 the Medikro® SpiroStar flow-volume spirometer and Medikro ® Spiro2000 software, was used. To ensure comparability between the measurements a validation study was performed, which showed no significant difference between the two devices [24]. The spirometers were calibrated with a one-litre calibration pump, and the equipment was checked every morning before the measurements. The measurements were made by specially trained laboratory technicians following standard guidelines and instructions. The technicians demonstrated the test procedure to all subjects individually. When the subject had learned the technique and rehearsed it once or twice, the aim was to produce at least two as consistent curves as possible. For forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) the technician instructed the subjects to fill their lungs with air and then to exhale as forcefully and completely as possible, urging them towards the end of the test. Failed efforts and those with questionable performance due to fatigue, or otherwise poor co-operation were excluded from the analysis. The quotient FEV_1/FVC was calculated using the highest readings of FEV_1 and FVC from technically acceptable efforts recorded in BTPS (body temperature and pressure, saturated with water vapour) values. FEV_1/FVC below the lower limit of normal (< LLN) was considered to indicate airway obstruction. Bronchodilation was not performed for all subjects. The individual results were computed on the basis of the GLI reference values [4] for corresponding age, sex and height were used. Development of a new airway obstruction was analysed from the spirometry performed in Health 2011.

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Health 2000 study was approved by the Ethics Committee for Epidemiology and Public Health in the Hospital District of Helsinki and Uusimaa and Health 2011 in the Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa. All participants gave their written informed consent.

The sampling design was accounted for in all analyses using the survey package [28, 29] of the R statistical software package [R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/]. The effects of oversampling of the 80-year old and older in 2000, and nonresponse were accounted for using the inverse probability weighting [30].

Regression analyses were based on generalised linear models. In addition to the simple regression models containing the risk factors one at a time, in which only age and sex were adjusted for (model 1), we adjusted also for age, sex and level of education (model 2), for age, sex and smoking (model 3), for age, sex, level of education and smoking (model 4) and also a fully adjusted multiple regression model containing all aforementioned risk factors (model 5) was analysed. Crude incidence rates and their 95% confidence intervals were calculated per 1000 person years.

Results

There were altogether 3863 subjects, 1651 (42.7%) males and 2212 (57.3%) females, with normal spirometry during the first survey and a re-performed spirometry 11 years later. Baseline

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characteristics in the study population including demographics, physical examinations, tested laboratory values and patient reported outcomes at baseline are described in Table 1.

New cases of airway obstruction occurred in 124 subjects, with a cumulative 11-year incidence of 3.2% corresponding to an incidence rate of 5.6/1000 person-years (PY) (95% CI 3.8–5.6) (Table 2). The incidence rate of males was higher (6.3/1000PY, 95% CI 4.9–8.2) and that of females (5.0/1000PY, 95% CI 3.9–6.6). The highest incidence rate, 9.9/1000PY (95% CI 4.8–16.7), was in the age group of 65–100 years.

The development of airway obstruction associated in fully adjusted multiple regression model with current smoking, previously diagnosed asthma, increasing sCRP and decreasing AHEI index, and of these current smoking and previously diagnosed asthma were the strongest risks for airway obstruction (Table 1). In basic model with age and sex adjustment development of airway obstruction associated also with low physical activity, chronic bronchitis, decreasing BMI and waist circumference, and additionally, decreasing AHEI index meaning healthy diet protected from airway obstruction whereas the total energy intake did not have an effect. Cotinine had no association with airway obstruction in fully adjusted model (not reported). Cotinine and self-reported smoking are indicators of same phenomenon taking power in analysis from each other, though cotinine ≥ 100 µg/mL had an association with airway obstruction in other models (Table 1).

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Discussion

In this study the incidence of airway obstruction based on spirometry (FEV_1/FVC below the lower limit of normal) was evaluated in a population based cohort (age > 30 years of age) with a follow-up of 11 years. The overall incidence rate was 5.6/1000 PY, 6.3/1000 PY for males and 5.0/1000 PY for females. The main determinants for the development of airway obstruction were current smoking, previously diagnosed asthma, increased sCRP and low AHEI index.

In previous studies the incidence rates of COPD have varied from 2.6–16.0 per 1000 PY [5-12]. The wide variation can be at least partially explained by differences in study approaches. When the incidence rates are based on retrospective health registries, such as given diagnoses, hospital admission data or use of medication, the data is highly dependent on the probability of a patient seeking for medical help, the diagnostic practices of different kind of health-care facilities as well as the coverage of register data. Studies evaluating self-reported physician-diagnosed COPD, symptoms or medications indicative of COPD are dependent on the participants' understanding on his or her health.

When the estimates are based on spirometry data, it is possible to find also the undiagnosed cases. Spirometry based incidence studies are also more comparable to each other, even though the definition of the cut-off value for airway obstruction can vary. Fixed FEV_1/FVC –ratio used frequently in many epidemiological studies is naturally lower in tall subjects and reduces with normal ageing. In the present study we used the lower limit of normal (LLN) which is individually

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predicted to determine airway obstruction in comparison to age and body size match healthy, non-smoking population. These estimates do not cause age or size related bias in the results. In the Rotterdam Study, the pre-bronchodilator $FEV_1/FVC < 0.70$ or in the absence of spirometry, COPD diagnosis verified from medical records, resulted in an incidence rate of 8.9/1000 PY. Based on spirometry data alone the incidence rate of 11.7/1000 PY was observed with fixed ratio and much lower incidence of 5.2/1000PY with LLN criteria [7]. This was in line with our results. In the Netherlands, however smoking was more prevalent. Only 35% of subjects were non-smokers, compared to 53% in the Finnish population [7].

Current smoking and previous diagnosis of asthma associated independently to incident airway obstruction, both well recognised risk factors of COPD [2]. Smoking had decreased in the Health 2000 survey significantly during the follow-up time of 11 years, among the men in all age cohorts and among the women in age cohorts of 30–54 years [23]. The earlier finding of an association between sCRP and COPD was also confirmed in this study [16].

The protective effect of a healthy diet has been under recent research interest. In this study, an inverse association between AHEI index and incident, spirometry based airway obstruction was observed. The association reminded significant in all models performed which means healthy diet protected from airway obstruction regardless of energy intake. High AHEI index reflects the protective effect of high intakes of whole grains, polyunsaturated fatty acids, nuts and long chain omega-3 fats and low intakes of red/processed meats, refined grains and sugar sweetened drinks. Earlier studies have reported that high fruit and vegetable consumption [20] and more-frequent fish intake [26] can protect from the disease. AHEI score has been studied in clinical COPD only once

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and an inverse association between higher AHEI score and the incidence of COPD was observed [21]. In this large prospective study diagnosis of COPD was based on self-reported questionnaire. As a validation study, a random sample of medical records of the participants were assessed. In 71% of the COPD cases spirometry was available confirming the self-reported COPD [21].

A limitation in our study is that bronchodilation test was not performed for all, and therefore, we could not separate reversible and non-reversible airway obstruction. However, our study population was aged 30 and over at baseline and only 14 subjects (11.2%, Table 1) with new airway obstruction reported to have asthma in Health 2011, and therefore apparently most of these with new airway obstruction are COPD (33). Values of the risk factors, such as smoking status, sCRP and AHEI index, might have changed during follow-up and have some effect on our results, but as our objective was to assess the potential predictors of obstruction incidence we did not evaluate the associations of risk factor changes during the follow-up and the obstruction incidence. Furthermore, these associations are likely to operate in two directions as, for example, weight changes according to the lifestyle factors (daily energy intake and physical activity). Additionally, we had no data about smoked pack-years and respiratory medications used in pulmonary diseases. The follow-up time of 11 years might be, especially, in the younger age groups too short for the development of airway obstruction, and correspondingly, in older age groups too long.

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Conclusions

Using the similar study approach our findings on the incidence of airway obstruction are in line with the previously published figures in Europe. Our study nicely completed the previous findings and further addressed the importance of healthy diet as an independent risk factor for the development of airway obstruction.

The authors report no conflicts of interest.

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