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Predictors of COPD symptoms – does gender matter?

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Abstract

Though COPD patients frequently report symptoms, it is not known which factors determine the course of symptoms over time and if these differ by gender. This study investigated predictors for presence, development and remission of COPD symptoms in 816 men and 312 women completing three years follow-up in the Euroscop Study.

Explanatory variables of treatment, pack-years smoking, age, FEV_1 % predicted, annual increase in FEV_1 and number of cigarettes smoked, body mass index and phadiatop were included in GEE logistic regression analyses. Interaction terms of gender*explanatory variables were tested.

Over three years, similar proportions of men and women reported symptoms. In men only, higher FEV_1 % predicted was associated with reduction in new symptoms of wheeze and dyspnea and symptom prevalence reduced with annual FEV_1 improvement and phlegm prevalence reduced with budesonide treatment (OR 0.66 95%CI 0.52-0.83). Additionally an increase in the number of cigarettes smoked between visits increased the risk of developing phlegm 1.40(1.14 - 1.70) and wheeze 1.24(1.03 - 1.51) in men but not women.

This study shows that longitudinally symptom reporting is similar by gender. The clinical course of COPD can differ by gender as men show greater response to cigarette exposure and treatment.

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Introduction

It is of clinical importance to understand the key factors that will influence the course of Chronic Obstructive Lung Disease (COPD). Factors possibly altering the course and presentation of the disease are for instance medication, anti-smoking advice or lung function. To apply appropriate medical interventions it is also essential to understand if there may be differences in the cause and outcome of the disease between male and female patients. Despite symptoms being one of the most troublesome features for an individual with COPD, virtually nothing is known about gender differences in risk factors for the course of symptoms of patients with mild to moderate COPD. There is only limited literature that describes risk factors such as age, smoking history and industrial exposure for the presence, development and remission of respiratory symptoms in the general population, and in patients diagnosed with Chronic Obstructive Lung Disease who quit smoking (1-4). In light of the increase in incidence and prevalence of COPD and its mortality in females (5;6) and evidence from cross-sectional studies indicating that the presence of respiratory symptoms in COPD is associated with gender as well as lung function, smoking, and treatment (7-11) it is now imperative to investigate how these factors are associated with the course of symptoms longitudinally.

It has been reported that women report more frequently dyspnea and cough but less often phlegm, than males in the general population (12). This may be in part biologically driven,

since females have smaller airway size compared to males (13) and lower threshold of cough reflex sensitivity (14). Furthermore, the sociological aspect of women not liking to admit to having phlegm may play a role in this respect (12). A lower lung function has also been associated with the presence of respiratory symptoms, both in the general population and patients with COPD (15-17). Since this has been established in several cross-sectional studies, the question arises as to whether longitudinal changes in forced expiratory volume in one second (FEV_1) are associated with subsequent incidence and remission of symptoms and whether this differs by gender.

Treatment with inhaled corticosteroid (ICS) is another factor that may affect symptoms of COPD, although evidence to date is inconclusive with regard to improvement in symptoms after treatment with ICS (7;18-21). Symptoms were not the primary outcome in any of the published long term intervention studies with ICS in COPD patients, all of which assessed lung function as the main outcome. Gender differences were also not assessed which may have masked differences between men and women.

Smoking is another important factor that may influence symptom incidence or remission and may show gender differences. Interestingly, the Tucson Epidemiological Study combined with data from a Polish study showed that smoking cessation or reduction diminished symptoms of chronic cough, phlegm and dyspnea by up to 50% in both sexes (3).

The differences in prevalence, incidence and remission of COPD symptoms over a three year period will be reported for men and women with mild to moderate COPD patients using data

from the Euroscop Study, which has already been published(19). The study will additionally assess the association of these key risk factors with the development or remission of symptoms.

Methods

The design of the Euroscop study has been discussed elsewhere (19). In brief, 39 study centres in 9 European countries participated in a randomised double blind placebo controlled study testing twice-daily treatment with 400μg budesonide (via Turbuhaler) versus placebo. Persons were aged 30 to 65 years and were currently smoking at least 5 cigarettes a day and had smoked cigarettes for at least 10 years or had a smoking history of at least five pack-years. They had an FEV_1 post bronchodilation between 50 and 100% and the ratio of pre-bronchodilator FEV_1 to slow vital capacity less than 70%. Increase in FEV_1 after inhalation of 1mg terbutaline had to be <10% of normal predicted value. Patients with a history of asthma, allergic rhinitis or who had used oral glucocorticosteroids for more than 4 weeks during the six months prior to study entry were excluded.

Baseline data regarding height, weight, smoking and smoking history were taken. Symptoms were measured at the baseline randomisation visit (Month 0), with three more measurements taken at 12-monthly intervals (12 months, 24 months and 36 months post-randomisation). The symptoms analysed were: wheezing or whistling in the chest at any time; attacks of shortness of breath after activity; cough during the day or night in winter; phlegm during the day or at night in the winter. Although other symptom data such as ever trouble with breathing, bringing up phlegm first thing in the morning in winter and cough first thing in the

morning in winter were collected, the main symptoms chosen were considered the most clinically appropriate, most accurate for patients to recall, and with high prevalence. Spirometry was performed at each visit for up to 36 months and the process is described elsewhere(19). The largest values for slow vital capacity and FEV_1 were accepted from three maneuvers, provided the second largest measure was within 0.1L or 5% of the largest. FEV_1 was obtained 15 minutes after the inhalation of 1mg terbutaline. Information regarding smoking habit was also collected at each three monthly visit. Specific IgE was measured at baseline, using the Phadiatop test (Pharmacia & Upjohn, Uppsala, Sweden).

Statistical analyses: The prevalence of symptoms at the four annual visits and the incidence and remission between those visits were analyzed using Generalized Estimating Equations (GEE) for the binomial family with identity link and unstructured correlation-structure, with clusters identified by persons, using the package Geepack of R (22;23)

For the incidence and remission models, the change in symptom status was used between randomization and the first 12 monthly visit (0-12 months) and then between 12-24 months and 24-36 months. In the analysis of the incidence only those observations of a person were included with no symptom at the start of the three 12 month's pairs and for remission only those observations with the symptom under study present at the start. Each person could contribute with 1 to 3 observations. Time (or net change over time) was a variable included in the prevalence models only. Net change over time was calculated using observations at months 0, 12, 24 and 36. In the prevalence models each person could participate with 1 to 4 observations. The GEE Logistic regression models allow for within-person repeated

measures and unequal numbers of observations and were used to calculate odds ratios for risk factors associated with prevalence, incidence and remission of each individual symptom. Time invariant co-variates were treatment group, gender, age (10-year units), BMI (calculated as weight (kilograms) divided by height (metres^2) and divided into categories: underweight = < 18.5 kg/m^2; normal weight = 18.5 – 24.9 kg/m^2; overweight = 25.0 – 29.9 kg/m^2; obese ≥ 30 kg/m^2), atopy (Phadiatop positive) and pack-years of smoking, all measured at randomization (month 0). FEV_1% predicted (in 10% units), measured at the previous visit or at the start of a pair of visits, FEV_1 12 month change between a pair of visits (100ml) and change in daily number of cigarettes (per 10 cigarettes) smoked since previous visits or between visits were used as time-varying covariates. A variable of actual number of cigarettes smoked per day at time of randomization was tested in the models instead of, or together with pack-years, but gave no additional information and was omitted from current analyses. Interaction terms of gender with all variables were tested in all models to assess any differences in associations between men and women. Interaction terms of time with all the variables within the prevalence models were also tested. Additional models stratified by treatment were tested to investigate if findings within the gender models held true. Results are presented as odds ratios (OR) with 95% confidence intervals (CI). Binary variables were evaluated using the Pearson Chi-square test, continuous and categorical variables by the Wilcoxon and the Kruskal-Wallis test respectively, using the F distribution. The power of this study was based on the power calculated for the primary variable in the original Euroscop analysis i.e. decline in FEV_1. For this post-hoc analysis a power calculation was not performed as it was not possible to change the numbers of patients observed.. The power of the study to assess the outcomes under consideration can be assessed by the 95% CI's.

Results

Demographics

The demographics and baseline characteristics of the population with complete data on symptoms and covariates are shown in Table 1. Men had significantly greater pack-years of smoking than women and more frequently a positive Phadiatop test and overweight or obesity compared to women. Women compared to men reported significantly more cough symptoms with a similar trend towards wheeze at randomization. Fifty-seven male and 7 female patients quit during the study and sustained quitting for 4 or more visits (1 year) and did not return to smoking. All other patients either smoked continuously or had failed quit attempts that lasted less than one year. There were no significant differences in the proportions of male and female continuous smokers.

Prevalence of symptoms

The prevalence of symptoms at randomization (month 0), stratified by gender is shown in figure 1. Respiratory symptoms were rather prevalent in this population, ranging from 34 to 59 per cent depending on type of symptom and gender. Women have greater prevalence of all symptoms at all time points except phlegm. However it should be noted that by 36 months any significant differences have disappeared for all symptoms despite the underlying population proportions at each time point remaining relatively stable.

Incidence and remission of symptoms

The subsequent incidence and remission of symptoms by paired visits (i.e. from 0-12 months, 12-24 and 24-36 months) are shown in figure 2. The figure shows the number of men and women with new development (incidence) or remission of a symptom during any given time period out of the number within the population from the same time period. Only wheeze showed difference in incidence with women reporting greater incidence at 12-24 months. Women also reported greater remission for wheeze, dyspnea and cough than men in the first 12 months. There were no other significant differences in incidence or remission.

Risk factors for prevalence, incidence and remission of symptoms by gender

Table 2 shows adjusted odds ratios for prevalence, incidence and remission of COPD symptoms by gender in association with significant risk factors. The table only shows the key factors which had a significantly different effect in men and women for *any* of prevalence, incidence or remission. This is indicated by a # symbol. Covariates of pack years of smoking and atopy were tested in the models but did not show any significant gender differences in association with symptoms. BMI showed a significant gender difference for incidence of cough with women who are underweight showing increased incidence of cough (OR 12.23 95% CI 1.48-101.03) whilst men showed a decrease (OR 0.80 95% CI 0.16-4.08). However, these estimates are very wide for women due to small numbers with low BMI (n=17).. BMI showed no other significant gender differences. Time, only included as a covariate in the prevalence model, showed that for every year of observation, men had a significant reduction in phlegm symptoms (OR 0.87 95%CI 0.82-0.93), an effect not seen in women (OR 0.99 95%CI 0.90-1.09). Age only showed a significant difference between men and women for incidence of dyspnea with women showing a significant reduction in new symptoms of

dyspnea for every ten year increase in age, recorded at the first visit (OR 0.47 95% CI (0.30-0.74) an effect not seen in men (OR 0.88 95% CI (0.70-1.10).

The table shows that for every 10% increase in FEV_1 at the previous visit men had significantly reduced risk of wheeze and dyspnea, which was not observed in women. For every 100 ml increase in FEV_1 over time men were significantly likely to have remission of their cough symptoms, whilst women were not.

Change in smoking (increasing cigarettes by 10 per day during the year of observation) had a significantly different effect in men and women for development of new symptoms only. An increase in 10 cigarettes smoked per day was associated with an increased risk to develop new symptoms of wheeze and phlegm in men but not women, in whom the risk of wheeze even decreased. There were no significant gender differences in the association of change in smoking with symptom prevalence or remission. Figure 3 illustrates how change in lung function (10% units) and increasing the number of cigarettes smoked impacts upon symptom incidence prevalence and remission. It illustrates that generally, there is little difference between men and women longitudinally for symptom incidence, prevalence or remission in association with either smoking or change in lung function after adjusting for confounding factors.

Treatment with budesonide significantly reduced phlegm in men but not women and had no differential effect on any other symptoms.

The results outlined above all refer to significant differences *between* men and women The * symbol in table 2 illustrates where there are differences *within* sexes. For example, males who increase their FEV_1 by 10% during any time period reduce their incidence and increase their remission of wheeze and cough during that year compared to those who do not show an improvement in FEV_1. This effect is not observed in women. Similarly for men who have incremental increases in FEV_1 over time compared to men who do not, incidence and prevalence of wheeze and cough is again reduced, an effect not experienced by women. Phlegm and dyspnea also have greater remission for this change in lung function in men but not women.

Discussion

This study has shown that gender can be important when assessing predictors of symptoms in male and female patients with mild to moderate COPD. We performed stratified, adjusted analyses and discovered different risk factors for symptoms in men and women. Of particular note was the observed beneficial effect of higher FEV_1 % predicted at randomization and larger increase in FEV_1 over time on symptoms, and this was more frequently observed in males. Men additionally had reduced likelihood of phlegm, and particularly so if treated with budesonide, which was not the case in women. Increasing the number of cigarettes smoked between visits was associated with more new symptoms of phlegm and wheeze in men only. Whilst we performed a large number of analyses we do not believe that these findings are the result of multiple comparisons because only *a priori* hypotheses were tested that were postulated based on the literature.

Symptom prevalence over the study period showed significantly greater wheeze, dyspnea and cough for women up to 24 months but all significant differences had disappeared by 36 months, despite underlying population proportions remaining relatively static. The loss to follow up would not likely explain the changes in proportion. The proportion of patients reporting symptoms in this trial remained high for both sexes at 36 months ranging from 30% to over 50% according to symptom. Why the gender difference disappears is not known but could be merely an artifact of the time scale enforced by the study and could potentially reappear at a later time, as other studies have reported women report more symptoms of asthma and have different pain and tolerance thresholds (25-27). However, that the gender differences for remissions are only observed in the first year of the study- with women reporting greater remission – suggests that time may impact upon reporting. This study shows symptom reporting in mild to moderate COPD is similar between men and women longitudinally.

The finding that FEV_1 % predicted values and the change in FEV_1 are related to symptom incidence, prevalence and remission in male COPD patients, indicates that in men particularly, symptoms are a good predictor of disease status and/or underlying disease activity. To our knowledge no other study to date has assessed how lung function predicts change in symptoms in COPD patients. Wang et al recently reported data from the Vlagtwedde/Vlaardingen study in the Netherlands, studying subjects aged 15-35 years (17). They found that presence of all symptoms was associated with a reduced maximal FEV_1 in men and having wheeze and dyspnea was strongly predictive of lower vital capacity. In

women only cough, wheeze and dyspnea were associated with lower FEV_1 but phlegm was not. Sherrill et al found in the longitudinal Tucson Study with up to 14 years follow up, that symptomatic males had significantly lower FEV_1 and FVC measures than symptomatic women (16). The relationship of cough and reduced lung function was limited only to men, supporting our findings of a stronger male relationship between symptoms and lung function.

Stratified analyses showed that the risk of developing new symptoms caused by a change in smoking significantly differed by gender (table 2 and figure 3). Men exhibited a positive association, i.e. an increase in the number of cigarettes smoked was associated with an increased risk to develop new symptoms of wheeze and phlegm, whereas conversely wheeze was less likely to develop in women. We hypothesise that a reason for the observed differences could be a different physiological response to the oxidation process resulting from exposure to the components of cigarette smoke. We choose to show the effects associated with an increase in smoking, but we could have conversely shown how a decrease in smoking affected symptoms, using the reciprocal data. Whichever data is used, there appears to be a gender difference and this clearly requires further research.

Treatment with budesonide appeared to make little difference to symptoms, except with regard to phlegm, where prevalence was reduced, particularly in males. Previous studies were not designed to assess the impact of inhaled steroid use on symptoms in COPD, did not report symptoms (18), showed a beneficial effect on a composite score (20), on dyspnea only (7), or did not show any significant effect (21). However, none of these studies stratified

analyses by gender. When this was done in our study the beneficial effect of budesonide treatment on phlegm was limited to men with an odds ratio of 0.66(CI 0.52-0.83), compared to an OR in women of 1.22(CI 0.84-1.77). This outcome is unlikely to have been related to smoking as all models were adjusted for smoking history and any changes in smoking between visits. When other smoking variables such as quitting smoking since the last visit, quitting at baseline or absolute number of cigarettes smoked were tested separately in the models the results remained the same. Compliance with treatment was not measured in the EUROSCOP study and possibly there was a difference in compliance between men and women. However, if compliance were greater in males, one would expect men to report significantly greater remission of symptoms compared to women throughout three years of follow up. This was not the case and women initially reported greater remission all other symptoms in the first year of follow up. Another more likely explanation may be a modifying effect of gender on steroid effectiveness as has been previously shown in asthma (24).. Our results stress that future epidemiological and longitudinal clinical trials in COPD should analyze treatment effects on symptoms stratified by gender due to possible benefits that may be obscured by analyzing both sexes together.

This study for the first time addressed the course of symptoms in men and women with mild to moderate COPD, half of whom were treated with budesonide. A relatively high proportion of all patients reported symptoms throughout the study period, but longitudinally the differences between men and women disappeared. After adjusting for covariates that could confound the outcome, men were found to have a significantly stronger association between both higher FEV_1 % predicted at randomization and higher increase in FEV_1 over time and a

reduced prevalence and incidence of symptoms. Treatment with budesonide reduced symptoms of phlegm in men only. Increasing the number of cigarettes smoked caused a contrasting effect by gender, with only men exhibiting an increase in wheeze and phlegm. These results show that in the clinical course and presentation of mild to moderate COPD gender can matter and men show greater response longitudinally to both steroid treatment and smoking.

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Table 1: Characteristics of patients at baseline (Month 0)

	Women (n=312)	**Men (n=816)**	**p-value**
Treatment with budesonide, n (%)	150 (48)	408 (50)	0.56
Pack-years of smoking, median (range)	30 (22 - 38)	39 (29 - 51)	< 0.001
Age, median (range)	52 (47-58)	53 (48 - 59)	0.06
FEV_1 % predicted, median (range)	81.1 (70.2 - 88.6)	79.2 (68.3 - 88.4)	0.42
BMI class < 18.5, n (%)	17 (5)	9 (1)	<0.001
BMI class 18.5 - 24.9, n (%)	203 (65)	404 (50)	
BMI class 25.0 - 30.0, n (%)	75 (24)	322 (39)	
BMI class 30.1 - 43.9, n (%)	17 (5)	81 (10)	
Phadiatop positive, n (%)	30 (10)	173 (21)	< 0.001
Wheeze, n (%)	185 (59)	435 (53)	0.07
Dyspnea, n (%)	124 (40)	290 (36)	0.19
Cough, n (%)	185 (59)	386 (47)	< 0.001
Phlegm, n (%)	112 (36)	320 (39)	0.31

Data are presented with the median and inter-quartile range where appropriate. Binary variables were evaluated using the Pearson Chi-square test,continuous and categorical variables by the Wilcoxon and the Kruskal-Wallis test respectively, using the F distribution.
BMI = body mass index
FEV_1 = forced expiratory volume in one second

Table 2: Generalized Estimation Equations (GEE) model showing adjusted odds ratios for prevalence, incidence and remission of COPD symptoms by gender in association with significant risk factors of smoking, treatment and lung function.

	Phlegm day or night		Wheeze		Dyspnea		Cough day or night	
	Women	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95%CI)	OR (95%CI)	OR (95% CI0	OR (95% CI)
FEV_1%predicted baseline (10%)								
Prevalence	0.92 (0.81-1.05)	0.78 (0.72-0.85)*#	0.88 (0.77-1.01)	0.72 (0.66-0.79)*#	0.84 (0.73 0.96)*	0.74 (0.68 0.80)*	0.90 (0.79-1.04)	0.77 (0.71-0.84)*
Incidence	0.81 (0.65-1.01)	0.80 (0.71-0.89)*	0.90 (0.70-1.16)	0.82 (0.72-0.92)*	0.82 (0.65-1.04)	0.84 (0.74-0.96)*	0.90 (0.72-1.12)	0.74 (0.65-0.84)*
Remission	0.97 (0.81-1.17)	1.20 (1.06-1.35)*	1.09 (0.89-1.34)	1.30 (1.14-1.48)*	1.07 (0.90-1.27)	1.28 (1.15-1.43)*	1.17 (0.96-1.42)	1.10 (0.97-1.24)
Change in FEV_1 per year (10%)								
Prevalence	1.02 (0.97-1.07)	0.97 (0.94 0.99)*	1.00 (0.95-1.05)	0.96 (0.93-0.98)*	0.99 (0.95-1.04)	0.96 (0.94-0.99)*	1.02 (0.97-1.07)	0.98 (0.95-1.00)
Incidence	0.98 (0.86-1.12)	0.92 (0.85-0.99)*	1.04 (0.92-1.19)	0.99 (0.91-1.06)	0.86 (0.75-0.97)*	0.90 (0.84-0.96)*	1.04 (0.90-1.19)	0.93 (0.87- 0.99)*
Remission	0.97 (0.86-1.10)	1.04 (0.98-1.10)	1.07 (0.93-1.22)	1.10 (1.01-1.19)*	0.94 (0.83-1.06)	1.08 (1.01-1.15)*#	1.03 (0.92-1.14)	1.08 (1.01-1.16)*
Change in cigarettes smoked (10/year)								
Prevalence	0.89 (0.75-1.05)	1.00 (0.92-1.08)	0.91 (0.76-1.10)	0.91 (0.83-1.00)*	0.94 (0.79-1.11)	1.04 (0.94-1.15)	0.91 (0.75-1.10)	1.10 (1.01-1.20)*

Incidence 1.40 (1.14-1.70)*#	0.65 (0.43-0.98)*	1.24.(1.03-1.51)*#	0.63 (0.37-1.05)	0.85 (0.70-1.03)	1.18 (0.74-1.88)	1.27 (0.98-1.64)	0.90 (0.63-1.29)
Remission 0.89 (0.76-1.06)	1.03 (0.72-1.48)	0.99 (0.82-1.20)	1.15 (.77-1.73)	0.93 (0.75-1.15)	1.20 (0.84-1.73)	0.84 (0.69-1.01)	1.15 (0.80-1.66)
Treatment with Budesonide							
Prevalence 0.66 (0.52-0.83)*#	1.10 (0.76-1.58)	0.95 (0.76-1.19)	1.03 (0.70-1.52)	0.91 (0.72-1.16)	1.09 (0.76-1.55)	0.90 (0.72-1.13)	1.22 (0.84-1.77)
Incidence 0.84 (0.60-1.17)	1.63 (0.91-2.94)	0.99 (0.71-1.38)	1.27 (0.71-2.26)	0.94 (0.67-1.32)	1.14 (0.64-2.04)	0.84 (0.61-1.17)	1.28 (0.77-2.12)
Remission 1.10 (0.76-1.58)	0.95 (0.58-1.56)	1.01 (0.73-1.41)	1.07 (0.58-2.00)	1.41 (0.94-2.11)	1.04 (0.65-1.66)	0.96 (0.70-1.33)	0.70 (0.38-1.27)

*p <0.05

difference between women and men is significant at p < 0.05

ORs are adjusted additionally for pack years of smoking, body mass index category,, skin prick test positive and age at baseline (10 years).

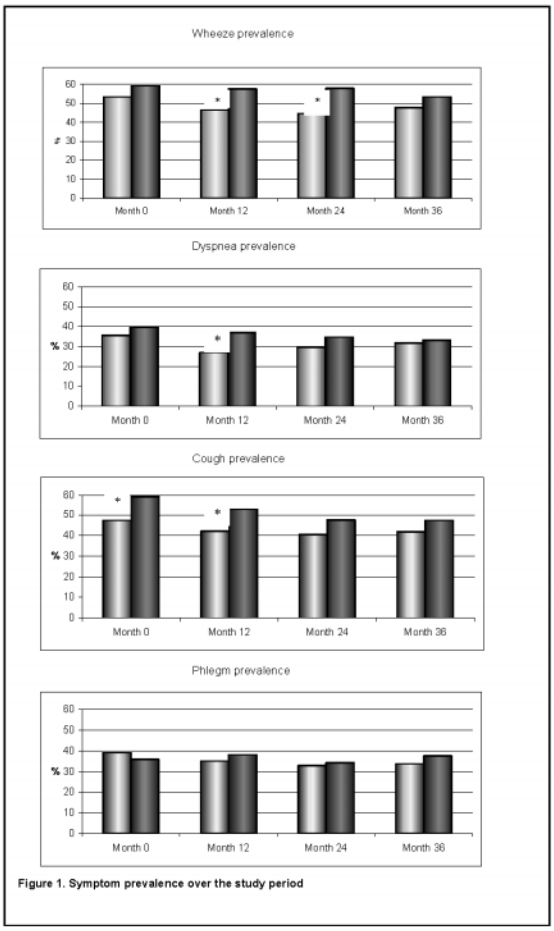
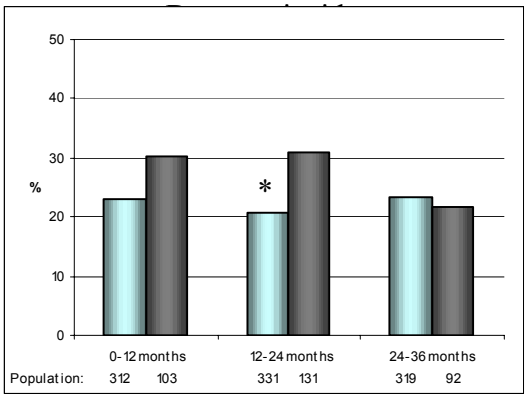
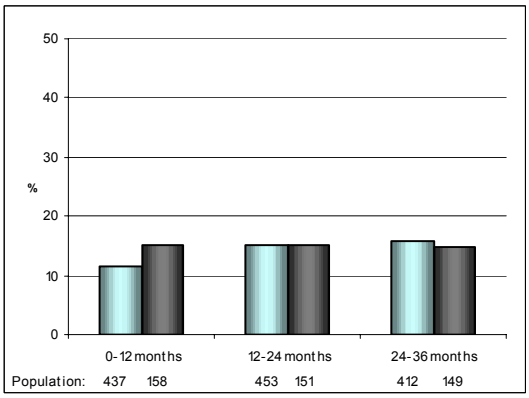


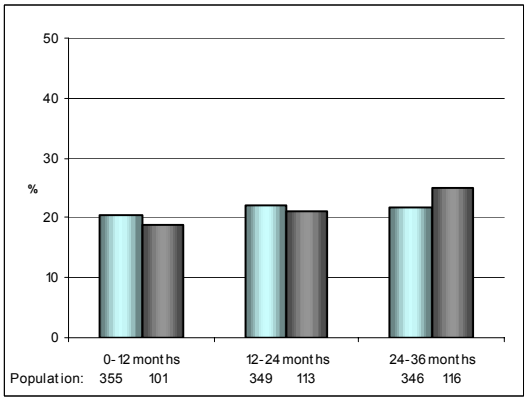
Figure 1. Symptom prevalence over the study period

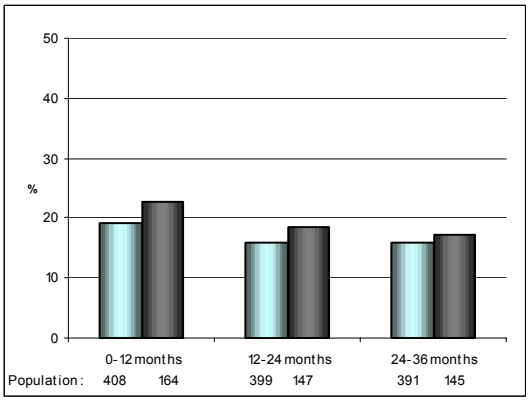
Figure 1 – prevalence of symptoms by time period for men and women (women darker grey bands). * denotes a significant ($p<0.05$) difference in proportion
Population per time period: : Month 0 M =816/F=312 Month 12 M=675/F=260 Month 24 M=616/F=242 Month 36 M=594/F=226

Wheeze incidence

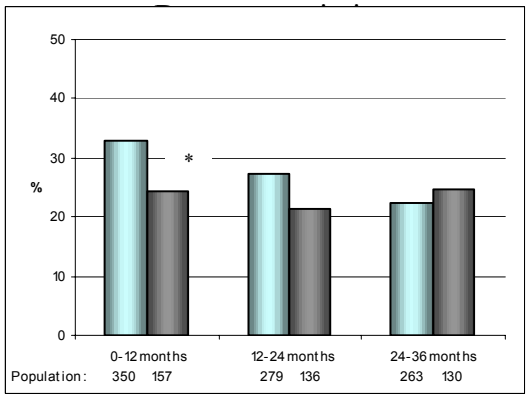


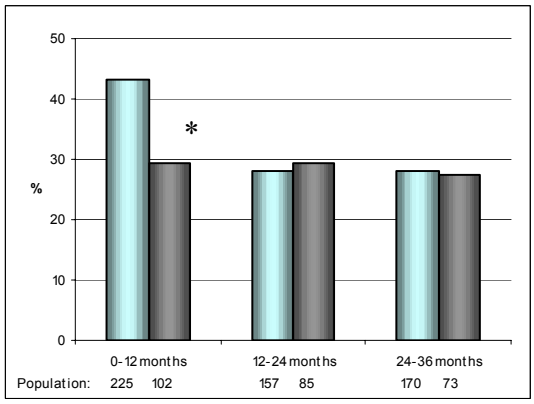


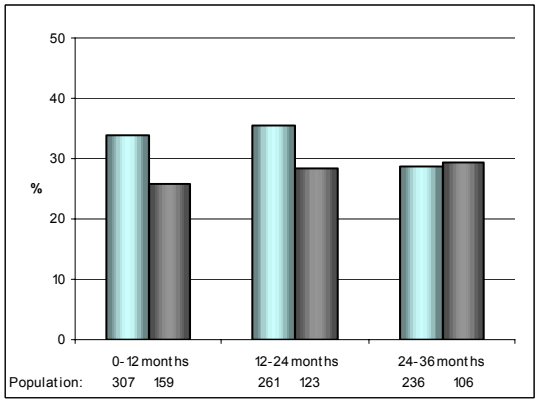




Wheeze remission







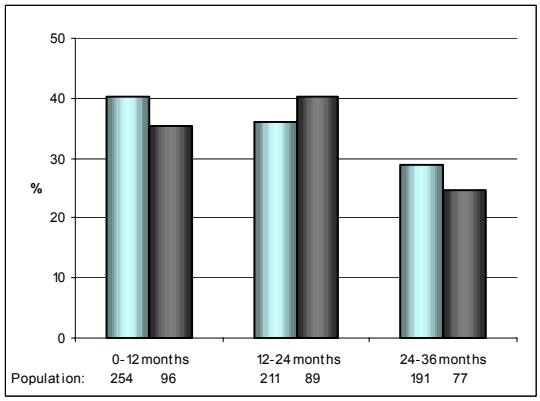
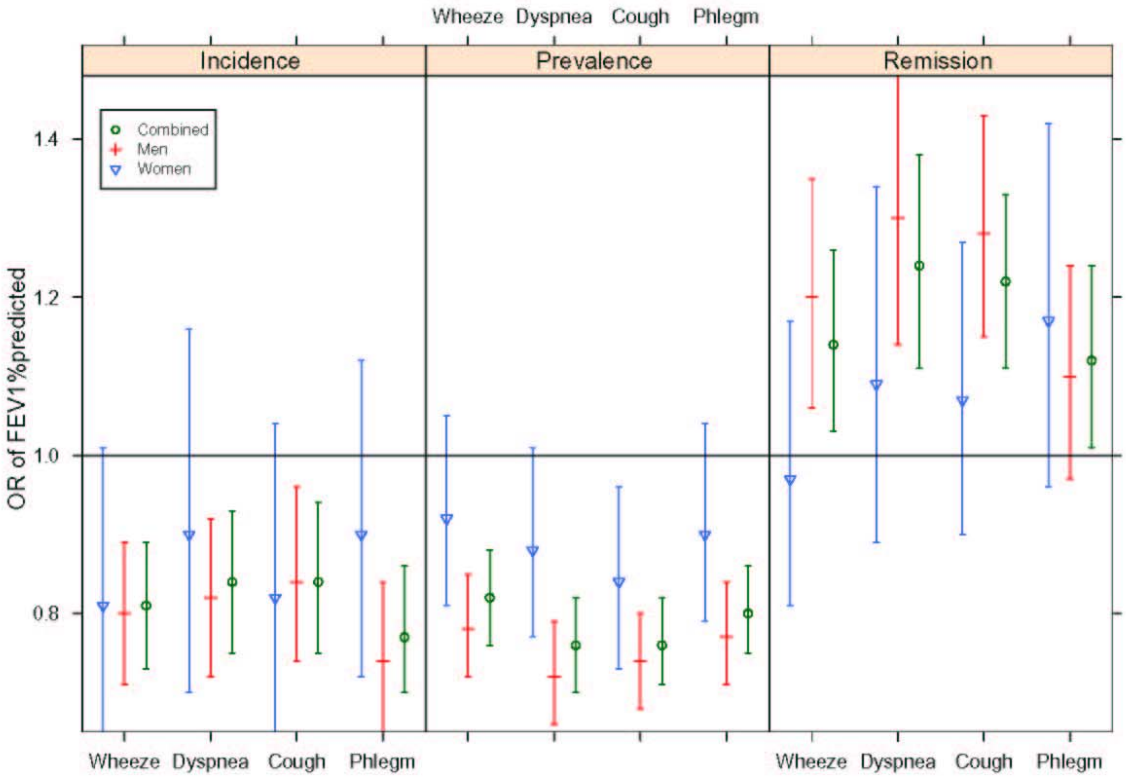
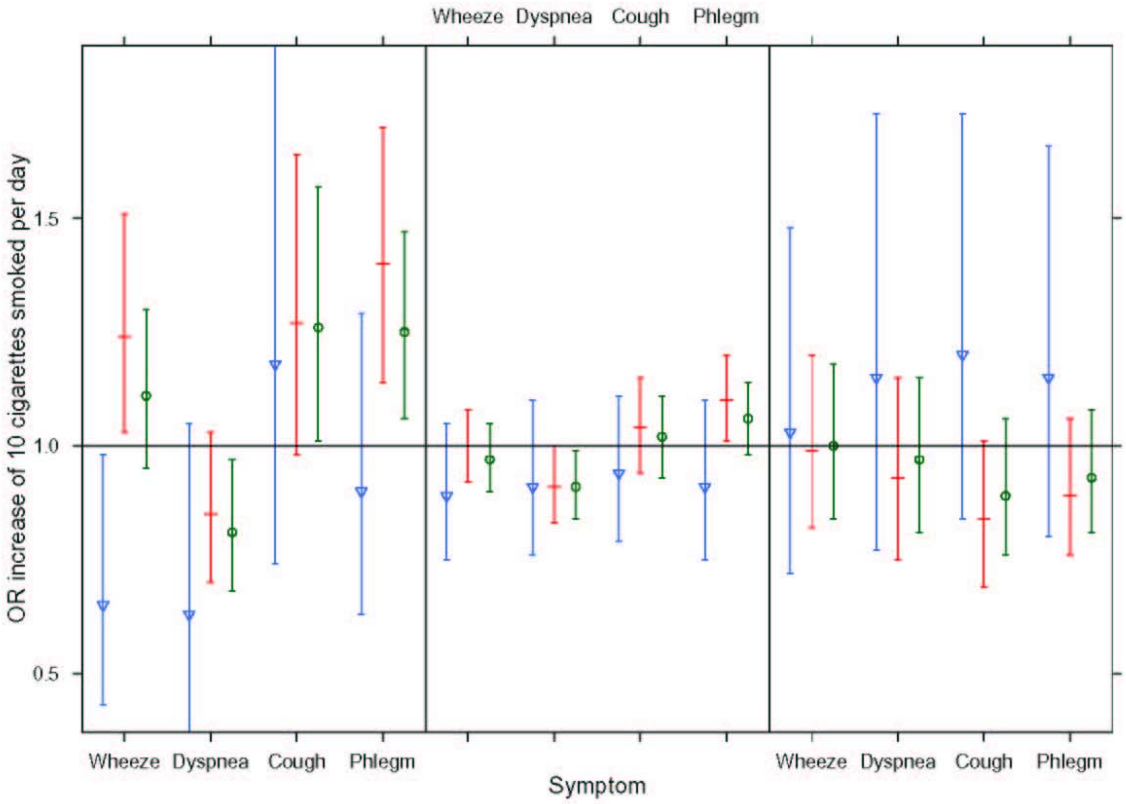


Figure 2 - incidence and remission of symptoms for men and women (women dark grey bars). The population for each time period is shown below the relevant bars. Patients were only included in the calculation of incidence if they were symptom free at the start of each of the three 12 month pairs and for remission only if they had symptoms at the start of each of the three pairs.


Wheeze Dyspnea Cough Phlegm
Incidence
Prevalence
Remission
Combined
Men
Women
OR of FEV1%predicted
1.4
1.2
1.0
0.8
Wheeze Dyspnea Cough Phlegm
Wheeze Dyspnea Cough Phlegm


Wheeze Dyspnea Cough Phlegm
OR increase of 10 cigarettes smoked per day
1.5
1.0
0.5
Wheeze Dyspnea Cough Phlegm
Wheeze Dyspnea Cough Phlegm
Symptom