Spirometry utilisation among Danish adults initiating medication targeting obstructive lung disease

Mette Marie Koefoed, MD

This review has been accepted as a thesis together with three previously published papers by University of Southern Denmark 28 February 2013 and defended on 21 June 2013

Tutor(s): Dorte Ejg Jarbøl, Jens Søndergaard and Rene dePont Christensen

Official opponents: David Price, Peter Lange and Ingrid Louise Titlestad

Correspondence: Institute of public health, Faculty of Health Sciences, University of Southern Denmark, J.B.Winsløws Vej 9A, DK- 5000 Odense C, Denmark

E-mail: mkoefoed@health.sdu.dk

Dan Med J 2015;62(2):B5004

The papers

Lack of Spirometry use in Danish Patients initiating medication targeting obstructive lung disease: Koefoed MM, dePont Christensen R, Søndergaard J, Jarbøl DE. *Respir Med*. 2012 Dec;106(12)

Influence of socioeconomic and demographic status on spirometry testing in patients initiating medication targeting obstructive lung disease. A population based cohort study. Koefoed MM, Søndergaard J, Christensen R, Jarbøl DE. *BMC Public Health*. 2013 Jun 14;13:580

General practice variation in spirometry testing among patients receiving first-time prescriptions for medication targeting obstructive lung disease in Denmark: A population-based observational study Koefoed MM, Søndergaard J, Christensen R, Jarbøl DE. *BMC Fam Pract*. 2013 Aug 7;14:113

1. BACKGROUND

RESPIRATORY SYMPTOMS IN GENERAL PRACTICE

Dyspnoea, cough and wheezing are symptoms with high prevalence rates among the population in Scandinavia[1] and other western countries.[2] Among the elderly, the prevalence of dyspnoea is reported to be over 30%[3] and a similar result is found among adults where approximately 30% reported symptoms of asthma or chronic bronchitis.[4]

Respiratory symptoms are a common cause for seeking a primary care physician[5] and it has been estimated that 10% of the consultations in general practice in Denmark are concerning respiratory conditions and many of these consultations are due to non-infectious respiratory symptoms.[6]

The literature has shown a high probability of obstructive lung diseases among adults attending general practice with a cough persisting for at least 2 weeks, and not known to have asthma or other pulmonary diseases. Among these patients over one third has airflow limitation due to asthma or chronic obstructive pulmonary disease (COPD); among middle-aged and older patients airflow limitation is predominantly due to COPD,[7] whereas asthma is the most common cause among younger age groups.[8] Also, over one third of the patients presenting with symptoms of acute bronchitis (coughing more than two weeks, but no more than four weeks, and presence of either expectoration of purulent sputum and/or rhonchi assessed by auscultation) in general practice have airflow limitation due to obstructive lung disease.[9]

Asthma and COPD are common chronic illnesses[10-13] and there is evidence that the prevalence may be higher as a proportion of patients with respiratory symptoms are suffering from these diseases, but are not diagnosed.

Management of patients attending general practice with symptoms like dyspnoea, coughing and wheezing is only sparsely studied. A study found that the majority of these patients are treated empirically with pharmacotherapy targeting obstructive lung disease and that only few have additional tests carried out. However, many of the patients were offered follow-up consultations.[5]

MEDICATION TARGETING OBSTRUCTIVE LUNG DISEASE

Medication targeting obstructive lung disease is commonly prescribed and approximately 8% of the population redeem prescriptions for this type of medication in Denmark each year[14]. The prevalent use of medication is highly age-specific, increasing with age and among patients >65 years of age over 12% redeem this type of medication. Pharmacies sold medication targeting obstructive lung disease for over 1198 million DKK in 2008, accounting for nearly 10% all medication costs in the primary health care system that year. Thus, medication targeting obstructive lung disease is costly for the individual[15] as well as the health care system[14].

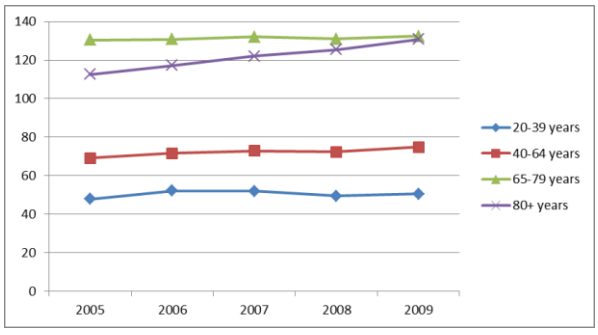


Fig 1: Number of persons per 1000 redeeming medication targeting obstructive lung disease according to age.

There are several types of medication targeting obstructive lung disease, but they will be only briefly described. The three major mediations targeting obstructive lung disease are beta-2-adrenoreceptor agonists, glucocorticoids inhalants and anticholinergics, and they account for nearly 95% of the medication targeting obstructive lung disease sold in Denmark in 2008.[14] Other medications prescribed are xanthines, leukotriene receptor antagonists and antiallergic agents such as cromoglicic acid and nedocromil. These medications are only prescribed to a small minority of patients receiving medication targeting obstructive lung disease and the majority of these patients are children receiving leukotriene receptor antagonists.[14]

Beta-2-adrenoreceptor agonists and anticholinergics are bronchodilator drugs and available as short-acting (duration 4-6 hours) or long-acting (duration > 12 hours). These medications relax the bronchial smooth muscle, lowering airway resistance and reducing symptoms.[16-18] Beta-2-adrenoreceptor agonists have adverse effects like tremor and tachycardia,[19] when administered in higher doses. Anticholinergics mainly have dryness of the mouth as an adverse effect. However an increase of cardiovascular events has been reported among COPD patients,[20] but this has not been confirmed and anticholinergics are still recommended.

Inhaled corticosteroids are anti-inflammatory medications, which decrease airway hyper responsiveness, control airway inflammation and reduce symptoms, especially among asthma patients.[21, 22] Also, they reduce the frequency and severity of exacerbations and increase health status in both asthma and COPD patients.[17, 18, 23] Inhaled corticosteroids have a risk of side effects, the most common being harmless such as candida fungus in the mouth, but serious side effects have also been reported. An increased risk of pneumonia among COPD patients using inhaled corticosteroids is seen,[24] adrenal suppression,[25] increased incidence of cataract[26] and decreased bone mineral density[23] are also reported. Inhaled corticosteroids are the cornerstone of the treatment of obstructive lung disease, but it is not beneficial for all patients with obstructive lung disease[27] and it is important to ensure that only patients for whom medication is relevant receive it, thereby avoiding unnecessary exposure to medication risks and costs.

OBSTRUCTIVE LUNG DISEASE AMONG MEDICATION USERS

There is only sparse literature on patients using medication targeting obstructive lung disease, especially among patients initiating medication. Most studies have explored medication use among COPD and asthma patients.

Patients using medication targeting obstructive lung disease almost all report one or more respiratory symptom indicating airway obstruction, two thirds have self-reported obstructive lung disease, but only one third report a history of spirometry testing and most of these patients have no obstruction when tested with spirometry.[28] Also, a gap of over a year has been reported from medication initiation to diagnosis among those COPD patients who used medication prior to diagnosis,[29] and this may indicate a diagnostic delay due to medication usage without confirmatory spirometry. While some medication users have no obstructive lung disease, it has also been shown that large proportions of patients with obstructive lung disease receive no medication or are undertreated.[30-32] Hence correlation between medication usage and obstructive lung disease may be low and focus on spirometry assessment among medication users seems therefore quite relevant.

PREDICTING AIRFLOW OBSTRUCTION ON THE BASIS OF HISTORY AND PHYSICAL EXAMINATION

Patients with respiratory symptoms have an increased risk of having obstructive lung disease[33-35] and the predictive value of respiratory symptoms for diagnosing airflow limitation has therefore been studied. However, symptoms alone seem to be a poor predictor of airway obstruction.[36, 37] A Norwegian study reported a positive predictive value of chronic cough with phlegm for any airflow limitation to be 37.0% in women and 40.4% in men.[38] Other studies exploring the value of respiratory symptoms for predicting COPD found similar results with positive predictive values not over 50% with the presence of one or more symptoms.[39-41] Smoking history of 70 pack-years has proven to be an independent strong predictor of COPD,[42] although 30 – 40 pack-years, a more common cut-off, also increases the likelihood of COPD.[43, 44] A combination of smoking history, self-reported symptoms and clinical findings like wheezing on auscultation or diminished breath sounds gives a very high likelihood of obstructive lung disease, and the absence of all three almost rules out COPD. However, between these two extremes, fewer findings or symptoms have low predictive values. Also, studies have reported low correlation between symptoms and the degree of objective airflow obstruction among patients with asthma[45, 46] and COPD.[47-50] Symptoms assessment and clinical examination are important in the diagnosis of asthma and COPD, but inadequate, and assessment of airflow limitation is essential.

SPIROMETRY

Spirometry is recommended as the gold standard for quantifying airflow obstruction.[51-53] A spirometer can estimate the amount and speed air can be exhaled. The two main measures obtained are Forced Vital Capacity (FVC) determining the vital lung capacity from a maximally forced expiratory effort, and Forced Expiratory Volume in 1 second (FEV1) indicating the volume of air exhaled under forced conditions in the first second. Airflow limitation is defined as post bronchodilator FEV1/FVC < 0.70, and guidelines use this cut-off value for obstructive lung disease.[51, 53] However, airways become slightly more obstructive with age, and the lower limit of normal (LLN) has been proposed as an alternative measure,[54-56] as a fixed FEV1/FVC < 0.7 entails the risk of overestimating airflow limitation among the elderly.[57] Underestimating airflow limitation in younger adults has also been proposed when using the fixed FEV1/FVC ratio of 0.7, and it has been suggested to raise the ratio to 0.75 or 0.8 in adults 22-44 years.[58, 59] although cut-off estimates have been debated, this has not influenced consensus on spirometry testing as the gold standard for confirming airflow obstruction.

To obtain an accurate measurement of FVC and FEV1, spirometry testing requires trained personnel to instruct and guide the patient, as the results are highly dependent on patient cooperation and effort. The procedure is normally repeated at least three times to ensure reproducibility. Interpreting spirometry results requires some routine and it has been debated whether spirometry could be performed accurately and interpreted correctly in primary care.[60] However, the majority of patients with obstructive lung disease are diagnosed and managed in primary care and studies mainly report acceptable levels of spirometry testing in primary care.[61-65]

SPIROMETRY RECOMMENDATIONS

International COPD guidelines recommend that "spirometry should be obtained to diagnose airflow obstruction in patients with respiratory symptoms" and spirometry is considered mandatory when diagnosing and monitoring COPD.[53, 66] Asthma guidelines are less specific with regard to spirometry as a mandatory diagnostic tool. Emphasis is on symptoms and confirmation of airflow obstruction, including variability and reversibility of airflow obstruction. Peak expiratory flow measurements and spirometry both assess airflow limitation. However, whenever available, spirometry is stated as the preferred initial test to assess the presence and severity of airflow obstruction in international asthma guidelines.[51] Also, an international guideline for spirometry use in primary care recommends that "spirometry should be considered for patients presenting with undiagnosed respiratory symptoms like dyspnoea, wheeze, and cough".[52] Hence, these guidelines all recommend spirometry in patients with respiratory symptoms.

SPIROMETRY UTILISATION AND FACTORS OF INFLUENCE

Numerous studies have reported underutilisation of spirometry testing among patients diagnosed with COPD or asthma.[67-75] However, there is a lack of studies assessing spirometry utilisation among patients using medication targeting obstructive lung disease.[28] This is despite the finding that spirometry improves diagnosis[76-79], management and prescribing patterns.[80-82]

Underutilisation of spirometry among COPD and asthma patients is reported to be unequally distributed. Gender of patients may influence spirometry testing; an underuse among both women[67, 83] and men[71] has been reported and some studies found no difference.[84] Further, patients' increasing age also seems to enhance an underutilisation of spirometry.[71]

Socioeconomic status is often used to classify an individual's position in society, and income, education, occupation and cohabitation status are considered key measures,[85-87] but no consensus on a definition of socioeconomic status exits. Many healthcare systems, including the Danish, provide equal access to care irrespective of socio-economic position. Irrespective of this, studies conducted in the past decade in Nordic healthcare systems have despite free access demonstrated unequal use of diagnostic testing in patients admitted to hospitals with myocardial infarction or ischemic stroke.[88-90] A study has shown no socioeconomic gradient in spirometry testing when monitoring COPD patients,[91] but it has not been studied whether a socioeconomic gradient in having diagnostic spirometry performed among patients initiating medication exits.

Doctor and practice factors have been studied to explain underutilisation of spirometry among asthma and COPD patients. Attitudes towards using spirometry have been reported in the literature; unfamiliarity with conducting or interpreting spirometry tests and spirometry being too time consuming are reported as barriers, whereas interest in research in general, high job satisfaction and participation in spirometry courses facilitate spirometry.[92-95] Also, doctors' interpretation of patients' expectations influenced whether spirometry was conducted; patients seeking an explanation for their symptoms and patients estimated to have resources to cooperate in the diagnostic process have spirometry conducted more often.[92] Whether the doctors' gender or age influences spirometry testing has not been assessed, but gender has been reported to generally influence the doctors' threshold for conducting tests, with female doctors performing more tests in other illnesses,[96] and we hypothesised that this association may also exist with regard to spirometry. It has also been reported that doctors' practice patterns are influenced by their age, with older doctors conducting fewer tests and prescribing more medication.[97] Organisation of general practice with a practice nurse and use of protocols has been reported to enhance spirometry testing[98] and quality of care assessment mostly seems in favour of larger practices and training practices.[99-101] We therefore found it relevant to assess whether doctor and practice characteristics influence spirometry testing among medication users.

Overall, there is a lack of studies assessing spirometry utilisation among new users of respiratory medication. In addition, knowledge on factors associated with spirometry use is needed to enhance spirometry testing in this group.

2. AIMS OF THE THESIS

The overall aim of this thesis is to analyse to what extent spirometry testing is conducted, when patients initiate medication targeting obstructive lung disease, and to assess if specific patient, doctor or practice characteristics are associated with spirometry testing.

The more detailed aims of the present thesis are the following:

1. To assess to what extent spirometry is conducted when initiating medication targeting obstructive lung disease in Denmark and to assess if patient characteristics like age, gender or severity of respiratory symptoms influence spirometry testing when initiating medication. (Article I)
2. To assess whether there is an association between socioeconomic and demographic factors like education, income, affiliation to the labour market, cohabitation status and spirometry testing when initiating medication. (Article II)
3. To assess whether there is an association between practice characteristics like training practice status, workload, practice organisation or doctor characteristics like gender or age and spirometry testing. (Article III)

3. MATERIAL AND METHODS

SETTING AND DESIGN

These studies were designed as population-based, cross-sectional cohort studies. They were conducted among all Danish adults initiating medication targeting obstructive lung disease in 2008 and are exclusively based on national registry data.

THE DANISH HEALTH CARE SYSTEM

The Danish healthcare system is tax-financed and provides free access to general practice and hospital care. More than 98% of Danish citizens are registered with a general practitioner, who acts as a gatekeeper to the rest of the healthcare system by carrying out initial diagnostic investigations and referring patients to secondary care if necessary.[102] Most patients with respiratory symptoms are initially diagnosed and managed in general practice. The majority of general practitioners have direct access to spirometry and conduct these themselves, but if preferred, GPs can also refer patients to spirometry testing at hospitals or outpatient clinics. Some patients receive initial treatment at out-of-hours clinics or at a hospital due to acute onset, and in these cases the GP receives information on all health-care services

provided. As a gatekeeper, the GP can choose to refer the patient or conduct follow-up himself or herself, if needed.

DATA SOURCES

The Danish Civil Registration System

All individuals living in Denmark are registered in the Danish Civil Registration System and are assigned a unique personal identification (CPR) number. Since 1968, the Danish Civil Registration System has contained information on name, gender, date of birth, citizenship and identity of parents on each individual. Further, the system is continuously updated with regard to each individual's vital status, place of residence and spouses. The Danish Civil Registration System has been complete with detailed place of residence since 1977. The CPR number assigned to each individual can be used to link data from all national Danish registries.[103, 104]

The Danish National Prescription Register

The register contains information on every medical product sold on prescription to outpatient use by Danish pharmacies since 1994. Each prescription record includes numerous variables, including CPR number of the drug user, identification code of the prescriber and a code of the dispensing pharmacy, the date of dispensing and type of drug. Information on drug substances is classified according to the World Health Organization anatomical therapeutic chemical (ATC) system, which classifies drugs according to the organ on which they act and subgroups are according to therapeutic-, pharmacological-, chemical subgroup and substance. Medications with ATC code R03 indicate the medication being targeted: R respiratory system and 03 obstructive airways diseases. Within R03 there are several subgroups and each chemical substance is identifiable by a unique code. For example, a long-acting anticholingergic medication tiotropium (Spiriva®) has the ATC code R03BB04.[105]

The Danish National Patient Register

The register contains records of all hospital admissions since 1977. From 2007 onwards the register also has complete information on all other hospital contacts, including contacts to emergency departments and outpatient clinics. Each record includes the patient's CPR number, date of contact or admission, data on the hospital and department and diagnostic and procedure codes, including spirometry.[106]

The Danish National Health Service Register

Since 1990, the register has collected data from health contractors in primary health care. It includes information about citizens, providers, and health services, but minimal clinical information. The data are connected to reimbursement and therefore assumed to be reliable. Several clinical procedures, e.g. taking blood tests, performing spirometry, peak expiratory flow (PEF) measurements, give supplemental reimbursement and are recorded in the register. Results of tests and diagnoses are not recorded. Each registration includes the patient's CPR number, identification for type of contact or type of clinical procedure performed, identification code for the health contractor providing the service and the week of reimbursement of the health care service.[107]

Demographic and socioeconomic registers

Statistics Denmark has a number of registers containing socioeconomic and demographic information on every citizen. Data on labour market affiliation were obtained from the Employment Classification Module (AKM),[108] highest attained education was obtained from the Population's Education Register (PER),[109] income was obtained from the E-income Register[110] and cohabitation status from the E-family Register. The data in these registries are primarily obtained from administrative registries such as tax and customs register and educational institutions and are updated annually.

The Danish National Health Service Provider Register

This register contains information on every health contractor in primary care in Denmark. For each general practice, the register contains the practice's unique provider number, a quarterly registration of patient list size, and detailed information on each physician providing health services using the provider number. Physician details include, gender, age, date of inclusion to the provider number, date of retirement from the provider number, affiliation to the provider number (resident doctor, owner).

SAMPLING PROCEDURE

Study cohort for Study I

The Danish National Prescription Registry was used to identify all adults who were first time users of medication targeting obstructive lung disease in 2008. Selection criteria were as follows: 1) All patients redeeming drugs with ATC code R03 in 2008 were identified, 2) patients under 18 years of age on 1 January 2008 were excluded, and 3) patients with records of previously redeemed prescriptions with ATC code R03 in the prescription database in the time period 1995-2007 were excluded. Sampling algorithm ia demonstrated in Figure 2. The date the first prescription was redeemed was defined as the index date.

Study cohort for Study II

In Study II we linked the cohort from study I with registries in statistics Denmark and defined that patients had to have 2008 data on all of the following variables to be included in Study II: highest attained education, income, affiliation to the labour market, and cohabitation status. Of the 40 969 drug users included in Study I, 92.1% (N=37734) fulfilled these criteria.

Study cohort for Study III

In Study III the study cohort from Study II (N=37734) was linked to general practice in the Danish National Health Service Register. The criteria for this linkage were that the patient had been in contact with their GP in the time period and had contact patterns enabling us to define with which general practice the patient was listed. A total of 35 677 corresponding to 94.5% of the cohort from Study II fulfilled these criteria, Figure 2.

General practice cohort for Study III

All data on general practice were extracted from the Danish National Health Service Provider Register. We extracted data covering the period July 2007 – December 2009 corresponding to the absolute observation time of the cohort. A total of 428 practices were omitted due to missing data at the beginning or end of the time period, indicating that these practices were established or

closed in this time period. A further 11 practices were omitted due to a small list size (<500 patients), because these practices are probably atypical and are not representative of general practice. A total of 1980 practices were included in our analyses.

Figure 2 Sampling algorithm of the study cohort

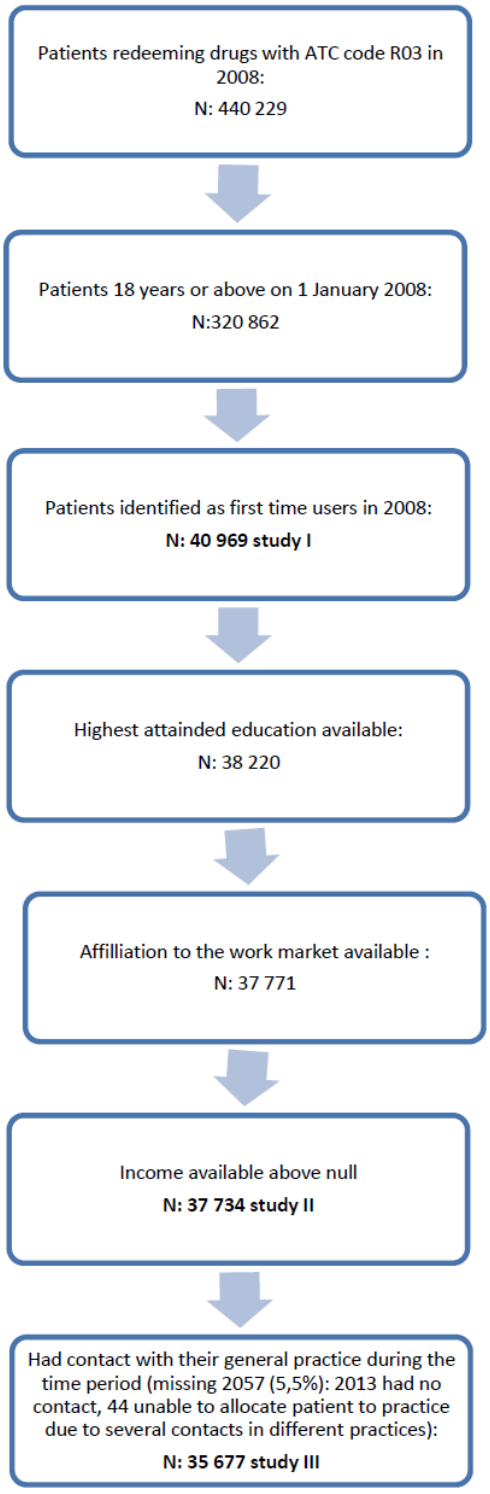
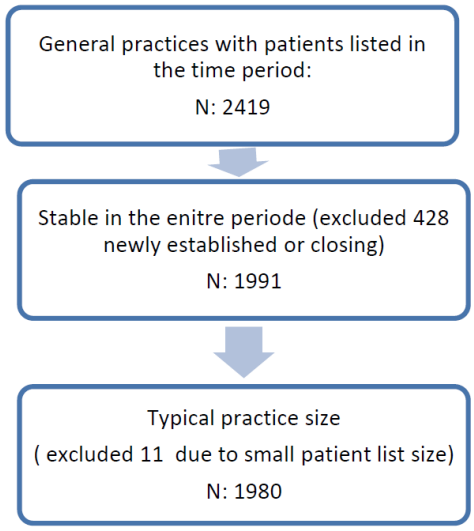


Figure 3: Sampling algorithm for general practice



OUTCOME VARIABLE

The outcome variable used in all three studies was *spirometry measurement recorded yes/no*. All records of spirometry tests provided to the study cohort in the time period 2007-2010 were extracted from the Danish National Health Service Register and the Danish National Patient Registry. For each patient we assessed if spirometry was conducted in an 18-month period from 6 months before to 12 months after the index date. The shortest time interval between the index date and spirometry was extracted. The spirometry tests were categorised according to whether they were conducted in general practice, other primary care clinics or in a hospital setting.

INDEPENDENT VARIABLES

Study I

We extracted all R03 medication from the index date and 12 months onwards for each individual from the Danish National Prescription database. We defined repeated redemption as redemption of more than one prescription of medication for obstructive lung disease (ATC R03) within a one-year interval (counting from index date) and the interval between the two prescriptions exceeding 30 days to ensure that the need for medication exceeded one month and was not limited to an acute episode. We also assessed the number of therapies redeemed within the first year from the index date within the three main categories of R03 medication: Beta-2-agonists, anticholinergics and inhaled corticosteroids. Other medications within the ATC R03 category were rarely prescribed and were therefore excluded from analyses with regard to number of therapies. Patients were categorised as initiating one, two or three types of therapy within the first year. Repeated redemption and number of therapies initiated within the first year were used as proxies for symptom severity. Further, patients' age and gender were extracted and age was categorised into the following categories: 18-27 years, 28-37 years, 38-47 years, 48-57 years, 58-67 years, 68-77 years, 78-87 years and over 87 years.

Study II

For each individual the highest educational level in 2008 was extracted from the Population's Education Register of Statistics Denmark. This register is based on administrative data from all educational institutions and has an eight digit code for each individual's highest educational level. The first two digits describe the main groups of educational level: 10 primary school, 20 upper secondary school, 25 basic vocational training, 35 vocational training with trade certificate, 40 higher education (short length), 50 higher education (medium length), 60 higher education (bachelor), 65 higher education (beyond bachelor), 70 PhD degree. We excluded subjects for whom information on education was missing (6.7%). Two-thirds of these missing's where due to immigration of the individual, the rest were primarily in the oldest age categories where registration is incomplete (>90 years). We categorised highest attained education into three categories: <10 years, (primary school), 10-12 years (vocational training and upper secondary school) and >12 years (higher education).

Information on income was extracted from the E-income register. We used the equivalent disposable income as our measure of the individual's economic capacity, defined as the entire household income after taxation, adjusted for number of persons in the household (the first adult counts 1, the following individuals over 15 years count 0.5, children under 15 years count 0.3). We used the average disposable income the previous 5 years (2003-2007) categorised income as low (first quartile), medium (second and third quartile) or high (fourth quartile). We excluded a total of 449 patients because they had no registered income in these 5 years and a further 37 because they only had a negative income registered.

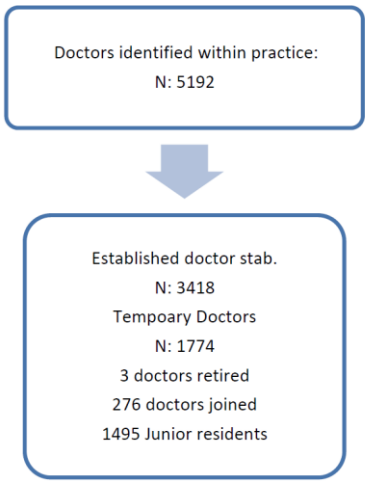
Affiliation to the labour market was extracted from the Employment Classification Module (AKM) in Statistics Denmark, which categorises the individual according to their main source of income each year. We categorised our cohort into three groups: working (employed or enrolled in an educational programme), receiving retirement pension or unemployed (all outside the workforce who were not retired).

Cohabitation status in 2008 was extracted from the E-Family register. Cohabitation status is coded in the register for all adults as: 1 married, 2 registered partnership, 3 living together and parents to one or more children in the household, 4 two adults of the opposite sex, not related, living together with less than 15 years age difference, 5 living alone. We categorised codes 1-4 as married/cohabitating and 5 as living alone (divorced, widowed or never married).

Study III

For each general practice we identified the number of doctors listed at each practice. Doctors listed in the entire period were defined "established doctors", the remaining doctors were defined temporary doctors. Temporary doctors where divided into two categories: junior residents (GP trainees) or other doctors joining or retiring from practice. The majority of the temporary doctors in general practice were junior residents. Practices with junior residents listed in the time period were defined training practices. Practices were defined single-handed practices if only one established doctor was listed and partnership practices if two or more established doctors were listed. The number of patients per doctor was defined as the mean practice list size divided by the number of established doctors. In single-handed practices we extracted the doctor's age and gender, in partnership practices we calculated the mean age of the established doctor group and defined whether these doctors were exclusively male or female, predominantly male or female or equally mixed gender. For each practice we calculated a "spirometry proportion", defined as the proportion of patients within practice initiating medication targeting obstructive lung disease who had spirometry performed in the 18-month interval.

Figure 4: Sampling algorithm for general practitioners



STATISTICS

Patient characteristics in Studies I & II are reported using means and standard deviations (SDs) to describe continuous variables and percentages (%) to describe categorical variables. In Study III we report the mean and standard deviation of the "spirometry proportion" for each practice characteristic.

In Study II analyses addressing socioeconomic and demographic variables were stratified into two age groups: < 65 years and ≥65 years, as this is the normal retirement age in Denmark, and we expected different effects of affiliation to the labour market, income and education in these two groups. These analyses were done with and without stratification according to gender, because studies have demonstrated that gender can influence socioeconomic factors' effect on health care.[111] In Study III the initial analyses were conducted with the entire cohort of general practices and were subsequently stratified into single-handed and partnership practices. This was done because this organisational factor modifies the effect of other practice characteristics, and because variables like age and gender of doctors were average values in partnership practices, but exact values in single-handed practices.

Logistic regression models were used to calculate crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for the associations between independent patient variables and having spirometry performed in the defined 18-month period. In Study I patient characteristics adjusted for were age, gender, number of therapies initiated in the first year and repeated redemption. In Study II we adjusted for gender, age and "high severity" of respiratory illness defined as initiating two or more medication categories within the first year and having repeated redemption of pulmonary medication.

In Study III we used mixed effects logistic regression models with patients nested within practice to calculate odds ratios (ORs) with

95% confidence intervals (CI) for the associations between practice characteristics and having spirometry performed. We used two models. Model one estimated the crude OR for the association of each practice characteristic with spirometry testing, model two estimated the OR for each practice characteristic, adjusted for patient characteristics: age, gender, income, highest attained education, affiliation to the labour market, cohabitation status, number of therapies initiated in the first year and repeated redemption, and the other practice characteristics included in the analysis. In study III we also conducted subgroup analyses of the association between practice characteristics and spirometry testing among 1) patients over 45 years of age receiving first-time prescriptions, and 2) patients receiving first-time prescriptions for at least two types of medication and redeeming medication repeatedly. This was done to assess if the associations shown among practice characteristics in the overall group of patients receiving first-time prescription for medication targeting obstructive lung disease were also present in subgroups of patients where COPD is more common and among patients with a continuous and more complex medication usage.

P-values < 0.05 were considered statistically significant. All statistical analyses were carried out using STATA 11 (STATACorp, College Station, TX, USA).

ETHICS

This project is register-based and according to "The Act on Research Ethics Review of Health Research Projects in Denmark" only questionnaire surveys and medical database research projects involving human biological material are required to be notified to the research ethics committee. The research ethics committee has, therefore, not been contacted. The study was approved by the Danish Data Protection Agency, J.nr. 2011-41-5798.

4. RESULTS

STUDY I

During 2008, 40 969 adults were identified as first time users of medication targeting obstructive lung disease. The mean age of the cohort was 55.6 years (SD18.7). There was a slight predominance of women (53.3% vs. 46.6%), and they were slightly younger (55.0 years (SD 19.1) vs. 56.3 years (SD 18.1)). The age distribution is shown in Figure 5. Approximately half of these patients had spirometry performed in the time period from 6 months before to 12 months after their first redeemed prescription (Table 1), and the majority of these patients had spirometry performed within two months of initiating medication, Figure 6. Most of the spirometry tests were performed in general practice.

Figure 5: Age distribution of first time users of medication targeting obstructive lung disease.

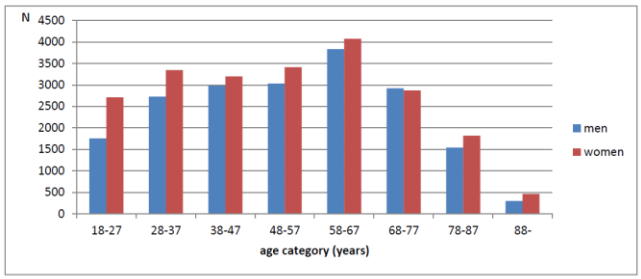
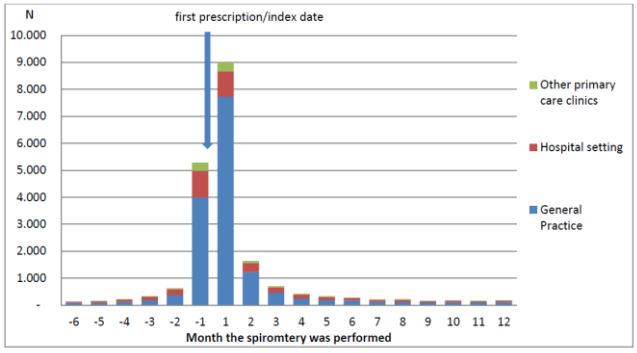


Figure 6: Time from the first prescription of medication targeting obstructive lung disease to spirometry*



* The shortest time interval between the index date and spirometry is illustrated

The proportion of patients having spirometry performed according to patient characteristics is shown in Table 1. We found several statistically significant associations between patient characteristics and having spirometry performed. Female gender, being in the age categories 28-47 years or over 68 years decreased the OR for spirometry testing. Repeated redemption and increasing number of therapies increased the OR for spirometry testing, Table 2.

Table 1 The proportion of patients having received at least one spirometry in the period from 6 months before to 12 months after their first prescription according to patient characteristics.

Characteristics		Spirometry recorded N (%)	Total N
All		20,262 (49.5)	40,969
Gender			
	Male	9970 (52.2)	19,083
	Female	10,292 (47.0)	21,886
Age categories			
	18-27	2123 (47.6)	4461
	28-37	2495 (41.1)	6072
	38-47	2847 (46.1)	6179
	48-57	3307 (51.3)	6441
	58-67	4486 (56.7)	7907
	68-77	3333 (57.6)	5791
	78-87	1527 (45.5)	3357
	88-	144 (18.9)	761
Repeated redemption			
	Yes	10,674 (69.9)	15,279
	No	9588 (37.3)	25,690
N. of pulmonary medication initiated			
	Monotherapy	9236 (37.3)	24,760
	Two therapies	9036 (65.7)	13,757
	Three therapies	1990 (81.2)	2452

Table 2 Logistic regression analysis to assess if there is an association between gender, age, number of pulmonary medication received, repeated redemption and spirometry.

		N	Crude OR	95% CI	Adjusted OR	95% CI
Gender						
	Male	19,083	1	-	-	
	Female	21,886	0.81*	0.78-0.84	0.86*	0.82-0.90
Age category						
	18-27	4461	1	-	-	
	28-37	6072	0.77*	0.71-0.83	0.73*	0.67-0.79
	38-47	6179	0.94	0.87-1.02	0.85*	0.79-0.92
	48-57	6441	1.16*	1.08-1.25	0.96	0.88-1.03
	58-67	7907	1.44*	1.34-1.55	1.02	0.94-1.11
	68-77	5791	1.49*	1.38-1.62	0.90*	0.83-0.98
	78-87	3357	0.92	0.84-1.01	0.51*	0.46-0.56
	88-	761	0.26*	0.21-0.31	0.15*	0.12-0.18
N. of pulmonary therapies initiated						
	1	24,760	1	-	-	
	2	13,757	3.22*	3.08-3.36	2.27*	2.16-2.38
	3	2452	7.24*	6.52-8.04	3.93*	3.51-4.40
Repeated redemption						
	No	25,690			-	
	Yes	15,279	3.89*	3.73-4.06	2.65*	2.52-2.78

*P-value< 0.05.

STUDY II

We found a variation between the proportions of patients having spirometry performed according to socio-demographic level, Table 3.

Table 3 Proportion of patients receiving spirometry in the 18-month time period by socioeconomic status

	All ages			<65 years			≥65 years		
	Men	Women	overall	Men	Women	overall	Men	Women	Overall
n (%)	9443 (53.5)	9676 (48.1)	19119 (50.7)	6336 (51.7)	6792 (47.0)	13128 (49.2)	3107 (57.6)	2884 (51.2)	5991 (54.3)
Highest attained education n (%)									
<10	3291 (53.7)	3839 (49.3)	7130 (51.2)	1963 (52.1)	2160 (48.8)	4123 (50.3)	1328 (56.3)	1679 (49.9)	3007 (52.5)
10-12	4376 (54.7)	3770 (48.8)	8146 (51.8)	3048 (52.8)	2921 (47.7)	5969 (50.2)	1328 (59.5)	849 (53.2)	2177 (56.9)
>12	1776 (50.6)	2067 (45.1)	3843 (47.5)	1325 (49.0)	1711 (43.8)	3036 (45.9)	451 (56.2)	356 (52.8)	807 (54.7)
Income n (%)									
Low (1st quartile)	2066 (51.5)	2430 (46.7)	4608 (48.8)	1099 (48.7)	1291 (45.0)	2390 (46.6)	1028 (55.5)	1190 (48.4)	2218 (51.5)
Medium (2nd+3rd quartile)	4952 (54.5)	4862 (48.3)	9658 (51.2)	3347 (52.4)	3502 (47.0)	6849 (49.5)	1512 (59.1)	1297 (52.6)	2809 (55.9)
High (4th quartile)	2425 (53.5)	2384 (49.5)	4853 (51.4)	1890 (52.5)	1999 (48.3)	3889 (50.3)	567 (57.8)	397 (55.7)	964 (56.9)
Labour status n (%)									
Working	5242 (51.6)	5170 (46.1)	10412 (48.7)	5008 (51.2)	5098 (46.1)	10106 (48.5)	234 (60.2)	72 (47.7)	306 (56.7)
Retirement pension	3177 (58.1)	3168 (51.8)	6345 (54.8)	335 (63.9)	389 (55.7)	724 (59.2)	2842 (57.5)	2779 (51.3)	5621 (54.2)
Unemployed	1024 (51.0)	1338 (48.4)	2362 (49.5)	993 (51.0)	1305 (48.2)	2298 (49.4)	31 (52.5)	33 (53.2)	64 (52.9)
Cohabitation n(%)									
Cohabitating	6457 (54.0)	5836 (48.2)	12293 (51.1)	4260 (51.6)	4534 (46.7)	8794 (49.0)	2197 (59.4)	1302 (54.3)	3499 (57.4)
Living alone	2986 (52.5)	3840 (48.0)	6826 (49.9)	2076 (52.0)	2258 (47.4)	4334 (49.5)	910 (53.8)	1582 (48.9)	2492 (50.5)

Among patients less than 65 years of age we found that being unemployed was significantly associated with a reduced OR for spirometry testing, the strongest association was seen in men, Table 4. We also found that higher income was associated with increased OR for spirometry testing in the total group and among men. However, only medium income was statistically significant. No association between income and spirometry was seen in women. High educational level (>12 years) was associated with a reduced chance of spirometry testing in the total group and in women, but did not reach statistical significance in men. Cohabitation status was not associated with having spirometry performed.

Table 4 Association between socioeconomic status and spirometry in patients < 65 years

Under 65 years	Men		Women		All	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI) p-value	Crude OR (95% CI) p-value	Adjusted OR (95% CI) p-value
Age (increasing)	1.01 (1.01-1.01) P<0.001	-	1.01 (1.01-1.01) P<0.001	-	1.01 (1.01-1.01) P<0.001	
Gender	-	-	-	-	0.83 (0.79-0.87) P<0.001	
High severity						
No	1	-	1	-	1	
Yes	6.19 (5.57-6.88) P<0.001	-	6.89 (6.25-7.60) P<0.001	-	6.57 (6.11-7.06) P<0.001	
Highest attained education						
<10	1	1	1	1	1	1
10-12	1.03 (0.95-1.11) P=0.534	1.04 (0.95-1.13) P=0.413	0.96 (0.89-1.03) P=0.262	1.00 (0.92-1.08) P=0.929	0.99 (94-1.05) p= 0.815	1.01(0.95-1.08) p=0.679
>12	0.88 (0.80-0.97) P=0.012	0.92 (0.83-1.03) P=0.137	0.82 (0.75-0.89) P<0.001	0.86 (0.78-0.94) P=0.001	0.84 (0.78-0.89) P<0.001	0.88 (0.82-0.95) P<0.001
Income (quartiles)						
1st	1	1	1	1	1	1
2nd+3rd	1.16 (1.05-1.28) P=0.002	1.18 (1.06-1.30) P=0.002	1.08 (0.99-1.18) P=0.079	0.99 (0.90-1.09) P=0.882	1.12 (1.05-1.19) p=0.001	1.08 (1.00-1-15) p=0.039
4th	1.16 (1.05-1.29) P=0.005	1.12 (1.00-1.26) P=0.052	1.14 (1.04-1.25) P=0.007	1.00 (0.89-1.11) P=0.981	1.16 (1.08-1.24) P<0.001	1.06 (0.98-1.14) p=0.177
Labour market status						
Working	1	1	1	1	1	1
Retirement pension	1.69 (1.41-2.02) P<0.001	1.20 (0.98-1.48) P=0.082	1.47 (1.26-1.71) P<0.001	1.07 (0.89-1.27) P=0.475	1.54 (1.37-1.73) P<0.001	1.12 (0.98-1.28) p=0.091
Unemployed	0.99 (0.90-1.09) P=0.849	0.82 (0.73-0.91) P<0.001	1.09 (1.00-1.19) P=0.045	0.91 (0.83-1.00) P=0.049	1.04 (0.97-1.10) p=0.272	0.87 (0.81-0.93) P<0.001
Cohabitation						
Cohabitating	1	1	1	1	1	1
Living alone	1.01 (0.94-1.09) P=0.703	0.99 (0.91-1.07) P=0.752	1.03 (0.96-1.10) P=0.438	1.03 (0.95-1.11) P=0.492	1.02 (0.97-1.07) p=0.423	1.01 (0.95-1.07) p=0.762

Among patients over 65 years of age we found living alone associated with reduced odds for spirometry testing in the total group and among men, but it did not reach statistical significance in women. Medium length education (10-12 years) and medium income were associated with increased OR for spirometry testing in the total group, but this was not statistically significant in the gender stratified analysis. No association between labour market affiliation and having spirometry performed was shown, Table 5.

Table 5 Association between socioeconomic status and spirometry in patients ≥ 65 years

Over 65 years	Men		Women		All	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI) (p-value)	Adjusted OR (95% CI) (p-value)
Age (increasing)	0.97 (0.96-0.98) P<0.001		0.96 (0.95-0.97) P<0.001		0.96 (0.96-0.97) P<0.001	
Gender					0.77 (0.72-0.83) P<0.001	
High severity						
No	1		1			
Yes	3.65 (3.23-4.11) P<0.001		4.09 (3.63-4.60) P<0.001		3.89 (3.57-4.23) P<0.001	
Highest attained education						
<10	1	1	1	1	1	1
10-12	1.14 (1.01-1.28) p=0.028	1.09 (0.96-1.23) p=0.197	1.14 (1.01-1.29) P=0.028	1.10 (0.97-1.26) P=0.130	1.19 (1.10-1.29) P<0.001	1.10 (1.00-1.120) p=0.042
>12	1.00 (0.85-1.17) p=0.967	0.98 (0.83-1.16) p=0.816	1.12 (0.95-1.33) P=0.166	1.13 (0.95-1.35) P=0.181	1.09 (0.97-1.22) p=0.143	1.05 (0.93-1.18) p=0.451
Income (quartiles)						
1st	1	1	1	1	1	1
2nd+3rd	1.16 (1.03-1.31) p=0.017	1.11 (0.98-1.27) p=0.113	1.18 (1.06-1.32) P=0.003	1.08 (0.95-1.22) P=0.241	1.20 (1.10-1.30) P<0.001	1.10 (1.00-1.20) p=0.047
4th	1.10 (0.94-1.28) p=0.242	1.08 (0.91-1.29) p=0.364	1.34 (1.13-1.58) P=0.001	1.19 (0.99-1.42) P=0.070	1.24(1.11-1.39) P<0.001	1.12 (0.99-1.27) p=0.069
Labour market status						
Working	1	1	1	1	1	1
Retirement pension	0.90 (0.73-1.11) p=0.307	1.01 (0.80-1.26) p=0.964	1.15 (0.83-1.60) P=0.386	1.40 (0.99-1.97) P=0.059	0.91 (0.76-1.08) p=0.269	1.13 (0.94-1.36) p=0.204
Unemployed	0.73 (0.42-1.27) p=269	0.65 (0.37-1.16) p=0.146	1.25 (0.69-2.26) P=0.463	0.94 (0.50-1.75) P=0.841	0.86 (0.58-1.28) p=0.450	0.75 (0.49-1.13) p=0.169
Cohabitation						
Cohabitating	1	1	1	1	1	1
Living alone	0.79 (0.71-0.89) P<0.001	0.78 (0.69-0.88) P<0.001	0.80 (0.72-0.89) P<0.001	0.91 (0.81-1.02) P=0.119	0.76 (0.70-0.82) P<0.001	0.84 (0.77-0.91) P<0.001

STUDY III

A total of 1980 practices and 35 677 patients were included in Study III. The mean "spirometry proportion" among general practice was 50.8%. The distribution of the "spirometry proportion" among general practice is illustrated in Figure 7 and it demonstrates quite a large variation between practices. An overview of practice characteristics and their mean "spirometry proportion" is shown in Table 6.

Figure 7: Distribution of the spirometry proportion among general practice in total numbers (N=1980)

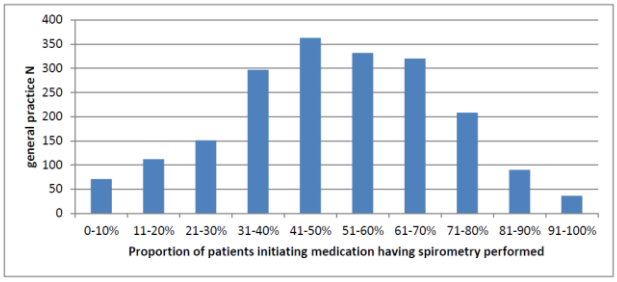


Table 6 Distribution of practice characteristics within the entire general practice cohort in absolute numbers (N). The mean and standard deviation of the variable "spirometry proportion" is reported for each practice characteristic.

		All practices		Single-handed practices		Partnership practices	
		N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Partnership practice	Yes	773	54.4 (16.8)	-	-	773	54.4 (16.8)
	No	1207	48.6 (22.7)	1207	48.6 (22.7)	-	-
Training practice	Yes	566	53.7 (18,0)	239	53.8 (20.2)	327	53.7 (16.1)
	No	1414	49.7 (21,8)	968	47.3(23.2)	446	54.8 (17.3)
No. of doctors	1	1207	48.6 (22,8)	1207	48.6 (22.8)	-	-
	2	388	54.2 (18,7)	-	-	388	54.2 (18.7)
	3	213	53.4 (15,6)	-	-	213	53.4 (15.6)
	4	94	57.2 (13,2)	-	-	94	57.2 (13.2)
	5	52	54.5 (14,2)	-	-	52	54.5 (14.2)
	>5	23	55.0 (11,3)	-	-	23	55.0 (11.3)
Age (mean for partnership practices)	<45	106	56.0 (19,1)	67	52.2 (18.8)	39	62.5 (18.1)
	45-49	238	55.8 (18,1)	122	54.5 (20.0)	116	57.2 (15,8)
	50-54	516	54.2 (18,8)	228	52.4 (21.4)	288	55.7 (16.3)
	55-59	609	49.7 (20,9)	366	48.3 (23.3)	243	51.7 (16.4)
	60-64	390	46.4 (22,4)	314	45.9 (23.3)	76	50.4 (17.8)
	>65	121	41.2 (23,9)	110	40,7 (24.3)	11	46.6 (-)
Gender	Male	1017	49.4 (22.1)	873	48.7 (22.7)	144	53.4 (17.5)
		189	54.4 (15.0)	-	-	189	54.4 (15.0)
	Equal	283	54.9 (18.6)	-	-	283	54.9 (18.6)
		98	54.3 (13.6)	-	-	98	54.3 (13.6)
	Female	393	49.2 (22.3)	334	48.3 (23.0)	59	54.0 (17.1)
Patients per doctor	<1347	513	49.8 (22.8)	227	43.9 (21.8)	286	54.4 (18.2)
	1347-1575	489	51.0 (19.8)	277	49.1 (21.8)	212	53.5 (16.4)
	1575-1756	489	52.3 (20.8)	307	49.9 (23.4)	182	56.5 (14.6)
	>1756	489	50.3 (19.7)	396	49.9 (20.3)	93	51.9 (17.0)

Some general practice characteristics were statistically significantly associated with spirometry testing; partnership practices had a higher OR for performing spirometry compared with single-handed practices, Table 7. We also found a significant association between increasing GP age and decreasing spirometry testing. The most pronounced effect of doctors' increasing age on spirometry was seen in partnership practices, Table 8. Training practice status was significantly associated with increased spirometry testing among single-handed practices, but not among partnership practices, Table 9. There was no association between the doctors' gender or number of patients per doctor and having spirometry performed in any of the analyses. Further, there was no association between number of doctors in a partnership practice and having spirometry performed.

Table 7 Association between practice characteristics and spirometry testing among all practices

	Model 1 Crude OR (95% CI)	Model 2** Adjusted OR (95% CI)
Training practice		
No	1	1
Yes	1.20 (1.06-1.36)*	1.10 (0.97-1.25)
Single-handed practice		
Yes	1	1
No	1.34 (1.16-1.55)*	1.24 (1.09-1.40)*
Mean age of doctors (years)		
≤ 45	1	1
45-49	0.94 (0.74-1.19)	0.87 (0.66-1.14)
50-54	0.88 (0.70-1.09)	0.78 (0.60-1.00)
55-59	0.68 (0.53-0.87)*	0.58 (0.44-0.76)*
60-64	0.58 (0.43-0.79)*	0.52 (0.39-0.70)*
≥65	0.41 (0.27-0.64)*	0.33 (0.22-0.50)*

*P-value< 0.05 **Adjusted for patient factors and practice characteristics

Subgroup analyses among patients over 45 years of age receiving first-time prescriptions and among patients receiving first-time prescriptions for at least two types of R03 medication and redeeming medication repeatedly both demonstrated the same significant associations: an increased OR was seen among partnership practices, practices with younger doctors and among single-handed practices with training practice status (data not shown).

Table 8 Association between practice characteristics and spirometry testing in partnership practices

	Model 1 Crude OR (95% CI)	Model 2** Adjusted OR (95% CI)
Training practice		
No	1	1
Yes	0.95 (0.84-1.08)	0.91 (0.79-1.04)
Mean age of doctors (years)		
≤ 45	1	1
45-49	0.72 (0.50-1.03)	0.66 (0.45-0.97)*
50-54	0.68 (0.47-0.98)*	0.61 (0.42-0.89)*
55-59	0.54 (0.34-0.86)*	0.45 (0.29-0.71)*
60-64	0.52 (0.31-0.86)*	0.43 (0.26-0.72)*
≥65	0.39 (0.17-0.90)*	0.25 (0.10-0.61)*
Number of doctors		
2	1	1
3	0.97 (0.84-1.13)	0.99 (0.77-1.27)
4	1.17 (0.95-1.45)	1.15 (0.90-1.45)
5	1.03 (0.82-1.30)	1.08 (0.77-1.51)
>5	1.05 (0.76-1.37)	1.03 (0.69-1.53)
Number of patients per doctor		
<1347	1	1
1347-1575	0.96 (0.82-1.12)	0.97 (0.82-1.15)
1576-1756	1.12 (0.94-1.34)	1.16 (0.96-1.34)
>1756	0.86 (0.69-1.07)	0.88 (0.70-1.11)
Gender of doctors		
Male	1	1
Predominantly male	1.05 (0.87-1.27)	0.99 (0.77-1.27)
Equal male/female	1.07 (0.89-1.29)	1.04 (0.85-1.28)
Predominantly female	1.05 (0.84-1.32)	0.94 (0.73-1.26)
Female	1.07 (0.81-1.42)	1.04 (0.76-1.42)

*P-value< 0.05 **Adjusted for patient factors and practice characteristics

Table 9 Association between practice characteristics and spirometry testing in single-handed practices

	Model 1 Crude OR (95% CI)	Model 2** Adjusted OR (95% CI)
Training practice		
No	1	1
Yes	1.40 (1.06-1.87)*	1.40 (1.10-1.79)*
Age of doctor (years)		
≤ 45	1	1
45-49	1.11 (0.78-1.58)	1.09 (0.73-1.61)
50-54	0.99 (0.78-1.58)	0.96 (0.67-1.38)
55-59	0.79 (0.73-1.35)	0.71 (0.49-1.03)
60-64	0.69 (0.56-1.10)	0.64 (0.43-0.95)*
≥65	0.50 (0.28-0.89)*	0.44 (0.28-0.76)*
Number of patients		
<1347	1	1
1347-1575	1.29 (0.97-1.71)	1.26 (0.95-1.67)
1576-1756	1.30 (0.99-1.72)	1.21 (0.92-1.59)
>1756	1.35 (1.02-1.79)*	1.17 (0.90-1.51)
Gender of doctor		
Male	1	1
Female	0.98 (0.84-1.15)	0.93 (0.77-1.12)

*P-value< 0.05 **Adjusted for patient factors and practice characteristics

5. DISCUSSION

MAIN FINDINGS

Spirometry testing among patients initiating medication targeting obstructive lung disease is low. Only half of the patients had spirometry performed in the 18-month time interval from 6 months before to 12 after medication initiation, the majority of these patients had spirometry performed within a two-month time interval around the time of initiating medication. We found increasing odds for spirometry testing if patients initiated two or three types of pulmonary medication within the first year and if patients redeemed medication repeatedly. Women and patients in the age categories 28-47 years or over 68 years were less likely to have spirometry performed. Among patients less than 65 years of age we found that being unemployed reduced the odds for having spirometry performed, higher income increased the odds of spirometry testing in men, and higher education among wom-

en reduced the odds of spirometry testing. Among men aged 65 or above living alone reduced the odds of spirometry testing. With regard to doctor and practice characteristics we found that patients had higher odds for having spirometry performed if their general practice was a partnership practice. Among single-handed practices, training practice status was associated with increased spirometry testing. We also found decreasing OR for spirometry testing with increasing age of doctors.

METHODOLOGICAL CONSIDERATIONS

Study design

The purpose of this thesis was to assess to what extent spirometry was conducted in the period 6 months before to 12 months following medication initiation medication targeting obstructive lung disease and to assess if patient, doctor or practice factors were associated with spirometry testing. To answer these questions we conducted three population-based cross-sectional cohort studies. We exclusively used register-based data, providing our studies with the major strength that they are population-based. We eliminated the risk of recall bias, as we have no questionnaire-based data, which are common limitations in studies assessing medication and health care utilisation. Selection bias, like healthy volunteer bias, was also avoided, as no participation was required.

Our cross-sectional cohort study design had two observation time intervals for each patient: two and 18 months. Defining these time intervals was based on clinical judgement. If spirometry is not conducted immediately when medication is prescribed, a follow-up consultation needs to take place before spirometry can be conducted, and due to waiting time at the GP follow-up consultations can be delayed several weeks or more. If the patient is referred to an outpatient clinic for evaluation or diagnostic clarification, several months' waiting time is quite normal, and we therefore found a broad time interval from medication to spirometry justifiable. Another, and just as plausible scenario could be that patients are tested with spirometry before prescribing takes place, and including a time interval prior to prescribing seemed rational. We assumed a shorter interval from spirometry to medication, because the above-mentioned "waiting time" is eliminated. We therefore made a cut-off 6 months prior to 12 months after prescription. After checking the time distribution of first spirometry (Figure 6) in our data we found an expected peak of spirometry testing around the time of prescribing with a steep decline the following months and a levelling out before reaching our two end points, and we therefore found no reason to adjust the defined 18-month time interval.

The observation time period for each practice was 30 months; this time interval is the maximum time period the individual practice could be observed with regard to whether spirometry was conducted in our cohort; from 6 months prior to January 2008 to 12 months after December 2008. We used this time interval to define practice variables instead of taking a single observation, and we believe this measure is more robust when categorising practices, as we were able to capture changes in the practice during the time period and take them into account.

Our cross-sectional cohort studies measured variables only once and we cannot reveal cause-effect relationships, but help identify associations. Associations found in cross-sectional studies can generate hypotheses on cause-effect relationships and can guide further research in hypothesis testing. As there are no studies addressing spirometry testing in patients initiating medication targeting obstructive lung disease, we found these explorative studies assessing associations to be the most appropriate preliminary studies.

The quality of the data sources

Prescription data

The Danish National Prescription Registry was the source for identifying our study cohort. This unique registry contains all reimbursed prescriptions redeemed in Danish pharmacies. The validity of these data is considered to be high, as the pharmacies have en economic incentive to collect prescription data as accurately as possible, as this optimises the pharmacies' reimbursement. Since all medication targeting obstructive lung disease with ATC code R03 requires a prescription, the registry captures all relevant medication users. However, some limitations are involved in using prescription data for identifying the study cohort and these must be kept in mind. Firstly, if a patient fails to redeem prescriptions (primary non-compliance) they will not be included in the study cohort, or the number of types of therapy prescribed may be underestimated. As medication use is not free of charge for patients in Denmark, there is a risk that patients with low economic resources are underrepresented in the study cohort and that their severity of illness is underestimated as we use number of types of medication initiated as a proxy of illness severity. Patients with self-limiting symptoms may also not redeem medication if their symptoms disappear. However, primary non-compliance is considered small[112] and we assume that is has no significant influence on our results assessing associations. Secondly, it is important to remember that the index date assigned each individual corresponds to the redemption date, not the date the drug was prescribed. Medication can be redeemed up to several months after prescription. However, the majority of prescriptions are collected within the week[112] and due to the broad observation time period we assume that this imprecision has no significant influence on our results.

Spirometry data

The Danish National Patient Registry and the Danish National Health Service Register were used to identify all spirometry procedures performed in primary and secondary care in the relevant time periods. Both registries are based on administrative data used for reimbursement of the health care system and are therefore considered to be quite accurate. The validity of COPD diagnoses registered in the Danish National Patient Registry has been shown to be high,[113] but no studies have assessed the validity of procedure codes in the two registries. We do not consider either over- or underreporting to the registries to be a major problem, although a minor imprecision in recording of spirometry testing cannot be excluded. If present, we hypothesise that this imprecision would be non-differential with regard to patient variables. With regard to practice variables one might speculate whether different organisational factors could influence over- or underreporting, but there is no evidence that certain practice organisations code less consistently.

Another limitation of these register data is that the spirometry date corresponds to the week of reimbursement, not the day the spirometry was performed. Reimbursements are usually done at the end of each week, but longer intervals are seen around New Year, where the interval can be up to two weeks. When including

the possible interval from prescribed to redeemed medications, we estimate that the time interval between prescriptions to spirometry testing may be inaccurate with a few weeks and up to one month. Time to first spirometry is therefore illustrated in months in Figure 6 and it is important to remember that the time period from one month before to one month after medication initiation solely reflects the fact that spirometry was conducted around the time the drug was redeemed, not specifically whether the drug was prescribed before or after the spirometry was performed. This does not influence our analyses assessing associations, as we do not differentiate between spirometry before or after prescription.

Socioeconomic and demographic data

We choose four socioeconomic and demographic variables to assess associations between SES and spirometry testing. Variables like cohabitation status, education, occupation and income are considered important measures of SES,[85, 114] SES is, however, not strictly defined. Multiple variables can be used and assessed at the level of the individual,[115, 116] aggregated from residential areas[70, 91]or at the level of practice[99, 117] according to availably of data, and this variation makes comparison a challenge. In Denmark, detailed socioeconomic and demographic data on an individual level are available and therefore used in these analyses. The four chosen variables are based on administrative data, and defined in Statistics Denmark. The quality of these data is high and there is a low risk of misclassification. The existing risks of misclassification are, however, described below.

Cohabitation status is based on housing registration, which is accurate with regard to where people live, but the classification of cohabitation status can, for some, be incorrect as it is generated on the assumption that couples are adults living together with no family relation, of the opposite sex, with less than a 15-years age gap. Hence, adults living together on a purely platonical basis will be registered as cohabitating, whereas homosexuals or other couples differing from the mentioned assumption will be registered as living alone. An alternative measure of "cohabitation" could have been using only registered partnerships as cohabitating, but many couples in Denmark live together without being married or registered, and they would be misclassified. We therefore believe that the definition of cohabitation used misclassifies fewer couples.

Affiliation to the labour market is categorised according to tax information in Statistics Denmark and is therefore quite accurate, and patients are placed in the category according to where most of their income source is from each year. However, if an individual has received financial benefits/support due to illness or maternity leave most of the year, they will be placed in the unemployment category, although in fact being employed, and thereby misclassified. Misclassification of patients in employment or retirement categories is unlikely, and it is, therefore, only the influence of being unemployed that risks a small dilution and being pushed towards the null.

Income in Statistics Denmark is also generated from tax information. Only few individuals had no income or negative income. Individuals in Denmark with no capital or income are by law guaranteed social benefits, and individuals not entitled to social benefits may have a large capital and their economic resources are difficult to assess, and individuals with no income were therefore excluded instead of being placed in the lowest income category. We used the average disposable income during the past 5 years, which we believe gives the best picture of the individual's economic capacity, levelling out short-term changes in income and making different family sizes comparable.

Highest attained education was generated from educational institutions' administrative data. Misclassification of subjects as having a higher education than was actually the case is unlikely, but a few work-related skills may not be registered in the education register, and these individuals may be misclassified.

General practice data

General practice data are based on administrative data and the risk of errors in data on doctors' age, gender, and number of patients listed at each general practice is negligible. Categorising doctors as established doctors, junior doctors or others was done on the basis of the length of employment registered. Hence temporary doctors registered in the entire period will be misclassified as established doctors. We do not expect this to be a significant problem. However, a small misclassification of single-handed practices in the partnership practice category cannot be excluded. We do, however, not risk overestimating the effect of being a partnership practice.

Immeasurable potentially influential variables

The Danish National Prescription Registry does not have complete data on the dose or indication for the drugs redeemed, making it impossible for us to differentiate between different indications for prescription. This does not influence our main aim: assessing whether spirometry is performed to confirm obstruction when medication targeting obstructive lung diseases is prescribed. However, if it had been possible, including the indication for prescription as a possible explanatory variable in our analyses could have been relevant. This may be possible in future research as the indication is being recorded in an increasing proportion of prescriptions. Another variable that could be of interest to include is the prescriber of the drug. This could assist in identifying in which setting the patient had the medication prescribed. It is plausible to hypothesise that if patients receive medication from out-of-hours clinics or emergency department settings, where no follow-up can be offered, it would reduce the likelihood of spirometry testing, as it necessitates a second action from the patient; they have to contact their GP to initiate follow-up. However, the registry has been shown to be imprecise with regard to correct labelling of the prescriber, and prescriptions may have the patient's GP incorrectly recorded. The registry contains no other data indicating where or when the prescription was issued. These administrative data document when and where prescriptions were redeemed.

Comorbidity could also have been relevant to include as comorbidity may influence spirometry testing. Including comorbidity is challenging as the registries only contain data on diagnoses from secondary care; comorbidity handled in primary care will not be adequately reflected using these secondary care data. Smoking status could also influence spirometry testing and could have been relevant to include if available in our data.

With regard to practice characteristics, variables like location of practice in rural or urban area, having a practice nurse and use of protocols would be relevant to include as explanatory variables, as these variables could also potentially influence spirometry testing. These data were not available in the registries.

GENERALISABILITY

Our study comprises the entire adult population initiating medication targeting obstructive lung disease in Denmark, and the generalisability is therefore focused on extrapolating our results to populations in other countries. We find it reasonable to generalise our findings to other countries with health-care systems similar to the Danish one (e.g. drug prescribing, health care services free of charge at the point of care, general practitioner as gatekeeper etc.). However, cultural differences with regard to symptom perception and health-care utilisation may be different across countries and have influence on the population initiating medication.

DISCUSSION OF STUDY RESULTS

To the best of our knowledge this is the first study to assess spirometry testing among patients initiating medication targeting obstructive lung disease. We therefore compare our study results with studies assessing spirometry testing among other study populations; medication users where length of medication is not specified, patients with a diagnosis of COPD or asthma, or populations comprising a combination of medication users and patients with obstructive lung diagnoses.

Study I

We found a low rate of spirometry testing among patients initiating medication targeting obstructive lung disease; only half of the patients receive spirometry within the 18-month time period of initiating medication. Another study assessing spirometry utilisation among medication users in five Latin American cities found that among patients reporting use of any bronchodilator or corticosteroid in the previous 12 months, only 37.5% reported a history of spirometry testing.[28] This lower rate of spirometry testing can be due to the differences in study design, but also the health care systems are quite different, e.g. medication is freely available in some areas of Latin America whereas prescriptions are needed in Denmark. A Swedish study assessing spirometry among patients with a new CODP diagnosis found that 59% had spirometry data recorded within a period of +/-6months of the diagnosis, but only half of these had FEV1/VC ratio <0.7 recorded.[67] A Canadian study assessed spirometry testing 1 year prior to 2.5 years following the time of an asthma diagnosis and only 43% had spirometry performed in this time period.[70] We therefore conclude that our findings are plausible. Why spirometry is not performed among patients initiating medication targeting obstructive lung disease is not answered by this study, but many of the barriers for performing spirometry reported in the literature could also influence spirometry testing when initiating medication.

The initial prescription could be a proxy for the first encounter, where the patients' reporting of symptoms has been interpreted as needing medication, and this initial contact between the patient and the healthcare system is of great interest. Increasing the rate of spirometry testing when patients initiate medication could enhance diagnosing of patients with obstructive lung diseases at earlier stages. All patients initiating medication may, however, not be in an early stage of the disease, as patients can be asymptomatic or fail to attend their physician to seek medical advice. Still, this initial prescription is a proxy for the first encounter where both the patient and doctor find a reason to act: the patient seeks medical advice and the doctor finds treatment with medication appropriate. Hence, failing to conduct spirometry testing at this point in time or at follow-up is a missed opportunity for assessing obstructive lung disease in symptomatic patients, and enhancing further diagnostic clarification through spirometry in these patients seems relevant.

Gender differences among patients in spirometry testing were in favour of men in our study, despite the fact that there was an overweight of women initiating medication in most age categories. Studies comparing gender differences in spirometry utilisation among COPD patients have found an underuse of spirometry testing among both women[67, 83] and men.[71] Possible reasons for difference in spirometry testing between genders could be different patient perceptions and reporting of symptoms[118] among the two sexes. Also, doctors could perceive different risks of obstructive lung disease with higher risk among men, despite the fact that asthma prevalence is higher among women,[10, 119] and the difference in prevalence of COPD between men and women has decreased.[120]

Another interesting finding in our study was variation in spirometry testing across different age categories, with highest spirometry rates in the youngest age group and patients in their sixties. Higher spirometry in these age groups could correspond to physicians' higher awareness of asthma and COPD among these sub groups. Patients in our study had a decreasing OR of having spirometry performed with increasing age after the age category 58-67 years, in concordance with the findings of others.[71] There is no obvious explanation for this but perhaps the patients or their doctors[121] find further diagnostic clarification irrelevant. Perhaps an uncertainty of interpreting the spirometry result due to the fixed cut-off ratio discourages some physicians from conducting spirometry testing in the oldest age categories. Correct diagnosis is, however, essential in the oldest age groups, as these patients have a higher risk of co-morbidities like for instance heart failure, and misinterpretation of respiratory symptoms caused by other illnesses is increased in this group.

We found that an increasing number of therapies initiated and repeated redemption both significantly increased the chance of undergoing spirometry. This association is not surprising as we hypothesised that they are a proxy for symptom severity. However, repeated redemption could also indicate several contacts with a physician due to respiratory symptoms and an increasing number of physician contacts may also increase the likelihood of spirometry testing.[122]

Study II

Overall we saw several socioeconomic and demographic variables influencing spirometry testing. Our study demonstrated that being unemployed was associated with not having spirometry performed. Unemployment is shown to have a great impact on health and mortality,[123-125] and this pattern is more pronounced among men, in concordance with our findings. We also found a significant association between higher income and having spirometry testing among men. This is in concordance with a Canadian study, finding that patients with higher income had increased likelihood of spirometry testing in the diagnostic process of asthma.[70] However, we found no influence of income on spirometry testing among women, but a more pronounced influence of socioeconomic status among men has also been demonstrated in other studies.[88] Higher educational level did on the other hand not increase the odds of spirometry testing; the opposite tendency was seen in both sexes but only statistically significant among women less than 65 years of age. A similar opposing finding was demonstrated in a study of management of myocardial infarction

in Denmark, where higher education decreased the use of a procedure.[90] There is no clear reason for this. One hypothesis could be that educated women with careers are too busy and less likely to engage in a diagnostic process.[92]
Among men over 65 years we found a reduced chance of spirometry if they lived alone. Being married has been associated with improved blood pressure control among the elderly.[115] Also, having a spouse is shown to improve management of diabetes, primarily due to the positive influence a spouse has on health behaviour, and men seem more receptive to this positive influence.[126]

Study III

Several doctor and practice characteristics were associated with spirometry testing. We found that single-handed practices had lower odds of performing spirometry compared to partnership practices in concordance with studies assessing scores for quality of care.[99, 100] Among partnership practices, there was, however, no association between number of doctors and odds of spirometry testing, indicating that size of partnership practices was not associated with spirometry testing. Further, we found no association between number of patients per doctor and spirometry testing. Although partnership practices and larger practices have been associated with higher scores for quality of care in several chronic illnesses, studies are not consistent with regard to this issue, as the opposite has also been shown.[127]
Increasing age among doctors has been reported to be associated with decreasing quality of care scores in studies,[128, 129] and these findings are in concordance with our study, where we see a clear tendency between increasing age and decreasing OR for spirometry testing. Our study does not clarify why older doctors perform fewer spirometry tests in patients initiating medication, but the GP's age has been shown to influence clinical practice patterns, with older GP's providing more home visits, doing fewer procedures and having higher prescribing rates.[97]
We saw no association between gender of doctor and spirometry testing. Other studies have reported that when assessing quality scores, female physicians are more often among high scorers and the majority of the lowest scoring physicians are men.[128, 130] Specifically, female GPs have been reported to attain higher scores in evaluation of antenatal care[131] and more often referring to bone mineral density testing.[96] We therefore hypothesised that female GPs perform more tests, but our data showed no indication of this pattern.
Training practices have been shown to influence quality of care,[99, 128] and in our study we also saw this tendency, but only among single-handed practices. Why training practice status influences single-handed practices but not partnership practices is unknown, but an explanation could be that this difference in effect is due to a greater interaction between the single-handed practitioner and the resident doctor compared to the interaction seen in a partnership practice with several doctors.

6. CONCLUSION

Many patients initiate medication targeting obstructive lung disease without spirometry testing: approximately half were still not tested one year after initiating medication targeting obstructive lung disease. We found several associations between spirometry testing and patient and practice characteristics. Among patient characteristics we found an association between being in the middle and oldest age categories, being a woman and not having spirometry performed. Also, socioeconomic and demographic variables like unemployment, high education or living alone seem to be associated with not having a spirometry test conducted.
We found a large variation between practices' "spirometry proportion", and some of this variation was associated with practice and doctor characteristics. Among practice and doctor characteristics we found associations between increasing age among doctors, being a single-handed practice, and among single-handed practices, not being a training practice, and decreasing odds of spirometry testing.

7. IMPLICATIONS AND PERSPECTIVES

Our studies have identified several associations between spirometry testing and patient and practice characteristics, and further exploration of these associations is warranted; we need to understand the mechanisms behind these associations to target adequate interventions. Most associations found in our study could only explain some of the overall low rate of spirometry testing. The association between increasing age among doctors and patients and decreasing spirometry testing showed, however, quite a strong association. Further exploration and intervention could be relevant here to enhance spirometry utilisation in these subgroups.
Besides targeting quality improvement interventions on the identified associations, the overall low rate of spirometry utilisation and wide variation between practices should be addressed. Spirometry is essential for diagnosing obstructive lung disease and could probably be used as a marker of good quality. However, it may not be relevant for all patients receiving first-time prescriptions for medication targeting obstructive lung disease to have spirometry performed. Among some patients it may be clinically meaningful not to conduct spirometry testing, for example among patients who are unable to cooperate sufficiently, who are terminally ill etc. Still, the overall low rate of spirometry utilisation and wide variation between practices cannot merely be a clinically meaningful variation; it must indicate a quality gap. This lack of spirometry testing exits not only in Denmark, but probably in other nations as well. There is a huge body of literature supporting the fact that patients with obstructive lung disease, especially COPD are diagnosed too late. Earlier diagnosis of obstructive lung disease may be improved by targeting interventions aiming at assessing airway obstruction with spirometry when patients initiate medication.
This underutilisation of spirometry among patients initiating medication should be reducible by applying some of the quality improvement interventions used in improving spirometry testing among COPD and asthma patients.[132-134] A new and interesting tool now available in Denmark is the Danish General Medicine Database (DAMD),[135] a data capture system soon integrated in all GPs' electronic patient journal (EPJ) systems. This system collects data from the GP's EPJ and can send feedback and reminders to the GP in the EPJ. Currently the system is used as a quality improvement tool in some chronic illnesses like COPD and diabetes. Briefly, a reminder appears on the doctor's computer screen in the EPJ, when activated by an ICPC code for diabetes or COPD. These reminders are structured as a type of checklist to ensure that important aspects of chronic illnesses are remembered and managed. Later the GPs receive structured feedback on all their patients with the illness of interest and can easily identify patients, who are not receiving optimal care.

The DAMD database could also be used to enhance spirometry testing among patients, who are not yet diagnosed with COPD or asthma: a reminder question could appear when prescriptions are issued. A question like "Is this patient tested for obstructive lung disease with spirometry?" could enhance awareness of conducting spirometry at this early stage. A randomised controlled trial assessing the effects of this type of quality improvement tool could be feasible in the near future and very interesting to conduct, as no studies have yet assessed, if the DAMD can be used to improve quality of care, although an observational study indicates this.[136] However, before such a study is conducted, it is important to assess if spirometry testing among medication users has improved over time, as proven among COPD patients in hospital settings.[137] A time-series cross-sectional study could supply data on the tendency towards spirometry testing over time from 2008-2012 and could easily be conducted.

8. SUMMARY IN ENGLISH

This PhD thesis was written during my employment at the Research Unit of General Practice in Odense, University of Southern Denmark. It comprises an overview and three papers, all published or submitted for publication in international peer-reviewed scientific journals.

Background: Non-infectious dyspnoea, chronic cough and wheezing are common symptoms in the population. Patients often present with these symptoms in general practice and have a high probability of having obstructive lung diseases. However, there is an indication that the majority of these patients are treated empirically with pharmacotherapy targeting obstructive lung disease and only few have additional tests conducted, although the predictive value of respiratory symptoms for diagnosing obstructive lung disease has proven to be low. Spirometry is recommended as the gold standard for confirming obstructive lung disease, and testing can also rule out airway obstruction in patients with respiratory symptoms caused by other illnesses, such as heart failure or lung cancer. Initiating medication for obstructive lung disease without spirometry entails the risk of these patients experiencing unnecessary delay in the diagnostic process and being exposed to unnecessary economic costs and medication risks. The literature has indicated that many users of medication targeting obstructive lung medication have not had spirometry performed and do not actually have obstructive lung disease. This potential quality gap needs to be assessed. Also, in order to target interventions enhancing earlier spirometry utilisation among patients initiating medication targeting obstructive lung disease, improved knowledge on patient and practice factors associated with spirometry testing is needed.

Aims: Among first time users of obstructive lung medication we aimed:

- To assess to what extent spirometry was performed within the first year of medication use (Study I)
- To assess if patient characteristics like socioeconomic and demographic status were associated with spirometry testing (Studies I & II)
- To assess if general practice characteristics were associated with spirometry testing (Study III)

Methods: Register-based observational studies on first time users of medication targeting obstructive lung disease among adults over 18 years of age in 2008. The patient cohort was identified in the Danish National Prescription Register where all redeemed prescriptions for medication targeting obstructive lung disease are registered. All spirometry tests provided to the patient cohort in the time period 2007-2010 were extracted from the Danish National Health Service Register and the Danish National Patient Register and we assessed if patients had a spirometry registered in an 18 month time period counting from 6 months before to 12 months after their first redemption of medication. We linked socioeconomic and demographic patient variables and variables on practice characteristics from National registers to assess their association with patients having spirometry performed.

Results: A total of 40 969 adults initiated medication targeting obstructive lung medication in 2008 in Denmark. The mean age of the cohort was 55.6 years (SD18.7) and approximately half of the mediations users had spirometry test performed. Initiating several types of medication targeting obstructive lung disease within the first year and redeeming medication repeatedly increased the odds of having spirometry performed. Women and patients in the oldest age categories had reduced odds of having spirometry performed. Being unemployed reduced the odds for spirometry testing among adults less than 65 years of age. Also, among the elderly (>65 years) living alone reduced the odds for spirometry testing; however this was only statistically significant among men. Some practice characteristics also influenced the odds for spirometry testing. Patients in partnership practices had higher odds for spirometry testing. Among singlehanded practices higher odds for spirometry testing was seen if practice had training practice status. We saw decreasing odds for spirometry testing with increasing age among doctors.

Conclusion and perspectives: This study has shown a lack of spirometry testing among patients initiating medication targeting obstructive lung disease. This underuse of spirometry testing indicates a quality gap and increased focus of spirometry utilization is needed when patients initiate medication targeting obstructive lung disease. The variation reported in spirometry testing across patient and practice characteristics was most predominant with regard to increasing age among patients and doctors, the remaining variables only account for small variations. However identification of these variations can help guide general practitioners to identify patients at increased risk of not having spirometry performed and help target future interventions for primary care.

9. REFERENCE LIST

1. Lindstrom M, Kotaniemi J, Jonsson E, Lundback B. Smoking, respiratory symptoms, and diseases : a comparative study between northern Sweden and northern Finland: report from the FinEsS study. Chest 2001;119(3):852-861.
2. Mannino DM, Gagnon RC, Petty TL, Lydick E. Obstructive lung disease and low lung function in adults in the United States: data from the National Health and Nutrition Examination Survey, 1988-1994. Arch Intern Med 2000;160(11):1683-1689.

3. Ahmed T, Steward JA, O'Mahony MS. Dyspnoea and mortality in older people in the community: a 10-year follow-up. Age Ageing 2012;41(4):545-549.
4. Renwick DS, Connolly MJ. Prevalence and treatment of chronic airways obstruction in adults over the age of 45. Thorax 1996;51(2):164-168.
5. Frese T, Sobeck C, Herrmann K, Sandholzer H. Dyspnea as the reason for encounter in general practice. J Clin Med Res 2011;3(5):239-246.
6. Moth G, Vedsted P, Olesen F. Kontakt og sygdomsmønsteret i almen praksis: KOS 2008. 2013. Ref Type: Unpublished Work
7. Thiadens HA, de Bock GH, Dekker FW et al. Identifying asthma and chronic obstructive pulmonary disease in patients with persistent cough presenting to general practitioners: descriptive study. BMJ 1998;316(7140):1286-1290.
8. Broekhuizen BD, Sachs AP, Hoes AW et al. Undetected chronic obstructive pulmonary disease and asthma in people over 50 years with persistent cough. Br J Gen Pract 2010;60(576):489-494.
9. Thiadens HA, Postma DS, de Bock GH, Huysman DA, van Houwelingen HC, Springer MP. Asthma in adult patients presenting with symptoms of acute bronchitis in general practice. Scand J Prim Health Care 2000;18(3):188-192.
10. Browatzki A, Ulrik CS, Lange P. Prevalence and severity of self-reported asthma in young adults, 1976-2004. Eur Respir J 2009;34(5):1046-1051.
11. Hansen EF, Rappeport Y, Vestbo J, Lange P. [Prevalence of asthma among young adults in Copenhagen]. Ugeskr Laeger 2001;163(44):6128-6130.
12. Fabricius P, Lokke A, Marott JL, Vestbo J, Lange P. Prevalence of COPD in Copenhagen. Respir Med 2011;105(3):410-417.
13. Hansen JG, Pedersen L, Overvad K, Omland O, Jensen HK, Sorensen HT. The Prevalence of chronic obstructive pulmonary disease among Danes aged 45-84 years: population-based study. COPD 2008;5(6):347-352.
14. Medstat. Available at: http://www.medstat.dk Accessed. 10-12-2012. Ref Type: Unpublished Work
15. Jakobsen M, Anker N, Dolleru J, Poulsen PB, Lange P. Study on drug costs associated with COPD prescription medicine in Denmark Clin Respir J 2012;10.
16. Barr RG, Bourbeau J, Camargo CA, Ram FS. Inhaled tiotropium for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2005;(2):CD002876.
17. Calverley PM, Anderson JA, Celli B et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007;356(8):775-789.
18. Pauwels RA, Lofdahl CG, Postma DS et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. N Engl J Med 1997;337(20):1405-1411.
19. Bengtsson B, Fagerstrom PO. Extrapulmonary effects of terbutaline during prolonged administration. Clin Pharmacol Ther 1982;31(6):726-732.
20. Michele TM, Pinheiro S, Iyasu S. The safety of tiotropium--the FDA's conclusions. N Engl J Med 2010;363(12):1097-1099.
21. Jeffery PK, Godfrey RW, Adelroth E, Nelson F, Rogers A, Johansson SA. Effects of treatment on airway inflammation and thickening of basement membrane reticular collagen in asthma. A quantitative light and electron microscopic study. Am Rev Respir Dis 1992;145(4 Pt 1):890-899.
22. Juniper EF, Kline PA, Vanzieleghem MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. Am Rev Respir Dis 1990;142(4):832-836.
23. Pauwels RA, Yernault JC, Demedts MG, Geusens P. Safety and efficacy of fluticasone and beclomethasone in moderate to severe asthma. Belgian Multicenter Study Group. Am J Respir Crit Care Med 1998;157(3 Pt 1):827-832.
24. Calverley PM, Stockley RA, Seemungal TA et al. Reported pneumonia in patients with COPD: findings from the INSPIRE study. Chest 2011;139(3):505-512.
25. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. Arch Intern Med 1999;159(9):941-955.
26. Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. N Engl J Med 1997;337(1):8-14.
27. Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 1999;353(9167):1819-1823.
28. Montes de OM, Talamo C, Perez-Padilla R et al. Use of respiratory medication in five Latin American cities: The PLATINO study. Pulm Pharmacol Ther 2008;21(5):788-793.
29. Joish VN, Brady E, Stockdale W, Brixner DI, Dirani R. Evaluating Diagnosis and Treatment Patterns of COPD in Primary Care. Treat Respir Med 2006;5(4):283-293.
30. Anthonisen NR, Woodlrage K, Manfreda J. Use of spirometry and respiratory drugs in Manitobans over 35 years of age with obstructive lung diseases. Can Respir J 2005;12(2):69-74.
31. Seaman J, Leonard AC, Panos RJ. Health care utilization history, GOLD guidelines, and respiratory medication prescriptions in patients with COPD. Int J Chron Obstruct Pulmon Dis 2010;5:89-97.
32. Simoni M, Carrozzi L, Baldacci S et al. Respiratory symptoms/diseases, impaired lung function, and drug use in two Italian general population samples. Respir Med 2008;102(1):82-91.
33. Lokke A, Ulrik CS, Dahl R et al. Detection of previously undiagnosed cases of COPD in a high-risk population identified in general practice. COPD 2012;9(5):458-465.
34. Miravitlles M, de la Roza C, Morera J et al. Chronic respiratory symptoms, spirometry and knowledge of COPD among general population. Respir Med 2006;100(11):1973-1980.

35. Nihlen U, Montnemery P, Lindholm LH, Lofdahl CG. Detection of chronic obstructive pulmonary disease (COPD) in primary health care: role of spirometry and respiratory symptoms. Scand J Prim Health Care 1999;17(4):232-237.
36. Broekhuizen BD, Sachs AP, Oostvogels R, Hoes AW, Verheij TJ, Moons KG. The diagnostic value of history and physical examination for COPD in suspected or known cases: a systematic review. Fam Pract 2009;26(4):260-268.
37. Mannino DM, Etzel RA, Flanders WD. Do the medical history and physical examination predict low lung function? Arch Intern Med 1993;153(16):1892-1897.
38. Medbo A, Melbye H. What role may symptoms play in the diagnosis of airflow limitation? A study in an elderly population. Scand J Prim Health Care 2008;26(2):92-98.
39. Ohar JA, Sadeghnejad A, Meyers DA, Donohue JF, Bleecker ER. Do symptoms predict COPD in smokers? Chest 2010;137(6):1345-1353.
40. Renwick DS, Connolly MJ. Do respiratory symptoms predict chronic airflow obstruction and bronchial hyperresponsiveness in older adults? J Gerontol A Biol Sci Med Sci 1999;54(3):M136-M139.
41. Straus SE, McAlister FA, Sackett DL, Deeks JJ. Accuracy of history, wheezing, and forced expiratory time in the diagnosis of chronic obstructive pulmonary disease. J Gen Intern Med 2002;17(9):684-688.
42. Holleman DR, Jr., Simel DL, Goldberg JS. Diagnosis of obstructive airways disease from the clinical examination. J Gen Intern Med 1993;8(2):63-68.
43. Badgett RG, Tanaka DJ, Hunt DK et al. Can moderate chronic obstructive pulmonary disease be diagnosed by historical and physical findings alone? Am J Med 1993;94(2):188-196.
44. Badgett RG, Tanaka DJ, Hunt DK et al. The clinical evaluation for diagnosing obstructive airways disease in high-risk patients. Chest 1994;106(5):1427-1431.
45. Cowie RL, Underwood MF, Field SK. Asthma symptoms do not predict spirometry. Can Respir J 2007;14(6):339-342.
46. Teeter JG, Bleecker ER. Relationship between airway obstruction and respiratory symptoms in adult asthmatics. Chest 1998;113(2):272-277.
47. Anderson WJ, Lipworth BJ. Relationships between impulse oscillometry, spirometry and dyspnoea in COPD. J R Coll Physicians Edinb 2012;42(2):111-115.
48. Boer LM, Asijee GM, van Schayck OC, Schermer TR. How do dyspnoea scales compare with measurement of functional capacity in patients with COPD and at risk of COPD? Prim Care Respir J 2012;21(2):202-207.
49. Mahut B, Caumont-Prim A, Plantier L et al. Relationships between respiratory and airway resistances and activity-related dyspnea in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2012;7:165-171.
50. Wegner RE, Jorres RA, Kirsten DK, Magnussen H. Factor analysis of exercise capacity, dyspnoea ratings and lung function in patients with severe COPD. Eur Respir J 1994;7(4):725-729.
51. Bateman ED, Hurd SS, Barnes PJ et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J 2008;31(1):143-178.
52. Levy ML, Quanjer PH, Booker R, Cooper BG, Holmes S, Small I. Diagnostic spirometry in primary care: Proposed standards for general practice compliant with American Thoracic Society and European Respiratory Society recommendations: a General Practice Airways Group (GPIAG)1 document, in association with the Association for Respiratory Technology & Physiology (ARTP)2 and Education for Health3 1 www.gpiag.org 2 www.artp.org 3 www.educationforhealth.org.uk. Prim Care Respir J 2009;18(3):130-147.
53. Vestbo J, Hurd SS, Agusti AG et al. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, GOLD Executive Summary. Am J Respir Crit Care Med 2012.
54. Akkermans RP, Berrevoets MA, Smeele IJ et al. Lung function decline in relation to diagnostic criteria for airflow obstruction in respiratory symptomatic subjects. BMC Pulm Med 2012;12:12.
55. Hardie JA, Buist AS, Vollmer WM, Ellingsen I, Bakke PS, Morkve O. Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. Eur Respir J 2002;20(5):1117-1122.
56. Mohamed Hoesein FA, Zanen P, Lammers JW. Lower limit of normal or FEV1/FVC < 0.70 in diagnosing COPD: an evidence-based review. Respir Med 2011;105(6):907-915.
57. Mohamed Hoesein FA, Zanen P, Sachs AP, Verheij TJ, Lammers JW, Broekhuizen BD. Spirometric thresholds for diagnosing COPD: 0.70 or LLN, pre- or post-dilator values? COPD 2012;9(4):338-343.
58. Cerveri I, Corsico AG, Accordini S et al. Underestimation of airflow obstruction among young adults using FEV1/FVC <70% as a fixed cut-off: a longitudinal evaluation of clinical and functional outcomes. Thorax 2008;63(12):1040-1045.
59. Cerveri I, Corsico AG, Accordini S et al. What defines airflow obstruction in asthma? Eur Respir J 2009;34(3):568-573.
60. Enright PL. Should we keep pushing for a spirometer in every doctor's office? Respir Care 2012;57(1):146-151.
61. Schermer TR, Jacobs JE, Chavannes NH et al. Validity of spirometric testing in a general practice population of patients with chronic obstructive pulmonary disease (COPD). Thorax 2003;58(10):861-866.
62. Schermer TR, Crockett AJ, Poels PJ et al. Quality of routine spirometry tests in Dutch general practices. Br J Gen Pract 2009;59(569):e376-e382.
63. Schermer TR, Verweij EH, Cretier R, Pellegrino A, Crockett AJ, Poels PJ. Accuracy and precision of desktop spirometers in general practices. Respiration 2012;83(4):344-352.
64. Schneider A, Gindner L, Tilemann L et al. Diagnostic accuracy of spirometry in primary care. BMC Pulm Med 2009;9:31.
65. van Schayck CP, Loozen JM, Wagena E, Akkermans RP, Wesseling GJ. Detecting patients at a high risk of developing chronic obstructive pulmonary disease in general

practice: cross sectional case finding study. BMJ 2002;324(7350):1370.
66. Qaseem A, Wilt TJ, Weinberger SE et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med 2011;155(3):179-191.
67. Arne M, Lisspers K, Stallberg B et al. How often is diagnosis of COPD confirmed with spirometry? Respir Med 2010;104(4):550-556.
68. Bourbeau J, Sebaldt RJ, Day A et al. Practice patterns in the management of chronic obstructive pulmonary disease in primary practice: the CAGE study. Can Respir J 2008;15(1):13-19.
69. Buffels J, Degryse J, Liistro G. Diagnostic certainty, comorbidity and medication in a primary care population with presumed airway obstruction: the DIDASCO2 study. Prim Care Respir J 2009;18(1):34-40.
70. Gershon AS, Victor JC, Guan J, Aaron SD, To T. Pulmonary function testing in the diagnosis of asthma: a population study. Chest 2012;141(5):1190-1196.
71. Han MK, Kim MG, Mardon R et al. Spirometry utilization for COPD: how do we measure up? Chest 2007;132(2):403-409.
72. Lee TA, Bartle B, Weiss KB. Spirometry use in clinical practice following diagnosis of COPD. Chest 2006;129(6):1509-1515.
73. Lofdahl CG, Tilling B, Ekstrom T, Jorgensen L, Johansson G, Larsson K. COPD health care in Sweden - A study in primary and secondary care. Respir Med 2010;104(3):404-411.
74. Miravitlles M, de la Roza C, Naberan K, Lamban M, Gobartt E, Martin A. Use of spirometry and patterns of prescribing in COPD in primary care. Respir Med 2007;101(8):1753-1760.
75. Weidinger P, Nilsson JL, Lindblad U. Adherence to diagnostic guidelines and quality indicators in asthma and COPD in Swedish primary care. Pharmacoepidemiol Drug Saf 2009;18(5):393-400.
76. Averame G, Bonavia M, Ferri P et al. Office spirometry can improve the diagnosis of obstructive airway disease in primary care setting. Respir Med 2009;103(6):866-872.
77. Buffels J, Degryse J, Liistro G, Decramer M. Differential Diagnosis in a Primary Care Population with Presumed Airway Obstruction: A Real-Life Study. Respiration 2011.
78. Pearson M, Ayres JG, Sarno M, Massey D, Price D. Diagnosis of airway obstruction in primary care in the UK: the CADRE (COPD and Asthma Diagnostic/management REassessment) programme 1997-2001. Int J Chron Obstruct Pulmon Dis 2006;1(4):435-443.
79. Yawn BP, Enright PL, Lemanske RF, Jr. et al. Spirometry can be done in family physicians' offices and alters clinical decisions in management of asthma and COPD. Chest 2007;132(4):1162-1168.
80. Dales RE, Vandemheen KL, Clinch J, Aaron SD. Spirometry in the primary care setting: influence on clinical diagnosis and management of airflow obstruction. Chest 2005;128(4):2443-2447.
81. Joo MJ, Lee TA, Au DH, Fitzgibbon ML, Weiss KB. Medication use patterns associated with spirometry in diagnosing COPD. COPD 2008;5(6):360-368.
82. Walker PP, Mitchell P, Diamantea F, Warburton CJ, Davies L. Effect of primary-care spirometry on the diagnosis and management of COPD. Eur Respir J 2006;28(5):945-952.
83. Watson L, Vestbo J, Postma DS et al. Gender differences in the management and experience of Chronic Obstructive Pulmonary Disease. Respir Med 2004;98(12):1207-1213.
84. Martinez CH, Raparla S, Plauschinat CA et al. Gender differences in symptoms and care delivery for chronic obstructive pulmonary disease. J Womens Health (Larchmt) 2012;21(12):1267-1274.
85. Dalton SO, Steding-Jessen M, Gislum M, Frederiksen K, Engholm G, Schuz J. Social inequality and incidence of and survival from cancer in a population-based study in Denmark, 1994-2003: Background, aims, material and methods. Eur J Cancer 2008;44(14):1938-1949.
86. Krieger N, Williams DR, Moss NE. Measuring social class in US public health research: concepts, methodologies, and guidelines. Annu Rev Public Health 1997;18:341-378.
87. Regidor E. Social determinants of health: a veil that hides socioeconomic position and its relation with health. J Epidemiol Community Health 2006;60(10):896-901.
88. Haglund B, Koster M, Nilsson T, Rosen M. Inequality in access to coronary revascularization in Sweden. Scand Cardiovasc J 2004;38(6):334-339.
89. Jakovljevic D, Sarti C, Sivenius J et al. Socioeconomic status and ischemic stroke: The FINMONICA Stroke Register. Stroke 2001;32(7):1492-1498.
90. Rasmussen JN, Rasmussen S, Gislason GH et al. Persistent socio-economic differences in revascularization after acute myocardial infarction despite a universal health care system-a Danish study. Cardiovasc Drugs Ther 2007;21(6):449-457.
91. Smith CJ, Gribbin J, Challen KB, Hubbard RB. The impact of the 2004 NICE guideline and 2003 General Medical Services contract on COPD in primary care in the UK. QJM 2008;101(2):145-153.
92. Dennis SM, Zwar NA, Marks GB. Diagnosing asthma in adults in primary care: a qualitative study of Australian GPs' experiences. Prim Care Respir J 2010;19(1):52-56.
93. Roberts NJ, Smith SF, Partridge MR. Why is spirometry underused in the diagnosis of the breathless patient: a qualitative study. BMC Pulm Med 2011;11:37.
94. Salinas GD, Williamson JC, Kalhan R et al. Barriers to adherence to chronic obstructive pulmonary disease guidelines by primary care physicians. Int J Chron Obstruct Pulmon Dis 2011;6:171-179.
95. Walters JA, Hansen E, Mudge P, Johns DP, Walters EH, Wood-Baker R. Barriers to the use of spirometry in general practice. Aust Fam Physician 2005;34(3):201-203.
96. Ioannidis G, Papaioannou A, Thabane L et al. Family physicians' personal and practice characteristics that are associated with improved utilization of bone mineral density testing and osteoporosis medication prescribing. Popul Health Manag 2009;12(3):131-138.

97. Charles J, Britt H, Valenti L. The independent effect of age of general practitioner on clinical practice. Med J Aust 2006;185(2):105-109.
98. Poels PJ, Schermer TR, Jacobs A et al. Variation in spirometry utilization between trained general practitioners in practices equipped with a spirometer. Scand J Prim Health Care 2006;24(2):81-87.
99. Ashworth M, Armstrong D. The relationship between general practice characteristics and quality of care: a national survey of quality indicators used in the UK Quality and Outcomes Framework, 2004-5. BMC Fam Pract 2006;7:68.
100. Millett C, Car J, Eldred D, Khunti K, Mainous AG, III, Majeed A. Diabetes prevalence, process of care and outcomes in relation to practice size, caseload and deprivation: national cross-sectional study in primary care. J R Soc Med 2007;100(6):275-283.
101. Nielen MM, Schellevis FG, Verheij RA. Inter-practice variation in diagnosing hypertension and diabetes mellitus: a cross-sectional study in general practice. BMC Fam Pract 2009;10:6.
102. Pedersen KM, Andersen JS, Sondergaard J. General practice and primary health care in Denmark. J Am Board Fam Med 2012;25 Suppl 1:S34-S38.
103. Pedersen CB. The Danish Civil Registration System. Scand J Public Health 2011;39(7 Suppl):22-25.
104. Thygesen LC, Daasnes C, Thaulow I, Bronnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. Scand J Public Health 2011;39(7 Suppl):12-16.
105. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health 2011;39(7 Suppl):38-41.
106. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health 2011;39(7 Suppl):30-33.
107. Andersen JS, Olivarius NF, Krasnik A. The Danish National Health Service Register. Scand J Public Health 2011;39(7 Suppl):34-37.
108. Petersson F, Baadsgaard M, Thygesen LC. Danish registers on personal labour market affiliation. Scand J Public Health 2011;39(7 Suppl):95-98.
109. Jensen VM, Rasmussen AW. Danish Education Registers. Scand J Public Health 2011;39(7 Suppl):91-94.
110. Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. Scand J Public Health 2011;39(7 Suppl):103-105.
111. Chittleborough CR, Taylor AW, Dal GE et al. Gender differences in asthma prevalence: variations with socioeconomic disadvantage. Respirology 2010;15(1):107-114.
112. Tobi H, van den Heuvel NJ, de Jong-van den Berg LT. Does uncollected medication reduce the validity of pharmacy dispensing data? Pharmacoepidemiol Drug Saf 2004;13(7):497-500.
113. Thomsen RW, Lange P, Hellquist B et al. Validity and underrecording of diagnosis of COPD in the Danish National Patient Registry. Respir Med 2011;105(7):1063-1068.
114. Prescott E, Godtfredsen N, Vestbo J, Osler M. Social position and mortality from respiratory diseases in males and females. Eur Respir J 2003;21(5):821-826.
115. Paulsen MS, Andersen M, Munck AP et al. Socioeconomic status influences blood pressure control despite equal access to care. Fam Pract 2012;29(5):503-510.
116. Svendsen RP, Paulsen MS, Larsen PV et al. Associations between reporting of cancer alarm symptoms and socioeconomic and demographic determinants: a population-based, cross-sectional study. BMC Public Health 2012;12(1):686.
117. Ashworth M, Medina J, Morgan M. Effect of social deprivation on blood pressure monitoring and control in England: a survey of data from the quality and outcomes framework. BMJ 2008;337:a2030.
118. Kynyk JA, Mastronarde JG, McCallister JW. Asthma, the sex difference. Curr Opin Pulm Med 2011;17(1):6-11.
119. Leynaert B, Sunyer J, Garcia-Esteban R et al. Gender differences in prevalence, diagnosis and incidence of allergic and non-allergic asthma: a population-based coh- Thorax 2012;67(7):625-631.
120. Rycroft CE, Heyes A, Lanza L, Becker K. Epidemiology of chronic obstructive pulmonary disease: a literature review. Int J Chron Obstruct Pulmon Dis 2012;7:457-494.
121. Bond M, Bowling A, McKee D et al. Does ageism affect the management of ischaemic heart disease? J Health Serv Res Policy 2003;8(1):40-47.
122. Anthonisen NR, Dik N, Manfreda J, Roos LL. Spirometry and obstructive lung disease in Manitoba. Can Respir J 2001;8(6):421-426.
123. Bartley M. Unemployment and ill health: understanding the relationship. J Epidemiol Community Health 1994;48(4):333-337.
124. Roelfs DJ, Shor E, Davidson KW, Schwartz JE. Losing life and livelihood: a systematic review and meta-analysis of unemployment and all-cause mortality. Soc Sci Med 2011;72(6):840-854.
125. Stronks K, van de Mheen H, van den Bos J, Mackenbach JP. Smaller socioeconomic inequalities in health among women: the role of employment status. Int J Epidemiol 1995;24(3):559-568.
126. August KJ, Sorkin DH. Marital status and gender differences in managing a chronic illness: the function of health-related social control. Soc Sci Med 2010;71(10):1831-1838.
127. Khunti K, Gadsby R, Millett C, Majeed A, Davies M. Quality of diabetes care in the UK: comparison of published quality-of-care reports with results of the Quality and Outcomes Framework for Diabetes. Diabet Med 2007;24(12):1436-1441.
128. Ashworth M, Schofield P, Seed P, Durbaba S, Kordowicz M, Jones R. Identifying poorly performing general practices in England: a longitudinal study using data from the quality and outcomes framework. J Health Serv Res Policy 2011;16(1):21-27.
129. McAuley RG, Paul WM, Morrison GH, Beckett RF, Goldsmith CH. Five-year results of the peer assessment program of the College of Physicians and Surgeons of Ontario. CMAJ 1990;143(11):1193-1199.
130. Thind A, Feightner J, Stewart M, Thorpe C, Burt A. Who delivers preventive care as recommended?: Analysis of physician and practice characteristics. Can Fam Physician 2008;54(11):1574-1575.

131. Backe B, Jacobsen G. General practitioners' compliance with guidelines for antenatal care. Scand J Prim Health Care 1994;12(2):100-105.
132. Joo MJ, Au DH, Lee TA. Use of spirometry in the diagnosis of chronic obstructive pulmonary disease and efforts to improve quality of care. Transl Res 2009;154(3):103-110.
133. Lange P, Rasmussen FV, Borgeskov H et al. The quality of COPD care in general practice in Denmark: the KVA-SIMODO study. Prim Care Respir J 2007;16(3):174-181.
134. Price DB, Yawn BP, Jones RC. Improving the differential diagnosis of chronic obstructive pulmonary disease in primary care. Mayo Clin Proc 2010;85(12):1122-1129.
135. Schroll H, Christensen B, Andersen JS, Sondergaard J. [Danish General Medicine Database--future tool! The Danish Society of General Medicine]. Ugeskr Laeger 2008;170(12):1013.
136. Schroll H, Christensen RD, Thomsen JL, Andersen M, Friborg S, Sondergaard J. The danish model for improvement of diabetes care in general practice: impact of automated collection and feedback of patient data. Int J Family Med 2012;2012:208123.
137. Tottenborg SS, Thomsen RW, Statistician HN, Johnsen SP, Frausing E, Lange P. Improving Quality of Care among COPD outpatients in Denmark 2008-2011. Clin Respir J 2012.