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Gender differences in asthma and COPD

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Asthma and Chronic Obstructive Disease (COPD) both have a high prevalence worldwide and many clinical and epidemiology studies have been performed assessing natural history of the diseases and therapies. However, until recently little research was undertaken assessing any differences between males and females for either disease. This thesis was developed to firstly review the existing literature in the area of gender differences in asthma and COPD and then to undertake epidemiological research in areas where data was lacking.

Chapter 2 of this thesis is a literature review on the differences between males and females in the natural history of asthma and COPD. It was written in 2001 and since that time new (but relatively little) research has been undertaken in the field. New literature was included as part of the manuscript submissions (chapters 3-8) where appropriate. The review identified that gender research in obstructive lung disease lags behind other diseases such as cardio-vascular disease which is more advanced in assessing care and therapy opportunities for men and women. In obstructive airways disease there was a good literature on incidence and prevalence throughout the human lifespan, but relatively scant information with regard to gender differences associated with: childhood smoking and risk of subsequent disease; in utero smoking exposure and effect on infant lung development; body mass index as a risk factor; severe asthma and high prevalence in women; genetic and environmental interactions in the disease process; interventions to prevent either disease; pharmacological treatment and rehabilitation. By definition, perimenstrual asthma and related biological mechanisms, and asthma at menopause are gender related, but have not been extensively studied. It is clear that not all of these areas could be studied during this research period using clinical or database cohorts. Therefore, research was limited to areas where epidemiological methods could be best utilised and where data quality would be adequate. The choice of studies was also driven by evidence available from existing epidemiological data. For example, COPD incidence and prevalence is increasing in women in recent years, in part due to the relative decline in smoking in males versus an increase in smoking especially in young women. Studies indicate that women may additionally have a different response to tobacco smoke compared to men, which may result in an increased risk of disease or decline in lung function¹⁻⁵. This led to the decision to investigate how lung function, symptoms, therapy and care may differ between men and women with COPD, adjusting for factors such as smoking history, age, body mass and so forth. Understanding the course of the disease and treatment differences will help improve care in the future for COPD patients, more and more of whom will be women.

The literature revealed that asthma prevalence also shows a gender bias, and it shows an increase in women in adulthood. Furthermore there exists a distinct proportional difference with severity of disease, severe asthma being far more prevalent in females than males⁶. This may be in part related to differences in lung physiology and possible differences in the inflammatory response but also due to differences in treatment between the sexes and in response to treatment. It was therefore decided to utilise the General Practice Research Database (GPRD) to undertake two studies to understand gender bias

in treating patients with supposedly mild to moderate asthma and to see how therapy can impact upon morbidity in both sexes after controlling for age, obesity, smoking habit and so forth. The fact that male and female asthmatic patients may not be treated similarly led to the hypothesis that severe asthma may result from not only an underlying difference in airway inflammation and/or remodelling and genetic risk, but also from differences in exposure to medication. A large scale clinical cohort study in severe asthma patients was included in this research to better understand and describe different severe asthma phenotypes.

This thesis is therefore divided equally between COPD and asthma, with 3 studies in each disease outlined below.

Summary of findings:

Chapter 3 describes the differences between male and female subjects enrolled in the Euroscop study with regard to COPD symptom incidence, prevalence and remission. The study found that after adjusting for covariates such as time, packyears of smoking, age at visit 3, FEV₁%predicted, change in FEV₁ per year, body mass index (BMI) and atopy that women had a greater prevalence of all symptoms apart from sputum i.e. odds ratio (OR) for wheeze 1.53(95% CI 1.22- 1.92); dyspnea 1.44(95% CI 1.13- 1.83); cough 1.61(95% CI 1.29- 2.01) and for sputum 1.06(95% CI 0.84- 1.34). Women also exhibited greater remission of symptoms. Men on the other hand, showed a much stronger association between their baseline lung function and symptoms and subsequent change in lung function and symptoms than did women. For example men showed a significant lower prevalence of wheezing symptoms in association with a higher level of baseline FEV₁%predicted, an effect not seen in women, and the difference between men and women was significant ($p < 0.05$) [women – Odds Ratio 0.92(95% CI 0.81-1.05): men - OR 0.78(95% CI 0.72-0.85). This significantly different effect was also seen for dyspnea. This suggests that symptom reporting between the sexes differs which may be due to sociocultural as well as physiological and psychological differences. As men exhibit a stronger association between lung function and symptoms this may mean that symptoms are a better indicator of disease status and/or underlying pathophysiology in men than women. Symptom reports in women may be misleading if relied upon to assess disease status or progression. This indicates that it has to be ensured that objective measures of lung function are utilised for both diagnosis and subsequent disease monitoring rather than placing reliance on symptoms alone as often happens currently⁷. This study also found that inhaled corticosteroids (ICS) were successful at reducing the prevalence of sputum in men only. Previously, the Lung Health Study found that treatment with triamcinolone was only found to reduce dyspnea⁸ and no other symptom showed any difference in prevalence between the groups, as was the case in other studies⁹⁻¹¹. However, all studies to date were not designed to assess the impact of inhaled steroid treatment on symptoms. Furthermore, and importantly analyses were always without stratification by gender and so any gender effects may have been masked. Issues about reporting sputum that women appear to have¹² may confound our finding that ICS works successfully in men for reducing sputum. In other words that we could see no apparent effect in women may well be due to the fact that women prefer not to discuss sputum or

report it accurately. When men changed their smoking habit by increasing the number of cigarettes smoked, phlegm and wheeze also increased, whilst this was not the case in women who exhibited no significant change in phlegm prevalence or any other symptom. In fact women showed little significant association with change in smoking habit, except for wheeze where there was a negative association, as women increase their use of cigarettes per day wheeze even decreased. The lack of female association with change in smoking and phlegm may again be due to symptom reporting issues, but it could also be that women simply do not produce as much sputum as men, or that in comparison to other symptoms, sputum is not so bothersome and thus under reported. Future research into symptom reporting and perception and the role of treatment and outcome by gender are required. The principle findings of this study are that smoking, treatment and lung function have different associations with symptoms in men with COPD than women with the disease. This indicates that future clinical and epidemiological studies should stratify analyses by gender to ensure that potential benefits of treatment are not obscured and that outcomes due to smoking exposure can be properly assessed.

Chapter 4 uses data from the placebo arm of the Euroscop study and analyses risk factors for decline in FEV₁ over three years follow-up. The effect of gender, amongst other co-variables such as age, BMI, FEV₁%VC (dichotomised into subjects above and below the median - women 64.5% and men 63.3% respectively), FEV₁%FVC (dichotomised into subjects above and below the median, women 65.5% and men 63.7% respectively), specific IgE, pack years of smoking, age at starting to smoke and change in the number of cigarettes smoked (10 per year), was evaluated. This study shows that having symptoms at baseline was only associated with lower baseline lung function in men but not women. Obese men additionally exhibited a reduced decline in lung function compared to other men, an effect not seen in women. However, women who had more severe airway obstruction at baseline (FEV₁%FVC below the median), showed an increased decline in lung function over time (32ml per year), compared to women with less airway obstruction (above the median). The difference between men who had above and below the median FEV₁%FVC value was only 8ml per year. This study indicates that women who develop more severe airway obstruction may expect to deteriorate more rapidly than their milder female counterparts. This could be due to the fact that adult women have smaller airway size and this might magnify any change in FEV₁ over time. Additionally one mechanism contributing to the development and progression of COPD in women, might be the observation that women have altered levels of cytokines such as interleukin-8 (IL-8) due to cyclical hormone activity.¹³ Increased IL-8 influences neutrophil migration and neutrophil chemotaxis in subjects with COPD¹⁴. IL-8 levels are partly controlled by progesterone, IL-8 levels rising as progesterone levels fall. Since smoking induces an attraction of neutrophils to the airways, higher circulating levels of IL-8 may enhance the susceptibility to cigarette smoke observed in women in some studies^{2,3}. Greater understanding of the role of sex-steroid hormones on cytokine activity and circulating free radicals from cigarette exposure is required to explain this observation. Another interesting finding from this study is that an increase in the number of cigarettes smoked caused a steeper annual decline in FEV₁ in men (17mls per year) without a significant effect in women. However, the difference between men and women was not significant when an interaction term was tested in the model. This finding does

support the observation made in Chapter 3, where smoking appears to have a more deleterious effect with respect to symptoms in men than in women with COPD. Together these observations also corroborate the intricate association between lung function and symptoms in males with COPD especially.

Chapter 5 concludes the studies regarding COPD and takes data from the Confronting COPD International survey. The survey was performed in the USA, Canada, France, Italy, Germany, The Netherlands, Spain and the UK in 2000 with 3,265 COPD participants. The study investigated if men and women were offered the same care for COPD. After adjusting for age, pack-years, country and severe dyspnea (MRC scores 5 and 4), women were less likely to have had spirometry (OR 0.84, 95% C.I. 0.72-0.98) but more likely to get smoking cessation advice (OR 1.57, 1.33-1.86). It is interesting that given the previous two studies indicating the poor association between women's symptom reports and lung function that women are less likely than men to be tested. Our data clearly show that women must be given spirometry if an accurate assessment of disease severity is to be undertaken. It may be that women receive more smoking advice because clinicians are aware of literature supporting the fact that women find it harder to give up smoking and thus encourage and support quit attempts with advice^{15,16}. Alternatively men may under report being given this advice.

Despite significantly lower pack-years of smoking women were more likely to report severe dyspnea than men despite similar reports of cough and less mention of sputum. There were no differences in the risk of hospitalisation or emergency room visit. This study indicates that care does differ for men and women for COPD and, supporting the Euroscop findings, that women report more frequently dyspnea for the same level of smoking exposure.

Chapter 6 turns the focus of the research to asthma. The study was a prospective database study performed within the General Practice Research Database in the United Kingdom. 6420 patients (0-45 years) diagnosed with asthma between 01/01/1995 and 31/12/2001 taking ≥ 2 scripts for short acting beta-agonist - SABA (SABA only group) or ≥ 3 scripts for inhaled corticosteroids - ICS (ICS group) in the first six months following diagnosis were included. Factors, including gender, which might be associated with drug utilisation were assessed. We found that a higher rate of oral steroid use was significantly associated with being female, using ICS, being an adult, and a smoker. 10.5% of SABA group and 13.4% of ICS group used oral steroids. Within the SABA group, 37% stepped up to ICS, the time to first ICS script being significantly associated with prior hospitalisation (RR 2.26, CI 1.65-3.10) and atopy (RR 1.47, CI 1.33-1.63). This study indicates that in some asthmatic patients, under-treatment can result in lack of asthma control and result in oral steroids being required to treat exacerbations. Being female as well as a smoker resulted in greater oral steroid requirement. This indicates that doctors should therefore advise all patients to quit smoking, but particularly women who may have greater requirement for oral steroids due to exacerbations. Data from the Confronting COPD study (see above) are encouraging in that women in that study do appear to get more frequently anti-smoking advice. However, asthmatics may not get the same level of advice as COPD patients as the disease is not caused directly by exposure to cigarette smoke. It is essential that all patients with obstructive lung disease are

actively encouraged by their clinician to quit smoking and that women in particular are supported through this process as their quit attempts are known to more frequently fail¹⁷.

Chapter 7 uses data from the same study but we performed a survey of the GPs who treated 400 of the newly diagnosed patients, 200 adults and 200 children, half of whom were SABA monotherapy users. Data was obtained for 255 of the 400 (63.75%). GPs reviewed patients' notes and provided information regarding symptoms and treatment at time of first prescription. We were interested to understand how GPs appreciate severity of asthma in relation to medication prescribed. According to GINA¹⁸, patients with daily or continuous symptoms which are indicative of persistent, uncontrolled asthma, would benefit from ICS therapy plus additional therapies such as long acting beta-agonists (LABAs). However, studies have shown that GPs routinely under estimate severity and under prescribe steroids, in part due to reliance on symptom presentation rather than using lung function measures^{7,19}. Originally the plan had been to assess any gender bias in prescribing and assessment of asthma severity status in these selected patients but due to the limited number of questionnaires returned, power became too low to definitively conclude anything about gender or age impact upon prescribing. Therefore the study focussed attention on the symptoms presented at time of first treatment, the estimate of each patient's severity at time of diagnosis by the reviewing physician and the medication prescribed at time of diagnosis. We found that 46% of patients who were prescribed SABA monotherapy had daily or continuous symptoms. Notwithstanding this finding, the logistic regression model of factors associated with intermittent severity status indicated that only symptom frequency was associated with this severity level. Those with daily or continuous symptoms were less likely to be labelled by the reviewing physician as "intermittent" (OR 0.22 95% CI 0.10-0.49). No other factors (gender, smoking, atopy, age or symptoms) were associated with obtaining this status. Therefore GPs, despite knowledge to the contrary, prescribed SABA alone when ICS and/or additional medication would have benefited the patient. We did find in a sub-analysis that more females reported daily symptoms than males (36.9% v 32.1% $p = 0.42$) and hypothesise that in a larger population this difference may become significant. SABA monotherapy was also given more frequently to symptomatic females of all ages than males. It is unfortunate that this study was not large enough to be able to expand more on the observed suggestion that females might be under treated compared to males. We propose that this should be studied in greater detail in future prospective studies

The final chapter (8) is a report of a study undertaken in severe asthmatics. The European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) performed an observational study in 163 subjects with severe asthma (severe group), comparing them to 158 subjects whose asthma was controlled by low doses of inhaled corticosteroids (median dose beclamethasone equivalent 666 μg - controlled group). The patients were predominantly female in the severe group (ratio 4.4:1) versus 1.6:1 in the controlled group. Females reported different trigger factors for exacerbations to men including sinusitis and work exposures. Peri-menstrual worsening of asthma was an additional risk factor in women. Additionally increased BMI was more predominant in females than males in the severe group. A number of hypotheses were generated by this study, including severe asthma sharing features with COPD as patients exhibited

neutrophilic inflammation, components of irreversible airway obstruction and had less frequent atopy. Additionally it was suggested that severe asthma might be characterised by diminished or sub-optimal sensitivity to glucocorticosteroids. None of these factors were tested in an interaction with sex and so we cannot therefore infer from this study if these factors differ for males and females.

FUTURE PERSPECTIVES

The Euroscop COPD sub-analyses have shown that lung function and symptoms are more closely associated in men than in women. This has important ramifications for clinical care of the patient and for clinical trials. Currently FEV₁ is the primary outcome in phase III trials for registration but agencies such as the FDA increasingly require evidence of symptom improvement or quality of life changes. This is because in milder patients, increments in FEV₁ from baseline can be very small and of little clinical consequence to the patient, but symptom improvements such as a reduction in nocturnal symptoms, can greatly improve the patients' quality of life. However, the subjective nature of symptom reporting makes validation of such data difficult. We therefore need to understand how initial lung function and changes in lung function over time are associated with symptom prevalence, remission and incidence in men and women for both asthma and COPD and alternatively how symptoms may predict or are related to changes in lung function. Our data suggest that analyses of clinical trial data particularly of symptoms, must be stratified by sex, as symptom reporting by women is not related to improvements in objective measures of lung function. Analysing both genders together may obscure positive findings of symptom improvements in men. Doctors also need to understand how symptom presentation at diagnosis may correspond to subsequent deterioration of lung function and how symptoms may relate to disease status. The studies have shown us that spirometry is vital if an accurate assessment of disease severity is to be established as the current general practice reliance of symptoms alone for disease assessment would be particularly unreliable in female patients. Further research is needed to understand symptom perception and the underlying mechanisms that may lead to symptoms, for example hyperinflation, under-nourishment, airway size, and hormonal status.

To be able to accurately assess how treatment may improve symptoms, further research is required to better understand why symptom reporting differs in men and women. Previous qualitative research in teenagers indicates that males do not find it socially acceptable to admit to illness of any kind and attempt to conceal illness from their peers, as being fit and tough was highly valued and that sickness was considered weak and incompetent²⁰. Females on the other hand, had no such social confines to admitting to illness, and rather sorority support was mobilised upon reporting illness. This could explain the greater reports of all symptoms by women, but sputum reporting appears to be affected by a different bias and is of particular relevance in smokers with COPD. Qualitative interview techniques are required to investigate why women may find it distasteful to admit to sputum and if they do indeed hide these symptoms. But in tandem