POPULATION-BASED STUDIES ON COPD

FROM A GENDER PERSPECTIVE

Inauguraldissertation

zur

Erlangung der Würde eines Doktors der Philosophie

vorgelegt der

Philosophisch-Naturwissenschaftlichen Fakultät

der Universität Basel

von

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aus Deutschland

Basel, 2010

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät der Universität Basel auf Antrag von

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Basel, den 30. März 2010

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Dekan

“On ne voit bien qu'avec le coeur.
L'essentiel est invisible pour les yeux.”

(Saint Exupéry)

ACKNOWLEDGEMENT

THANK YOU

Prof. Dr. Christoph Meier

Prof. Dr. Kurt Hersberger

Prof. Dr. Wolf-Dietrich Woggon

Prof. Dr. Matthias Hamburger

Nycomed GmbH

Dr. Ulrich Bothner

Basel Pharmacoepidemiology Unit

Dr. Yolanda Brauchli

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Boston Collaborative Drug Surveillance Program

Prof. Dr. Hershel Jick

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Dr. Lianne Parkin

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Klin. Pharmakologie und Toxikologie

Prof. Dr. Dr. Stephan Krähenbühl

Dr. Alexandra Rätz Bravo

Carmen Franz

Evelyne Rudin

The work presented here is (in part) published by the following journals:

COPD and the risk of depression

Schneider C., Bothner U., Jick SS., Meier CR.

Chest 2010;137;341-347

Chronic obstructive pulmonary disease and the risk of cardiovascular diseases

Schneider C., Bothner U., Jick SS., Meier CR.

European Journal of Epidemiology 2010 Apr; 25(4):253-60

Reflux Disease, Gastrointestinal Ulcer or Weight Loss in Patients with COPD

Schneider C., Bothner U., Jick SS., Meier CR.

In press in COPD: Journal of Chronic Obstructive Pulmonary Disease

Contents

Summary

Men are different, women too. A concept which has long been neglected in biomedical research. Except for reproductive differences women were regarded as smaller men, clinical guidelines did not differentiate between men and women. There are, however, further differences. Every cell has a sex, which might influence regulation of gene expression, disease phenotype and drug toxicity. In drug research it is important to understand the pathomechanism and clinical presentation of a disease as well as the mechanism of action of a drug. Information on drug safety and efficacy are collected in preclinical and clinical studies. Natural history of disease studies provide valuable information on the clinical presentation of a disease. It is important to provide this information gender stratified to be able to offer best care to future patients. Chronic obstructive pulmonary disease (COPD) has traditionally been regarded as a disease of white men but today almost as many women are affected by the disease as men. The burden of COPD is still projected to increase, particularly in women. Despite this there are few studies comparing the clinical manifestation and clinical course in men and women with COPD. It was the aim of this thesis to contribute new data to the natural history of COPD with a special focus on the effect of gender.

The studies of this thesis were conducted with data from the General Practice Research Database (GPRD), a large population-based database in the United Kingdom. The GPRD provides anonymized medical information on a 5% representative sample of the UK population. This thesis presents six studies focussing on a population of 35,772 COPD patients, aged 40-79 years, who received their incident COPD diagnosis between 1995 and 2005 and the same number of randomly matched COPD-free patients for comparison. In a case-control analysis we compared the prevalence of co-morbidities and respiratory drug utilization in men and women with COPD. In nested case control analyses COPD and COPD-free patients were compared with respect to their risk to develop cardiovascular or gastrointestinal outcomes, depression or cancer.

The first study described the COPD population with respect to co-morbidities, drug use and survival. Patients with COPD had more co-morbidities and a lower survival than COPD-free patients. In COPD patients the prevalence of diabetes, myocardial infarction, stroke /

transient ischemic attack (TIA), arrhythmia and peptic ulcer were higher in men than in women while depression and osteoporosis were more prevalent in women. We observed small but significant gender differences in drug utilization and survival. The second study analysed in more detail the association between COPD and the prevalence of diabetes. The prevalence of diabetes was lower in the COPD group than in the COPD-free comparison group. This association was significant in men but not women and mainly seen in users of sulfonylurea. Studies 3-6 were follow-up and nested case control analyses evaluating the risk of the cardiovascular outcomes (arrhythmia, pulmonary embolism, deep vein thrombosis, myocardial infarction and stroke / TIA), gastro-oesophageal reflux disease, peptic ulcer, depression and cancer risk in the population of COPD patients and compared it to a COPD-free population. The incidence of most cardiovascular diseases was higher in patients with COPD. COPD had a stronger impact on the risk of MI and stroke / TIA in women than in men. Relative risks of PE, DVT and arrhythmia were similar in men and women. Severe COPD materially increased the risk of MI and PE in both men and women. The incidence rates of GORD were slightly higher in men than in women while peptic ulcer incidence rates were higher in men. COPD did not materially alter the risk of GORD or peptic ulcer. Current use of long-acting beta agonists was associated with a decreased risk of peptic ulcer. Patients with COPD had a higher risk of cancer than COPD-free patients. The increased risk was mainly driven by a high lung cancer risk among COPD patients, which was higher in women than in men. This effect was seen independent of smoking status. Many patients with COPD developed depression during follow-up, particularly patients with severe COPD. The risk of depression was higher in women than in men but COPD seemed to have a greater impact in men than in women.

The studies of this thesis provide further evidence that patients with COPD are at an increased risk of depression, most cardiovascular diseases and lung cancer. They also demonstrate that gender-stratified analyses are important to adequately address the risk for a disease.

ABBREVIATIONS

ACE	angiotensin converting enzyme
Adj.	adjusted
BMI	body mass index
CI	confidence interval
CLL	chronic lymphocytic leukaemia
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
DVT	deep vein thrombosis
FDA	US Food and Drug Administration
FEV1	forced expiratory volume in 1 second
GP	general practitioner
GPRD	General Practice Research Database
GOLD	Global Initiative for Obstructive Lung Diseases
HIV	human immunodeficiency virus
HPV	Human Papilloma Virus
IBD	inflammatory bowel disease
IR	incidence rate
IRR	incidence rate ratio
ISAC	Independent Scientific Advisory Committee for MHRA database research
MAOA	monoaminooxidase A inhibitors
MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
MNRI	monoamine reuptake inhibitors
NICE	National Institute for Health and Clinical Excellence
NSAID	non-steroidal anti-inflammatory drugs
NSCLC	Non-small lung carcinoma cells
OC	oral contraceptive
OR	odds ratio

PE	pulmonary embolism
Py	person years
Sd	standard deviation
SSRI	selective serotonin reuptake inhibitors
TIA	transient ischemic attack
VTE	venous thromboembolism
Y	years

INTRODUCTION

1.1 GENDER IN DRUG SAFETY

Personalized medicine is nowadays an often used buzzword in healthcare. Personalized medicine can identify fast and slow drug metabolizers thus allowing to identify patients at high risk for adverse drug reactions or patients benefiting from targeted anti-tumour therapy and thus spare those from nasty adverse reactions who will not respond.(1) Seeing all this progress in medicine it is astonishing that the largest genetic difference - easily phaenotypical differentiable - has been neglected for decades in the analysis of the safety profile of new drugs. Sex.

1.1.1 WOMEN IN CLINICAL TRIALS – SHORT HISTORICAL OVERVIEW

Following the thalidomide scandal in the late 1950s and early 1960s,(2) women have almost completely been excluded from clinical trials due to worries about teratogenic effects (and to avoid legal liability from prenatal exposure). A policy paper published by the American Food and Drug Administration (FDA) required that women with child-bearing potential were excluded form early clinical trials (phase I and early phase II),(3) which led to a scenario where women were given drugs which were never thoroughly tested on their efficacy nor their safety. In the 1990s therefore the 'NIH Revitalization Act' (1993) (4) required that women should be included in clinical trials after the experience of many HIV positive women not having access to experimental drugs at a time when almost no HIV drugs were available on the market and thus the potential risk to the foetus was valued higher than the risk of death from a life-threatening disease. An analysis of randomized controlled trials published between 1994 and 1999 in the New England Journal of Medicine still only found 25% women to be enrolled and only 14% of the trials provided gender-specific data analyses.(5) Of 46 studies published in 2004, reporting results of clinical trials starting 1994 or later, only 13% reported gender-specific results.(6) Since 1999 the FDA can stop the development of a drug when the company tries to exclude women able to give birth from the studies of a drug

designed for life-threatening diseases.(7) An analysis of cardiovascular clinical trials from 1990 to 2006 found an increasing trend to report sex-specific data and a higher number of subgroup analyses by sex (53% in 169 studies) but raised the concern that these analyses are often not conducted properly.(8)

1.1.2 Different Drug Effects in Men and Women

What are the clinical consequences of not appropriately testing drugs in men and women; do women experience more adverse events than men? An analysis of all serious adverse events reported to the FDA between 1998 and 2005 revealed that more women (55.5%) than men (45.5%) experienced adverse events.(9) Adverse events were more serious in women than in men. Eight out of ten drugs withdrawn from the US market between 1997 and 2000 were withdrawn because of greater health risks for women than for men.(10) Results from an analysis of 48 prescription-event monitoring studies of newly marketed drugs in the UK show a similar picture; adult women had a 1.6 (95% CI, 1.5-1.7) increased risk of adverse events when compared with men.(11) Possible explanations for this observed sex-difference in reported adverse events include the observation that women take more drugs than men and thus have a greater risk to experience adverse events from drug-drug interactions, women are more frequently overdosed because of sex-related differences in pharmacokinetics, they might be more sensitive to the drug actions, they might be more likely to report adverse events, women become older than men and age has also been associated with increasing number of adverse events.(12) Age and the number of drugs taken are not sufficient to explain the gender difference.(13)

Another question, more difficult to answer, is whether the drugs are really as effective in men and women. Different effects in men and women have, for example, been reported in the literature for opioids, aspirin and digoxin. Aspirin had been recommended by the American Heart Association to reduce the incidence of coronary heart disease in high-risk patients. A clinical trial conducted in women, however, reported no overall effect on the risk of

myocardial infarction but a decreased risk of stroke.(14) A subsequent sex-specific meta-analysis of randomized controlled trials on aspirin and cardiovascular events showed different results in men and women: men profited for myocardial prevention while women did for stroke but not MI.(15) There is increasing evidence that opioids exert different effects in men and women although much more research is needed to understand the magnitude of this phenomena.(16) In patient controlled analgesia, men showed higher postoperative opioid use than women. Women were more affected by morphine-induced respiratory depression. Digoxin, a cardiac glycoside which had been used in the treatment of patients with heart failure, increased mortality in women with heart failure and depressed left ventricular function compared to women assigned to placebo while in men digoxin had no significant effect on survival.(17)

Why do men and women react different towards drugs? Men have a Y chromosome and women a second X chromosome. Although this answer is by far oversimplified accumulating evidence shows that sex chromosomes not only encode primary and secondary sexual organs but are in some way involved in many other processes in the body including drug metabolism. “Every cell has a sex. Whether a cell contains a XX or a XY chromosome may have an impact on everything from regulation of gene expression in a cell line to the efficacy or toxicity of a pharmaceutical in a living human.“(18) This difference may affect the pharmacokinetics and the pharmacodynamics of a drug but also the presentation of the treatable disease itself. The drug metabolism for example is affected by differences in the activity of P 450 cytochrome enzymes, CYP2D6 and CYP1A2 have been associated with gender differences.(19) The interindividual variation in the activity of CYP enzymes is, however, also high, so it is not easy to distinguish gender differences from individual differences. The angiotensin II type 2 receptor is an example for a direct genetic difference as its gene is located on the X chromosome. In women usually one X-chromosome is randomly inactivated thus it is not clear whether this difference has an important impact on normal physiology and drug treatment. Genes on the X chromosome or rather the incorrect silencing of the second X-chromosome have also been associated with the predominance of

women among patients with autoimmune diseases as important genes for immune function are located on the X-chromosome.(20) There are many more examples of gender differences known, but how these differences are manifested is often not clear. Gender differences in pharmacokinetics and pharmacodynamics have recently been reviewed by Franconi et al.(19) and Soldin and Mattison (12) and the book 'Gender Medizin' by Rieder and Lohff provides an overview about gender differences in human diseases.(21)

1.1.3 PHARMACOVIGILANCE & NATURAL HISTORY OF DISEASE STUDIES

To understand the safety of a drug it is also important to understand the molecular basis of the disease as this helps to understand the mechanism of action of a drug or to have at least a picture of the specific clinical presentation of the disease to be in a position to predict adverse events or put them into perspective. As part of the pharmacovigilance planning, the International Conference on Harmonisation (ICH) guideline E2E specifically requires companies to provide information on the epidemiology of the disease for which a drug is indicated. For important adverse events background incidence rates, i.e. the rate of an event in a population not exposed to the drug of interest, should be provided to be in a position to put the adverse events reported once the drug is on the market into perspective. This information has to be provided stratified by sex, whenever possible. Natural history of disease studies are listed as method to gain such information.(22) They employ epidemiological methods such as cohort and case-control studies to provide this information. More details on these study designs are provided in Excursus 1.

While randomized controlled trials actively recruit patients and often have very stringent in- and exclusion criteria thus often providing information on a rather small (maximally a few thousand patients), selective group the purpose of natural history of disease studies is to provide a snap-shot of the real world. The advent of administrative database has made this possible with a reasonable effort. Today health insurances, pharmacies and GPs often keep electronic records of their clients, respectively patients and in some countries this information

EXCURSUS 1 EPIDEMIOLOGICAL STUDY DESIGNS (23)

Cohort studies

Cohort studies are interested in certain exposures and how this exposure influences the health of people exposed to it. The exposure can, for example, be a drug, a disease or even more abstract the year of birth. To put the effect of the exposure into perspective a comparison group is needed, this are people who have not been exposed. Ideally the two groups would be identical except for the presence or absence of the exposure. These two groups are then followed from the start of the exposure until they develop an outcome of interest or are lost to follow-up. Loss of follow-up can be due to death of the patient, end of the study, or the patient leaving the study. With statistical methods then incidence rates and relative risks can be calculated to estimate the impact of the exposure on the outcome.

Case-control studies

Case-control studies start at the point of an outcome and look back in time. The outcome is often a disease but could e.g. also be marital status. First patients with the disease of interest are identified, they are the cases. Then, to investigate why these people developed the disease and other did not, a control group is identified. Controls are people who do not have the disease of interest at the time the study is conducted. Ideally the presence or absence of the disease of interest would be the only difference between cases and controls. As this is often hard to fulfil, one tries to ensure that the groups are at least identical with respect to the most important known confounders such as age, sex and timing. This is done by matching cases and controls. The statistical power increases with the number of controls matched to each case. In these groups, i.e. cases and controls, the proportion of people exposed to potential risk factors prior to the outcome will then be quantified and compared. The measure to quantify the risk difference is the odds ratio.

Nested case-control studies

Nested case-control studies combine the cohort and case-control design. The first part is a cohort study while the second part is a case-control study, which is nested in the cohort population. In a first step people with a specific exposure and a comparison group with people free of the exposure are identified and followed until they develop an outcome of interest, die or are otherwise lost to follow-up. Thus the crude incidence rate of the outcome can be calculated. For calculating adjusted risk estimates one, however, uses the case-control design. In this second part one identifies all patients who developed the outcome of interest, independent of whether they had been exposed or not and identifies a certain number of controls from the pool of the cohort who did not develop an outcome. Then again like in a normal case-control study cases and controls are compared with respect to certain risk factors, in this case the exposure from the cohort, and odds ratios are calculated. This design has been developed to reduce costs in traditional cohort studies but it also is more efficient in the use of computer resources in database research.

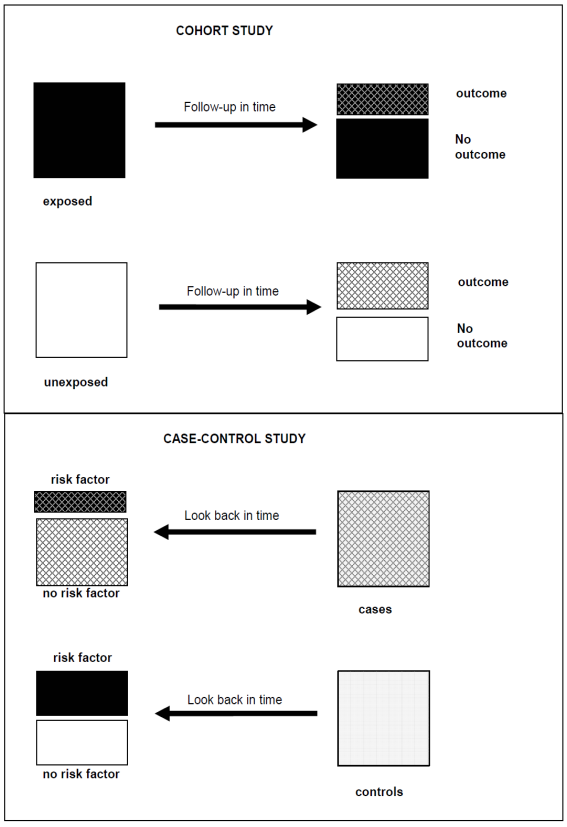


FIGURE 1 COHORT AND CASE-CONTROL DESIGNS

is available for research. Data from health insurances are provided in so-called claims databases; examples are the American PharMetrics® database covering information on medical and pharmacy claims from more than 55 million people and the Medicaid database, providing information of patients in the US with low income.(24) The General Practice Research Database (GPRD) in the UK is an example of a medical record database gaining information from GPs.(25) The Dutch PHARMO database provides information on patients from pharmacy databases, hospital databases, the Dutch medical register and the clinical laboratory register, the GP register, and the Dutch pathology register.(26) There are many more database available and probably much more to become available to research. These databases differ with respect to the number of people covered, the mean duration of follow-up, information on lifestyle factors, hospital data, drug information and laboratory values. All the mentioned databases contain information on men and women so there should be no reason why the natural history of a disease should not be sex-stratified, except for the case that the disease only occurs in men or women such as prostate or ovary cancer. Even for diseases which predominantly occur in one sex information should be collected on both men and women as this difference in occurrence might help to understand the disease process and thus offer new targets for drug development.

1.2 COPD – SHORT OVERVIEW

1.2.1 DEFINITION AND DIAGNOSIS

According to the 'Global Initiative for Obstructive Lung Diseases' (GOLD), chronic obstructive pulmonary disease (COPD) is a pulmonary disease with some extrapulmonary effects and its pulmonary component is associated with an abnormal inflammatory response of the lungs which is accompanied by a not fully reversible airflow limitation.(27) Most patients with this disease will present with chronic respiratory symptoms such as cough and dyspnoea on

exercise. The degree of airflow limitation can be determined by spirometry determining the forced vital capacity (FVC) and the forced expiratory volume in 1 second (FEV_1). Based on these examinations patients can be classified into different severity categories, stage I to IV, mild to very severe COPD. All Patients have a FEV_1/FVC ratio <0.70. Mild COPD (stage I) is in addition characterized by FEV_1≥80% predicted, moderate COPD (stage II) by 50≤ FEV_1<80% predicted, severe COPD (stage III) by 30≤ FEV_1<50% predicted and very severe COPD (stage IV) by FEV_1<30% predicted or FEV_1 <50% and chronic respiratory failure.(27) Another classification of the disease the BODE index (Body mass index, degree of airflow Obstruction, level of functional Dyspnoea and Exercise capacity) takes also extrapulmonary effects into consideration.(28) It is a better predictor of subsequent survival than staging by FEV_1 categories. In research a whole set of different definitions for COPD has been used as, for example, use of questionnaires asking for the presence of respiratory symptoms such as chronic cough, sputum production and dyspnoea, self-reported doctor diagnoses, or spirometric analysis.(29)

1.2.2 COPD BURDEN

The variety of methods used to define COPD makes it difficult to estimate the true burden of the disease. Prevalence estimates across studies vary enormously. Prevalence estimates for European countries during the 1990s range from 3.7% physician diagnosed COPD in Sweden to 11% for spirometry diagnosed COPD in Italy.(29) It is estimated that 1% of the general population has COPD and the prevalence increases strongly to 10% when considering only people ≥ 40 years.(30) The prevalence and burden of COPD are projected to increase.(31) COPD which had been the 6th leading cause of death in 1990 is estimated to become the 4th leading cause of death in 2030 worldwide.(32, 33) The driving forces behind this increase are an aging population and the tobacco epidemic; in particular the number of smoking women is still projected to increase.(34) Even if the world stopped smoking today

COPD would cause an immense burden to the health systems worldwide due to the lag-time between tobacco exposure and COPD development.

1.2.3 RISK FACTORS

Smoking is often called the most important risk factor for COPD and most patients with COPD are current smokers or have smoked for a long time but there is a significant number of never smokers developing COPD ranging between 25% and 45% worldwide. A recent review in the Lancet focused on COPD in non-smokers.(35) A large part of these never-smokers has, however, been exposed to other types of smoke. Smoke from biomass fuel, (36-38) or occupational exposure to smoke, which might be passive cigarette smoking (39), or exposure to gases and dust in, for example, textile and chemical industry or farming (40-42) have all been associated with COPD. Outdoor air pollution has also been discussed to be associated with COPD, but is unclear whether this is restricted to exacerbations in COPD or also contributes to the development of COPD.(43)

Respiratory infections are another environmental factor associated with an increased risk for COPD; a history of early-life respiratory infections (44, 45) as well as pulmonary tuberculosis in adulthood (46) have been associated with COPD. In patients already having COPD, respiratory infections are associated with acute exacerbations.(47) Low socioeconomic status (SES) is itself associated with COPD but it is unclear whether it represents a single risk factor or is a marker for an increased prevalence of other risk factors associated with COPD. (48) People with low SES have poorer nutritional status, are more likely to live in heavier polluted areas, are more likely to acquire respiratory infections, lung development of children born to mothers of low SES might be worse than of mothers with a higher SES. Age is also important and one of the major criteria to distinguish COPD from asthma as COPD usually only develops in middle aged or older people. The 'National Institute for Health and Clinical Excellence' (NICE) guidelines refer to an age >35 years in their diagnostic criteria.(49)

But except from all these environmental factors it is also the genetic setup of people as there are lifelong smokers who will never develop the disease. Estimates on how many smokers will develop COPD range from 15% to 20% up to 50%.(50) Evidence for a genetic component is indicated by the observed clustering of COPD in families and the fact that lung function impairment can be seen in both twins in monozygotic twins but not in dizygotic twins. COPD is a polygenic disease.(51) The best documented genetic risk factor for COPD is the hereditary deficiency of alpha-1 antitrypsin.(52) Other genes associated with COPD are α1-antichymotrypsin, cytochrome P450 A1, α2-macroglobulin, microsomal epoxide hydrolase.(53-55) A recent meta analysis of 12 genes of the inflammatory, proteinase/antiproteinase or oxidative stress pathways reported that the studied genes might have different effects in different ethnic populations.(56)

1.2.4 PATHOPHYSIOLOGY

Exposure to one or more of the listed environmental risk factors in combination with a genetic susceptibility of an individual will lead to characteristic pathophysiological changes in the lung. Inhaled particles induce an abnormal inflammatory response in the lung which is characterized by an increased number of neutrophils, macrophages and CD8+ lymphocytes.(57-59) These cells release proinflammatory cytokines such as interleukins and tumour necrosis factor (TNF)-alpha and growth factors such as transforming growth factor (TGF)-beta.(60, 61) They also release oxidants and proteases.(61) These inflammatory processes are associated with constant tissue repair and remodelling. Structural changes occur in the peripheral airways, lung parenchyma and pulmonary vessels.(62) Breakdown of elastin by proteases in lung parenchyma is seen in emphysema.(63) While the parenchymal destruction reduces the gas transfer, the chronic inflammation present in the lung and narrowing of the peripheral airways is mainly responsible for the reductions in FEV_1.(27)

1.2.5 CO-MORBIDITIES

Increased inflammatory markers have also been noticed outside the lungs (64) and systemic complications of COPD are increasingly recognized.(65, 66) The current GOLD definition of COPD states that COPD is a disease with “some significant extrapulmonary effects that may contribute to the severity in individual patients”.(27) Increased systemic inflammation has been associated with acute exacerbations.(67)

Cachexia and skeletal muscle wasting have early been recognized as systemic complication in COPD and are commonly seen in severe COPD.(68, 69) Prevalences of cachexia reported in COPD range between 20-40%.(68) Depression or anxiety (70-73) as well as heart failure (74-76) are highly prevalent co-morbid diseases in patients with COPD. Other cardiovascular or cerebrovascular co-morbid diseases in COPD patients include arrhythmias, angina pectoris, hypertension, myocardial infarction, stroke or pulmonary embolism.(74, 76) Lung cancer is a common neoplasm in patients with COPD, mainly resulting from smoking.(77-79) More detailed information on potential associations between COPD and cancer, cardiovascular diseases, depression, diabetes, gastro-oesophageal reflux disease or peptic ulcer are presented in the introduction sections of the respective studies (Studies 4.2-4.6).

1.2.6 TREATMENT (27, 49)

Smoking cessation is so far the only management shown to have an effect on lung function decline and thus success in halting or at least slowing down the disease process.(80) That is why current guidelines promote smoking cessation as the first step of intervention for all COPD patients no matter what disease stage they are in. Respiratory medication is introduced in a step-wise process. The main purpose is to relief symptoms and to slow disease progression but so far none of them is able to cure the disease. Short-acting bronchodilators - either beta 2 agonists or anticholinergics - are the first choice. In case patients remain symptomatic use of long-acting bronchodilators - tiotropium or beta 2

agonists - are recommended. Methylxanthines, inhaled and oral corticosteroids are further options in COPD management. Cases with severe COPD require oxygen therapy and finally pulmonary rehabilitation and lung surgery might be necessary. These procedures can be accompanied by alpha-1 antitrypsin replacement therapy, mucolytic therapy and anti-oxidant therapy where appropriate. In case of exacerbations antibiotic therapy is advised.

1.3 GENDER DIFFERENCES IN COPD

In an review article published in Thorax 1999 Becklake and Kauffmann stated “in population based (epidemiological) studies of airway disease, gender is invariably considered a standardising variable rather than a determinant worthy of investigation in its own right”.(81) Since then a number of studies on gender in COPD have been published but a clinical commentary on gender and COPD in 2007 still stated “investigations targeting gender-related differences are in their infancy”.(82) The German textbook on Gender Medicine, published in 2008 does not provide a chapter on pulmonology. The second edition of “Principles of Gender-specific Medicine” published in 2010 provides a chapter on COPD but still states “There have been relatively few studies comparing clinical manifestation and clinical course of COPD between men and women”.(83) The following paragraphs will provide a short summary on gender in COPD with respect to burden, risk factors, diagnosis and pharmacological management.

1.3.1 GENDER DIFFERENCE IN COPD BURDEN AND RISK FACTORS

COPD prevalences in women have historically been lower than in men but trends from the UK (84) as well as other countries such as Canada (85), the US (86) and Austria (87) suggest that women are catching up. In the UK COPD prevalence rates plateaued in the mid nineties in men while the prevalence rates in women continuously rose between 1990 and

1997 when the study by Soriano et al. ended, from 0.80% to 1.36%.(84) This increase of COPD in women is thought to arise from an increase in tobacco consumption.(88, 89) Cigarette smoking became the most popular form of tobacco consumption in the 20th century. In the UK tobacco consumption peaked at the end of the 1940s in men and in the 1960s in women.(90) The prevalence of smoking in women in developing countries is still projected to increase.(34) It is estimated that there will be about 532 million smoking women world-wide in 2025.(34) Thus it is likely that the number of women developing COPD due to tobacco exposure is still going to increase worldwide in the future. Although smoking is often reported the most important risk factor for COPD, there is also a significant number of non-smokers developing COPD, as stated above.(35) In this subgroup of COPD patients women outnumber men world-wide (91), mainly due to exposure to indoor air pollution derived from cooking (and heating) with biomass fuels such as coal and wood, which is still commonly seen in rural areas of developing countries. (36, 37, 92)

It is also controversially discussed whether women are more susceptible to the detrimental effects of tobacco smoke or not.(93-97) Dransfield et al., studied 328 patients older than 45 years and with ≥20 pack-years of smoking and $FEV_1/FVC>0.70$ and found that Caucasian women were more susceptible to tobacco associated loss of lung function than Caucasian men. Caucasian men had smoked much more pack-years at the same level of lung function loss.(93) The Copenhagen City Heart Study and the Glostrup population study both also reported a greater lung function decline in women compared to men per pack-years smoked; 7.4ml for women and 6.3 ml for men in the CCHS and 10.5ml and 8.4ml in the GPS.(98) Anthonisen et al., following patients from the Lung Health Study for 11 years did not find a gender difference in lung decline.(95) Two meta-analyses one published in 2000 the other in 2006 came to opposite conclusions.(96, 97) Xu et al., reporting a higher adverse smoking effect in women than in men, speculate that some of the difference might be due to incomparable non-smoking reference groups with high smoking prevalences in men compared to women suggesting that non-smoking men are unhealthier than non-smoking

women, as shown by their data that male non-smokers have lower mean predicted lung function values than female non-smokers.(99)

1.3.2 Gender Differences in Lung Physiology

Gender differences in susceptibility to tobacco smoke or other factors contributing to COPD might also originate from normal physiological differences in respiratory systems between men and women.(100) Comparing men and women of the same height reveals that men have larger diameter airways and larger lung volumes than women.(101) This difference is already present at birth and might be controlled by sex hormones already before birth.(102) During foetal life the lung of a female foetus matures earlier than the lung of a male foetus. At birth girls have on average smaller and less heavy lungs than boys and also might have fewer respiratory bronchioles. Lung maturation continues through childhood into adolescence. Age related increases in FVC cease earlier in girls than in boys. In men increases in FVC are seen into the mid twenties.(81) Measuring tobacco exposure in pack-years puts the lungs of women at a greater tobacco dose per lung surface area than lungs of height-matched men. Apart from mere anatomical differences in airway size, different hormonal and immunological status might contribute to physiological differences observed between pulmonary function in healthy men and women.(81, 100, 101)

1.3.3 Gender Differences in COPD Diagnosis and Management

Gender does not only affect the risk of an individual to develop COPD but seems also to have an effect on the likelihood to get diagnosed and treated. Studies from Spain and Canada with hypothetical COPD patients suggest that COPD will be underestimated in men and women. The researchers provided GPs with a hypothetical COPD patient history randomly assigned male or female gender, all other characteristics were identical. In case of male gender 65% of North-American GPs assigned a COPD diagnosis compared to 49% for female gender, presenting spirometry results increased the likelihood of a COPD diagnosis in

male and female hypothetical patients. (103) Forty-two percent of the Spanish GPs assigned a COPD diagnosis in case of male gender compared to 31% in case of female gender, presenting spirometry results again increased the likelihood of a COPD diagnosis in male and female hypothetical patients and the gender difference disappeared.(104) The 'Confronting COPD International Survey', conducted in the UK, some other European countries and North America, in addition reported that women were less likely to undergo spirometric investigation compared with men.(105) Thus women might be less likely to receive a COPD diagnosis than men.

There are only few studies comparing the pharmacological management in men and women with COPD and the results are controversial. In a small sample of 130 spirometry-evaluated patients in Canada, the authors found that women were twice as likely to take respiratory medication for mild or moderate COPD while there was no difference in severe COPD.(106) Data from the EPIDEPOC study showed a difference between male and female smokers with COPD with respect to medication use; men received more medication than women. Medication use in non-smokers with COPD was more similar, here women were more likely to receive prescriptions for corticosteroids and short-acting beta agonist than men. (91)

AIMS

The major objective of this PhD thesis was to provide further information on the natural history of COPD in particular to contribute to the understanding of the impact of gender and COPD severity on the incidence of co-morbidities using data form the GPRD.

Gender-specific information on COPD is still rare when put into perspective to all the literature available on COPD. The objective of the first study was to learn more about the gender-specific clinical presentation and drug utilization of patients with COPD. Diabetes had been associated with COPD in cross-sectional studies and was reported to develop more often after a COPD diagnosis but not much was known on the prevalence of diabetes prior to a COPD diagnosis. The aim of the second study was therefore to investigate the association between incident COPD and prevalent diabetes, stratified by gender. Several studies on the association between COPD and co-morbidities have been reported in the literature. However, these studies were often cross-sectional or did not investigate incident outcomes. In addition studies were seldom stratified by gender. Thus the true incidence rate of many outcomes in men and women were lacking. The aims of the studies 3-6 were to provide information on the gender-stratified incidence rates of arrhythmia, cancer, deep vein thrombosis, depression, gastro-oesophageal reflux disease, peptic ulcer, pulmonary embolism, myocardial infarction, stroke/ TIA in patients with COPD and compare the risk to develop one of these outcomes to a population of COPD-free patients.

Methods

3.1 DATA SOURCE

All studies presented in this thesis are based on data from the UK-based General Practice Research Database (GPRD). It is a large primary-care database established in 1987 which encompasses some five million patients who are enrolled with selected GPs throughout the UK. The General Practitioners (GPs) who contribute data to the GPRD have been trained to record medical information in a standard manner and to supply it anonymously. Patients are identifiable only via a unique identification number. Sex and year of birth are recorded for each patient in the database, but the exact date of birth of patients in the GPRD is not available for confidentiality reasons. In the beginning the GPs used office computers provided by Value Added Medical Products (VAMP). In the mid-nineties, a new Windows-based practice management software application called "Vision" was launched, which has then become the dominant practice software used by GPs in the GPRD scheme. The recorded information includes demographics, medical diagnoses, and virtually all drug prescriptions. Medical diagnoses are coded by Read and 'Oxford Medical Information System' (OXMIS) codes, drug prescriptions are entered using multilex codes and contain the name of the preparation, route of administration, dose, and number of tablets for each prescription. Hospital discharge and referral letters are available for review to validate the diagnoses recorded in the computer record. Researchers, however, cannot directly contact the GP, since they do not know the name and the address of the GP. Researchers will have to contact the administrators of the database (MHRA), and they will forward their request to the GP. Thus, anonymization is guaranteed. Patients enrolled in the GPRD are representative of the UK population with respect to age, sex and geographical distribution.(107)

The comprehensiveness and validity of the information recorded in the GPRD has been evaluated several times and has proven to be of high quality.(107-112) Today the GPRD is managed by the Medicines and Healthcare products Regulatory Agency (MHRA), who

constantly supervise GP practices via defined computer algorithms and manual checks. Practices can be eliminated from the GPRD if data recording is of poor quality, e.g. if they have obvious gaps in the longitudinal data or other problems. The procedures performed by MHRA to guarantee data integrity and completeness of data have been recently described in detail.(107) To guarantee high quality of research all study protocols have to be approved by the Independent Scientific Advisory Committee for MHRA database research (ISAC).

Up to March 2010 more than 750 research papers using the GPRD have been published including various studies focussing on COPD.(84, 113-116) Further information about the database can be found on the website (www.gprd.com).

3.2 STUDY DESIGN

3.2.1 STUDY POPULATION (studies 4.2-4.6)

We identified in the GPRD all patients with a first-time diagnosis of COPD between January 1, 1995 and December 31, 2005 who were aged 40 to 79 years old at the index date. We excluded patients with a diagnosis of COPD who had less than 3 years of active recording history before the COPD diagnosis. Thus, we excluded patients with prevalent or so-called 'historical diagnoses', i.e. diagnoses that were recorded as part of the medical history of a patient and for which the diagnosis date is often not known. Cases were defined without regard to the subsequent occurrence of any of the outcomes of interest in this study.

In addition, we identified at random in the GPRD one comparison subject without COPD for each patient with COPD, matched 1:1 on general practice, age (same year of birth), sex and index date (i.e. the date of the COPD diagnosis in the case group). These controls also had to have a history of at least 3 years in the GPRD prior to their index date (i.e. the COPD diagnosis date of the matched case).

3.2.2 FOLLOW-UP STUDY

For the follow-up part of the study, we excluded a priori patients with a malignancy diagnosis (except for non-melanoma skin cancer) as well as with HIV / AIDS or with a diagnosis of alcoholism prior to the date of the COPD diagnosis. Within this study population, we followed each subject from the diagnosis of COPD (or the corresponding date in the matched comparison group) until their end of follow-up; the end of follow-up was defined as the date when the subject developed a first-time diagnosis of one of the outcomes of interest (see Table 3.1), left the practice, died or when the last event was recorded in the patient record ('database stop date'), whatever came first. In other words, we only identified incident cases with an outcome of interest after the COPD diagnosis but did not search for prevalent diagnoses which were already present prior to the COPD diagnosis. If a subject developed more than one endpoint, he or she was allowed to contribute person-time to several outcomes, i.e. sampling of person time did not necessarily end after the first of several outcomes of interest had been recorded. In other words we conducted a variety of different person-time analyses, i.e. a separate analysis for each outcome of interest. The only exception to this is cancer: we first identified malignancies in COPD patients and their matched comparison subjects, and this diagnosis was the endpoint in a patients record in any case. We then identified the other outcomes in separate analyses. For these follow-up analyses we excluded subjects with the particular outcome of interest (as stated in Table 3.1) prior to the date of the COPD diagnosis, so that we included only incident cases for each particular outcome of interest. In addition, for certain outcomes we did not only exclude patients who already had the exact same diagnosis prior to the COPD diagnosis, but also conditions which were closely related and which are major risk factors for the outcome. For example, when we identified incident cases with myocardial infarction after the COPD diagnosis, we did not only exclude those who already had a myocardial infarction prior to COPD, but also patients with angina pectoris prior to the COPD diagnosis (see Table 3.1).

Thus, we had slightly different study populations for all the different outcomes in these separate follow-up studies.

TABLE 3.1 OUTCOMES OF INTEREST AND THE EXCLUSION CRITERIA FOR THE FOLLOW-UP ANALYSIS

	Incident event	Specific exclusion criteria prior to the index date
Cardiovascular events	Arrhythmia	History of MI, stroke / TIA, PE, DVT, arrhythmias, angina pectoris
	Pulmonary embolism (PE) and deep vein thrombosis (DVT)	
	Myocardial infarction (MI)	
	Stroke or transient ischemic attack (TIA)	
Gastrointestinal events	Gastroesophageal reflux disease (GORD)	History of GORD, Peptic ulcer or erosive gastritis
	Peptic ulcer or erosive gastritis	History of Peptic ulcer or erosive gastritis
Malignancies	Digestive, genitourinary, lung cancer and lymphoma	History of any cancer, except for non-melanoma skin cancer
Nervous system events	Depression	History of depression, suicide attempt

Patients with a history of a disease listed as specific exclusion criteria prior to the index date were excluded. All remaining patients were then followed from the index date until they developed one of the incident events, died, left the practice or the study ended.

3.2.3 NESTED CASE-CONTROL STUDIES

We conducted nested case-control analyses to further analyze the impact of COPD and various potential confounders on the risk of developing an outcome of interest. For this purpose we identified for each case with an outcome of interest four control patients who were selected at random from the study population (i.e. patients with or without COPD). Thus, controls did not develop the outcome of interest during follow-up. These controls were matched to cases on age, sex, practice and index date, i.e. the date when the case had the

incident diagnosis of an outcome of interest. For cases and controls the same exclusion criteria were applied.

3.3 VALIDATION OF DIAGNOSES

3.3.1 COPD DIAGNOSES

We identified COPD patients based on specific Read and OXMIS-codes recorded in the GPRD. Soriano et al. validated the COPD diagnoses in the GPRD by sending questionnaires to the GPs and showed that the diagnoses are of high quality, with a concordance of κ=0.54. (114)

3.3.2 DIAGNOSES OF OUTCOMES OF INTEREST

We applied a stepwise validation and analysis process for the follow-up analysis. In a first round we took all patients, who developed an outcome of interest, based on the clinical diagnosis entered in the form of a Read or OXMIS code, as this reflects the crude clinical picture. In a second step we then validated potential cases of interest in a two-step process: we first wrote a computer program to search for evidence in the computer record supporting the validity of the diagnosis. Then we reviewed a sample of computer profiles of cases to check this validation procedure. Below you find the case definitions for the outcomes of interest.

Arrhythmia: All patients with a recorded arrhythmia diagnosis were identified, in total 1191 cases.

Pulmonary embolism: Patients must have had a PE code and had to be hospitalised within 30 days after the diagnosis or die within 30 days after the diagnosis or start heparin or vitamin K antagonists or platelet aggregation inhibitors or direct thrombin inhibitors or fibrinolytic enzymes within 180 days after the diagnosis. Patients were not allowed to have a

prescription for heparin or vitamin K antagonists or platelet aggregation inhibitors or direct thrombin inhibitors or fibrinolytic enzymes more than 90 days before the diagnosis.

Deep vein thrombosis: Patients must have had a DVT code and had to be hospitalised within 30 days after the diagnosis or die within 30 days after the diagnosis or start heparin or vitamin K antagonists or platelet aggregation inhibitors or direct thrombin inhibitors or fibrinolytic enzymes within 90 days after the diagnosis. Patients were not allowed to have had a prescription for heparin or vitamin K antagonists or platelet aggregation inhibitors or direct thrombin inhibitors or fibrinolytic enzymes more than 90 days before the diagnosis

Myocardial infarction: Patients who were hospitalised within 30 days of the MI diagnosis, or who died within 30 days after the diagnosis or who started ACE antagonists or beta blockers or statins or vitamin K antagonists or platelet aggregation inhibitors or aspirin within 90 days after the diagnosis. Patients with heart surgery or who had been prescribed heparin, vitamin K antagonists, platelet aggregation inhibitors, direct thrombin inhibitors or fibrinolytic enzymes more than 30 days prior to the diagnosis date were excluded.

Stroke / TIA: Patients with a recorded stroke / TIA and who were hospitalised within 30 days around the stroke diagnosis, or who died within 30 days after the diagnosis or who had a prescription for aspirin or heparin or vitamin K antagonists or platelet aggregation inhibitors or direct thrombin inhibitors or fibrinolytic enzymes within 180 days after the diagnosis.

GORD: Patients with a recorded GORD or Barrett's oesophagus diagnosis, who received at least 1 prescription for PPIs within a year around the GORD or Barrett's oesophagus diagnosis and who did not have prescriptions for PPIs or H_2 antagonist prior to the COPD index date

Peptic Ulcer: Patients with a recorded ulcer or erosive gastritis, who received at least 1 prescription for PPIs within a year around the ulcer or erosive gastritis diagnosis and who did not have prescriptions for PPIs or H_2 antagonist prior to the COPD index date.

Cancer: All patients with a recorded malignant neoplasm.

Depression: All patients with a recorded depression were identified. For a sensitivity analysis we identified patients with a recorded depression, who received at least 1

prescription for selective serotonin reuptake inhibitors (SSRI), monoamine reuptake inhibitors (MNRI), monoaminooxidase A inhibitors (MAOA) or other antidepressive drugs within half a year around the depression diagnosis and who did not have prescriptions for the above mentioned drugs prior to the COPD index date.

3.4 STATISTICAL ANALYSES

Statistical analyses were performed with the statistical software SAS (release 9.1, SAS Institute, Inc., Cary, NC, USA).

3.4.1 INCIDENCE RATES

We estimated incidence rates and 95% confidence intervals separately for COPD and control patients stratified by gender and we calculated incidence rate ratios and 95% confidence intervals to compare incidence rates in men and women.

3.4.2 CASE-CONTROL ANALYSES

We conducted a case-control analysis to describe the COPD population with regard to co-morbidities as well as health care and drug utilization.

Drug utilization: For each COPD patient we assessed the exposure to respiratory medication and oxygen after the COPD diagnosis. We stratified drug exposure into any exposure after the diagnosis and exposure within 180 days after the diagnosis. To test whether drug exposure in women and men differed significantly we provided chi-square statistics.

Survival: We compared the survival after the index date by a Kaplan Meier analysis. Patients who did not die during follow-up were censored either at the end of the study or

when they left the database. The distributions were compared using a Log likelihood ratio test.

Diabetes: We used conditional logistic regression to analyze the impact of diabetes on the risk of COPD. We stratified the analyses by gender and adjusted the analyses for smoking status (none, current, past, unknown), body mass index (BMI; <18.5, 18.5-24.9, 25-29.9, 30-60 kg/m^2, or unknown), hypertension and hyperlipidemia. For each COPD patient and each patient of the control group we assessed the exposure to oral antidiabetics (metformin, sulfonylureas, thiazolidinediones and acarbose) prior to the COPD diagnosis or the corresponding date in the comparison group. We stratified drug exposure by duration of use using the following categories: unexposed, 1-2 prescriptions, 3-11 prescriptions, 12-35 prescriptions or 36+ prescriptions.

3.4.3 NESTED CASE-CONTROL ANALYSES

We conducted nested case-control analyses to further analyze the impact of COPD and various potential confounders on the risk of developing an outcome of interest. We compared the prevalence of COPD between case patients and their controls using conditional logistic regression analysis. We also stratified COPD patients by COPD severity. As a surrogate marker for COPD severity we used COPD treatment, similar to a previous approach published by Soriano et al..(114) We categorized COPD patients into 'mild' COPD (patients who received no drug treatment), 'moderate' COPD' (patients who received at least one prescription for short-acting anticholinergics, beta agonists, tiotropium, leukotriene receptor antagonists, inhaled steroids or xanthines, or 'severe' COPD (patients who needed oxygen treatment). We adjusted the case-control analyses for patient characteristics such as body mass index (BMI; <17.5, 17.5-24.9, 25-29.9, 30+ kg/m^2, or unknown), smoking history (no, current, past, unknown), as well as for various co-morbidities and drugs associated with the specific outcome of interest.

Arrhythmia: Arrhythmia analyses were adjusted for smoking status, hypertension, use of beta agonists, xanthines, quinolones, macrolides, vitamin K antagonists, beta blockers, calcium channel blockers, diuretics, cardiac glycosides and coronary dilatators.

PE & DVT: PE and DVT analyses were adjusted for smoking status, BMI, hypertension and NSAID use.

MI: MI analyses were adjusted for smoking status, BMI, hypertension, hyperlipidemia, diabetes and NSAID use. For the mortality analyses we followed all patients with a diagnosis of myocardial infarction until they died, left the practice, or the study ended, whatever came first. We then did a logistic regression analysis stratified by COPD status to evaluate the crude impact of gender on mortality.

Stroke / TIA analyses were adjusted for smoking status, BMI, hypertension, diabetes and use of aspirin. For the mortality analyses we followed all patients with a diagnosis of stroke / TIA until they died, left the practice, or the study ended, whatever came first. We then did a logistic regression analysis stratified by COPD status to evaluate the crude impact of gender on mortality.

GORD: GORD analyses were adjusted for smoking status, BMI, systemic steroid use and NSAID use; further adjustment for COX-2 inhibitor use did not have a major impact on the results.

Peptic ulcer: Peptic ulcer analyses were adjusted for smoking status, BMI, NSAID use, GORD and vitamin K antagonist use. We assessed respiratory drug exposure prior to the index date for both cases and controls. We conducted conditional logistic regression analyses to compare the type of exposure (long-acting beta 2 agonists, short-acting beta 2 agonists or no exposure) and the timing of exposure (current, recent or past). Current users had a last prescription for a study drug recorded within 60 days, recent users between 60 and 364 days, and past users ≥ 365 days prior to the index date. We adjusted these analyses for BMI, smoking status, use of NSAIDs, vitamin K antagonists, xanthines, inhaled steroids, inhaled short-acting anticholinergics or tiotropium and for the presence of diagnosed GORD prior to the index date.

Cancer: We provided the risk estimates stratified for different cancer sites and adjusted for patient characteristics such as BMI, smoking history, as well as for various cancer type specific confounders (breast cancer: contraceptive use, hormone replacement therapy use, benign neoplasms, non-melanoma skin cancer, and NSAID use; lymphoma: benign neoplasms, use of carcinogenic drugs; gastro-oesophageal cancer: gastro-oesophageal reflux disease, benign neoplasms, non-melanoma skin cancer; colorectal cancer: NSAID use, constipation, benign neoplasms, non-melanoma skin cancer; female reproductive system cancer: contraceptive use, hormone replacement therapy use, benign neoplasm, non-melanoma skin cancer, NSAID use; urinary system cancers: hypertension, benign neoplasms, use of diuretics, use of carcinogenic drugs, urinary dysfunction). We provided risk estimates for lung cancer stratified by smoking status and gender and adjusted for BMI.

Depression: Depression analyses were adjusted for smoking status, BMI, serious infections, sleeping disorders and cardiovascular diseases (deep vein thrombosis, pulmonary embolism, ischemic heart disease, or stroke / TIA). In addition to analyzing all cases with an incident diagnosis of depression, we also conducted sensitivity analyses in which we only included cases with an incident depression diagnosis followed by specific pharmacological treatment, (see case definition). We further assessed the time between the first COPD diagnosis and the first depression diagnosis in two-year intervals and explored whether the risk of developing a depression diagnosis was dependent on the duration of COPD. We stratified this conditional regression analysis by gender and adjusted for smoking status, BMI, cardiovascular diseases (pulmonary embolism, deep vein thrombosis, ischemic heart disease, stroke / TIA), a history of serious infections, sleeping disorders, and for COPD treatment (oxygen use, beta agonist use, anticholinergic use and use of xanthines), which have been associated with depression in univariate analyses. Statistical significance was set at $p < 0.05$.

In addition, we assessed among patients with COPD the proportion of cases who developed depression and who died within one year after the depression diagnosis. We compared this proportion to the proportion of COPD patients who died within a year after the index date

without having developed depression in order to assess the impact of depression on mortality among COPD-patients.

RESULTS

4.1 GENDER, CO-MORBIDITIES AND DRUG UTILIZATION IN COPD

4.1.1 ABSTRACT

The burden of COPD is still projected to increase, particularly in women. It is controversially discussed whether women are more susceptible to COPD than men. Self-reported health status is often lower in women than in men. Not much is known about gender-specific co-morbidity profiles and drug utilization. It was the aim of this study to learn more about gender differences and equalities in the clinical presentation at the first-time diagnosis of COPD and the use of respiratory medication in patients with COPD. We used the UK-based General Practice Research Database (GPRD) to assess the prevalence of various co-morbidities in COPD patients aged 40-79 between 1995 and 2008, and we randomly matched COPD-free control patients to COPD patients, matched on age, sex, general practice, calendar time and years of history in the database. We identified the prevalence of a range of co-morbidities prior to the COPD diagnosis and compared respiratory drug utilization after the index date. In addition we compared survival between patients with and without COPD. We identified 47,576 patients with COPD and the same number of COPD-free patients. The percentage of non-smokers among COPD patients was higher in women (22.9%) than in men (17.9%) and women tended to be slightly younger. In COPD patients the prevalence of diabetes, myocardial infarction, stroke / TIA, arrhythmia and peptic ulcer were higher in men than in women while depression and osteoporosis were more prevalent in women. Women received slightly more prescriptions for beta agonist (short-acting and long-acting) and inhaled corticosteroids while men received more prescriptions for tiotropium and combination preparations. Survival in patients with COPD was significantly decreased compared to COPD-free patients ($p<0.01$). The study provides further evidence that patients with COPD have more co-morbidities and decreased survival when compared to COPD-free patients. Gender differences exist with regard to the co-morbidity distribution, drug utilization and survival.

4.1.2 INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common disease among adults 40 years of age or older world-wide (104) and in contrast to other chronic diseases the burden of COPD is still projected to increase.(31) COPD had been the 6th leading cause of death in 1990 and is estimated to become the 4th leading cause of death in 2030 worldwide.(32, 33) This is contributed to an aging population and the tobacco epidemic.(88) Prevalences in women have historically been lower than in men but trends from the UK (84) as well as other countries such as Canada (85), the US (86) and Austria (87) suggest that women are catching up. This increase of COPD in women is thought to arise from an increase in tobacco consumption.(88) It is controversially discussed whether women are more susceptible to the detrimental effects of tobacco smoke or not.(93-97) World-wide the proportion of women among non-smoking COPD patients is higher than the proportion of men.(91)

There are only few studies analysing the co-morbidity profile or medication use in COPD patients stratified by gender.(91, 106, 117) Most studies focus on COPD-related symptoms or quality-of life.(82, 118, 119) Women with COPD report more often symptoms of breathlessness (106) and a lower health status, even after adjusting for smoking.(120) Using the Charlson co-morbidity index, in 53 FEV_1-matched men and women attending a Spanish pulmonary clinic, however, men were reported to experience more co-morbidities. The authors contribute this observation to older age of men when compared with women.(117) Data from the EPIDEPOC study in 10,711 patients with COPD, a quarter of them women, report a higher number of most studied co-morbidities in male smokers with COPD when compared with female smokers. Men had significant more hypertension, heart disease, gastroduodenal ulcer and women had more depression and anxiety. They also showed a difference between male and female smokers with COPD with respect to medication use; men received more medication than women. Medication use in non-smokers with COPD was more similar, here women were more likely to receive prescriptions for corticosteroids and short-acting beta agonist than men. (91) In a Canadian study women with mild or moderate

COPD received more prescriptions for respiratory medication than men, while men and women with severe COPD had a similar drug utilization pattern. (106)

It was the aim of the current study to learn more about the clinical presentation and management with respiratory medication of men and women with COPD at the time of their first diagnosis.

4.1.3 METHODS

For detailed information on the database and study design please refer to the general methods section here only the information on the study population, case validation and statistical analyses are repeated.

Study population: We identified in the GPRD all patients with a first-time diagnosis of COPD between January 1, 1995 and autumn 2008, who were aged 40-79 years. We excluded patients with less than 3 years of active recording history prior to the first COPD diagnosis. In addition, we identified at random from the GPRD one COPD-free comparison subject for each COPD patient, matched 1:1 on age (same year of birth), sex, general practice and calendar time (i.e. on the date of the first COPD diagnosis of the COPD patient). We applied the same exclusion criteria to the control group as to the COPD patients. Within this study population we assessed and compared the prevalence of diagnosed diabetes prior to the COPD diagnosis or the corresponding date in the comparison group.

Case validation: We identified patients with COPD based on recorded diagnoses. Soriano et al. validated the COPD diagnoses in the GPRD by sending questionnaires to the GPs and showed that the diagnoses are of high quality, with a concordance of κ=0.54. (114) So far at least 12 studies on COPD have been done using GPRD data.

Statistical Analysis: We stratified all analyses by gender. For each COPD patient we assessed the exposure to respiratory medication and oxygen after the COPD diagnosis. We stratified drug exposure into any exposure after the diagnosis and exposure within 180 day after the diagnosis. To test whether drug exposure in women and men differed significantly

we provided chi-square statistics. We compared the survival after the index date by a Kaplan Meier analysis. Patients who did not die during follow-up were censored either at the end of the study or when they left the database. The distributions were compared using a Log likelihood ratio test.

4.1.4 RESULTS

We identified 47'576 patients with COPD, 23'641 of them were women. The total number of first-time diagnoses of COPD rose from 1127 in men and 1030 in women in 1995 to 2126 and 2077, respectively in 2007. Time trends are similar in men and women. The crude incidence rate per 10,000 person years for the period 1995-2005 in men (IR 35.4, 95% CI 34.9-35.9) was higher than in women (IR 30.2, 95% CI 29.7-30.6) across all but the youngest (40-49 years old) age-groups (data not shown). Characteristics of the study population at the time of the COPD diagnosis are displayed in Table 4.1.1 Twenty-eight percent of all women with a COPD diagnosis received their diagnosis below the age of 60 years compared to 24% of all men. The proportion of women among non-smokers with COPD was higher than the proportion of men (23% and 17%, respectively). Asthma, hypertension, and depression were common co-morbidities seen in the COPD population in both men and women. The prevalence of depression was almost twice as high in women as in men. Patients with COPD were more likely to have seen their GP in the year prior to the index date and they had a significantly higher mean number of GP visits in the year prior to the index date ($p < 0.01$). Women had a higher number of mean GP-visits than men, both with and without COPD ($p < 0.01$). The distribution of GP visits in the year prior to the index date stratified by gender and COPD status is displayed in Table 4.1.2.

TABLE 4.1.1 POPULATION CHARACTERISTICS

	Men		Women	
	COPD (%)	**COPD-free (%)**	**COPD (%)**	**COPD-free (%)**
Age (in years)				
40-49	1264 (5.3)	1265 (5.3)	1792 (7.6)	1793 (7.6)
50-59	4451 (18.6)	4453 (18.6)	4852 (20.5)	4859 (20.6)
60-69	8640 (36.1)	8635 (36.1)	7799 (33.0)	7789 (32.9)
70+	9580 (40.0)	9572 (40.0)	9198 (38.9)	9200 (38.9)
Smoking status				
Non-smoker	4091 (17.1)	10684 (44.6)	5416 (22.9)	13882 (58.7)
Smoker	9505 (39.7)	4173 (17.4)	10319 (43.7)	3642 (15.4)
Ex-smoker	8398 (35.1)	6065 (25.3)	6180 (26.1)	3570 (15.1)
Unknown	1941 (8.1)	3013 (12.6)	1726 (7.3)	2547 (10.8)
BMI (in kg/m^2)				
<17.5	303 (1.3)	48 (0.2)	726 (3.1)	154 (0.7)
17.5-24.9	7968 (33.3)	6305 (26.3)	8740 (37.0)	7956 (33.7)
25.0-29.9	7348 (30.7)	8930 (37.3)	5971 (25.3)	6880 (29.1)
30.0-59.9	3945 (16.5)	3691 (15.4)	4800 (20.3)	4885 (20.7)
unknown	4371 (18.3)	4961 (20.7)	3404 (14.4)	3766 (15.9)
Co-morbidities				
Hypertension	6803 (28.4)	7680 (32.1)	7360 (31.1)	7931 (33.6)
Diabetes	1984 (8.3)	2472 (10.3)	1583 (6.7)	1634 (6.9)
MI	2288 (9.6)	1865 (7.8)	987 (4.2)	570 (2.4)
PE	340 (1.4)	233 (1.0)	412 (1.7)	215 (0.9)
DVT	438 (1.8)	450 (1.9)	656 (2.8)	431 (1.8)
Stroke / TIA	1770 (7.4)	1547 (6.5)	1331 (5.6)	1050 (4.4)
Arrhythmia	1992 (8.3)	1755 (7.3)	1649 (7.0)	1317 (5.6)
GORD	2176 (9.1)	1864 (7.8)	2565 (10.9)	2261 (9.6)
Ulcer	2157 (9.0)	1527 (6.4)	1360 (5.8)	819 (3.5)
Depression	3560 (14.9)	2728 (11.4)	7163 (30.3)	5297 (22.4)
Osteoporosis	455 (1.9)	198 (0.8)	1999 (8.5)	1222 (5.2)
Asthma	9227 (38.6)	1977 (8.3)	11194 (47.4)	2651 (11.2)

TABLE 4.1.2 GP-VISITS IN THE YEAR PRIOR TO THE INDEX DATE

	Men		Women	
	COPD (%)	**COPD-free (%)**	**COPD (%)**	**COPD-free (%)**
Mean (± sd)	10.7 (± 9.4)	6.9 (± 7.8)	12.7 (± 10.2)	8.1 (± 7.9)
Median	8	5	10	6
No GP visit	797 (3.3)	3160 (13.2)	541 (2.3)	1921 (8.1)
1-3 GP visits	4014 (16.8)	6651 (27.8)	2826 (12.0)	5805 (24.6)
4-6 GP visits	4477 (18.7)	4791 (20.0)	3724 (15.8)	4837 (20.5)
7-12 GP visits	7116 (29.7)	5349 (22.4)	6961 (29.4)	6126 (25.9)
13-24 GP visits	5693 (23.8)	3214 (13.4)	6962 (29.5)	3995 (16.9)
25+ GP visits	1838 (7.7)	770 (3.2)	2627 (11.1)	957 (4.1)

sd: standard deviation

There are small differences between men and women with regard to respiratory medication prescriptions. Women were more likely to receive a prescription for short-acting beta agonists than men, 78.4% versus 74.5% as well as long-acting beta agonists, 27.5% versus 26.3% ($p \leq 0.05$). Women also received more prescriptions of leukotriene receptor antagonists: 5.2% in women compared to 3.8% in men ($p \leq 0.05$). Men were more likely to receive a combination of short-acting anticholinergics and beta agonists or tiotropium. Details on the drug utilization after the COPD diagnosis stratified by gender and age are displayed in Table 4.1.3. Patients with COPD were more likely to die after the index date than COPD-free patients ($p<0.01$) and men were more likely to die than women ($p<0.01$), in COPD and COPD-free patients. In total 12 328 patients with COPD died compared to 5390 without COPD. The survival distributions are displayed in Figure 4.1.

TABLE 4.1.3 RESPIRATORY DRUG UTILIZATION AFTER THE COPD DIAGNOSIS

	Men			Women		
	All	**<60 years**	**≥ 60 years**	**All**	**<60 years**	**≥ 60 years**
Short-acting anticholinergics						
Ever	**7068 (28.5)**	1553 (27.2)	5515 (28.9)	**6896 (29.2)**	1794 (27.0)	5102 (30.0)
<180 days	**3725 (15.6)**	741 (13.0)	2984 (16.4)	**3577 (15.1)**	881 (13.3)	2696 (15.9)
Short-acting beta agonists						
Ever	**17829 (74.5) ***	4282 (74.9) *	13547 (74.4) *	**18528 (78.4)**	5263 (79.2)	13265 (78.0)
<180 days	**12448 (52.0) ***	2933 (51.3) *	9515 (52.2) *	**13301 (56.3)**	3729 (56.1)	9572 (56.3)
Combination short acting anticholinergics and beta agonists						
Ever	**6707 (28.0) ***	1353 (23.7)	5354 (29.4) *	**6222 (26.3)**	1574 (23.7)	4648 (27.4)
<180 days	**3633 (15.2) ***	718 (15.6)	2915 (16.0) *	**3339 (14.1)**	801 (12.1)	2538 (14.9)
Tiotropium						
Ever	**6938 (29.0) ***	1665 (29.1) *	5273 (28.9) *	**6386 (27.0)**	1813 (27.3)	4573 (26.9)
<180 days	**2014 (8.4)**	444 (7.8)	1570 (8.6)	**1923 (8.1)**	523 (7.9)	1400 (8.2)
Long-acting beta agonists						
Ever	**6303 (26.3) ***	1543 (27.0) *	4760 (26.1)	**6510 (27.5)**	1917 (28.9)	4593 (27.0)
<180 days	**2889 (12.1) ***	733 (12.8) *	2156 (11.8) *	**3162 (13.4)**	957 (14.4)	2205 (13.0)
Combinations with long-acting beta agonists						
Ever	**9632 (40.2) ***	2579 (45.1)	7053 (38.7)	**9763 (41.3)**	3083 (46.4)	6680 (39.3)
<180 days	**3793 (15.8) ***	1036 (18.1) *	2757 (15.1)	**3995 (16.9)**	1300 (56.1)	2695 (15.9)

TABLE 4.1.3 RESPIRATORY DRUG UTILIZATION AFTER THE COPD DIAGNOSIS

	Men			Women		
	All	**<60 years**	**≥ 60 years**	**All**	**<60 years**	**≥ 60 years**
Inhaled steroids						
Ever	**11079 (46.3) ***	2628 (46.0) *	8451 (46.4) *	**11781 (49.8)**	3320 (50.0)	8461 (49.8)
<180 days	**8179 (34.2) ***	1873 (39.5) *	6306 (40.7) *	**8768 (37.1)**	2405 (43.8)	6363 (44.2)
Leukotriene receptor antagonists						
Ever	**906 (3.8) ***	326 (5.7) *	580 (3.2) *	**1222 (5.2)**	525 (7.9)	697 (4.1)
<180 days	**305 (1.3) ***	105 (1.8) *	200 (1.1) *	**453 (1.9)**	207 (3.1)	246 (1.5)
Theophylline						
Ever	**1644 (6.9)**	386 (6.8) *	1258 (6.9)	**1632 (6.9)**	520 (7.8)	1112 (6.5)
<180 days	**697 (2.9)**	152 (2.7) *	545 (3.0)	**755 (3.2)**	245 (3.7)	510 (3.0)
Oxygen						
Ever	**1698 (7.1) ***	212 (3.7)	1486 (8.2)	**1609 (6.8)**	290 (4.4)	1319 (7.8)
<180 days	**431 (1.8)**	40 (0.7) *	391 (2.2)	**474 (2.0)**	69 (1.0)	405 (2.4)

* The difference between men and women is significant (p-value ≤0.05)

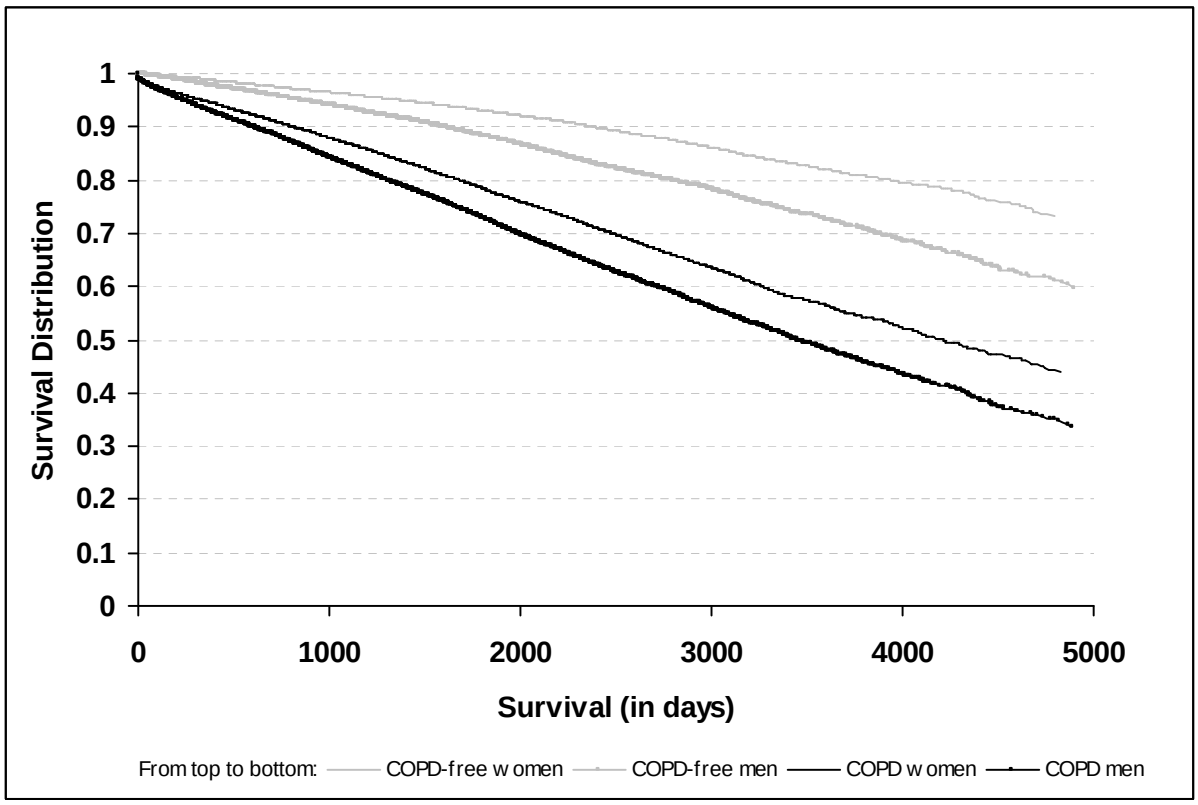


FIGURE 4.1 SURVIVAL AFTER THE INDEX DATE IN COPD AND COPD-FREE PATIENTS STRATIFIED BY GENDER

Based on the log likelihood ratio test the survival distributions differ significantly ($p<0.01$).

4.1.5 DISCUSSION

The prevalence of COPD has traditionally been lower in women than in men, however, trends from several countries have suggested that women are increasingly affected by COPD.(84-87) We identified almost the same number of men and women with COPD, thus providing further evidence for this trend. The incidence rates of COPD were, however, still higher in men than in women, except for the youngest age group. Women outnumber men in the elderly population this might explain why we observe almost the same total numbers but still higher incidence rates in men. The general higher life expectancy in women might also explain the difference in survival after the COPD diagnosis in men and women. Greater mortality in men compared to women had also been reported by de Torres et al..(121) Our results also confirm earlier reports that women tend to be younger at the time of the COPD diagnosis and account for a higher proportion among non-smoking COPD patients. (91, 117,

119) Whether non-smoking women had been exposed to environmental tobacco smoke could not be evaluated.

Patients with COPD had seen their GP more often than patients who did not receive a COPD diagnosis in the year prior to the index date. This difference might be explained by more intense and frequent examinations related to the establishment of a COPD diagnosis. As COPD is a disease which may only be diagnosed after a patient suffers from clinical symptoms, and the likelihood of getting a diagnosis may increase if a patient sees the GP more often we might have missed COPD-diagnoses since patients with early stages of non-symptomatic COPD might not have a diagnosis recorded. Thus, diagnostic bias may play a role when we included COPD patients. This sort of bias is not easy to control in observational studies. As there is a tendency of underreporting COPD in women (103, 104) it is important to stress that our results only reflect physician-diagnosed COPD, numbers of patients suffering from COPD might be higher. COPD diagnoses have been proven to be of high quality in earlier studies, thus we included all patients with a COPD diagnosis without further validation. (114)

Most co-morbidities were more prevalent in COPD patients than in COPD-free patients. Cardiovascular diseases and peptic ulcer disease share smoking as common risk factor with COPD which might at least explain some of the association observed.(122, 123) People with depression have been reported to be less likely to quit smoking, which might be one factor contributing to the association between depression and COPD.(124) The prevalence of depression was higher in women than in men, which is not specific to COPD but also seen in the COPD-free comparison group. In general the lifetime prevalence of depression is reported to be twice as high as in men.(125, 126). The prevalence of diabetes, myocardial infarction, stroke/ TIA, arrhythmia and peptic ulcer were higher in men than in women with COPD. This confirms earlier observations from the EPIDEPOC study in Spain.(91) The fact that men with COPD have a lower diabetes prevalence than men without COPD is an interesting observation, requiring further investigations.

Most COPD patients received short-acting bronchodilators, followed by long-acting bronchodilators. This pattern of drug utilization reflects the guidelines for COPD therapy.(27, 49) In contrast to Spanish data, patients in the UK have a higher exposure to short- and long-acting beta agonists and inhaled steroids.(91) Gender differences in drug utilization were observed for beta agonists, tiotropium, inhaled corticosteroids and leukotriene receptor antagonists. These differences were in general small but statistically significant. Whether these differences were due to different needs of men and women because of different disease manifestations or due to different prescribing preferences of GPs when treating men or women cannot be evaluated with this observational study. In the EPIDEPOC study men were more likely to use long-acting beta agonists, anticholinergic drugs, theophyllines and mucolytic agents.(91)

In summary, we provide further evidence for an increasing burden of COPD in women and showed that men and women present with different co-morbidities at the time of the diagnosis, the most prevalent being cardiovascular diseases and depression. Future research is needed to identify whether the observed differences in drug utilization reflect indeed best gender-specific care for the patients or are due a gender bias in prescribing.

4.2 DIABETES AND THE RISK OF COPD

4.2.1 ABSTRACT

Previous studies have reported an association between diabetes mellitus and COPD but most were cross-sectional or studied the incidence of diabetes in COPD populations. Analyses were seldom stratified by gender. We used the UK-based General Practice Research Database (GPRD) to assess the prevalence of diabetes mellitus in COPD patients aged 40-79 between 1995 and 2005, and we randomly matched COPD-free control patients to COPD patients, matched on age, sex, general practice, calendar time and years of history in the database. Conditional logistic regression analyses were used to estimate the odds ratio of developing a first-time COPD diagnosis in relation to pre-existing diabetes mellitus stratified by treatment. We identified 35,772 patients with COPD and the same number of COPD-free patients. The prevalence of diabetes was lower in the COPD group than in the control group, 7.0% and 9.6% in men, and 5.8% and 6.5% in women, respectively. Exposure to 36 or more prescriptions of sulfonylurea, but not to biguanides, PPARs or acarbose, was associated with a decreased incidence of COPD in men OR 0.69 (95% CI 0.55-0.87) but not in women OR 0.94 (95% CI 0.71-1.25). Diabetes is significantly underrepresented in men with COPD compared to men without COPD. An observation which may in part be explained by different smoking habits. In women there is no significant difference with regard to diabetes prevalence between women with and without COPD.

4.2.2 INTRODUCTION

Diabetes and chronic obstructive pulmonary disease (COPD) are often coexisting in elderly patients as shown by many cross-sectional studies.(91, 127-129) As both - COPD and diabetes - are prevalent diseases among the elderly one would expect a certain co-existence just by chance. Most studies, if they investigated the temporal relationship between COPD and diabetes, focussed on the incidence of diabetes in patients with COPD and reported inconsistent results: some showing a positive association (130, 131) while others did not find an association.(132) Some studies report an association between decreased lung function measured by FEV_1 and FCV but not the FEV_1/FVC ratio (130, 133) and other studies only measured lung function by FEV_1. (134) Stratified by GOLD categories Mannino et al. showed that stage 1 COPD is not associated with diabetes while stage 2, 3, 4 or 0 have been associated with diabetes.(130) Possible mechanisms to explain the association between COPD and diabetes include the presence of chronic inflammation and oxidative stress.(135)

Only few studies focussed on a potential association between incident COPD and prevalent diabetes. Measuring the lung function in a community-based cohort of diabetes patients over a period of 7 years showed that the lung function decreased over time relative to the age, height and sex specific predictive values.(136) Another study from the GPRD studying 1927 COPD patients registered in 1996 reported a protective association between diabetes and COPD (OR 0.57, 95% CI 0.44-0.72) when compared to COPD-free patients.(137)

Not much is known on the effect of gender in the temporal association between COPD and diabetes. Comparing the proportion of patients with diabetes in men and women with COPD gave inconsistent results. (91, 128), (138) The risk of diabetes in COPD seems to be increased in both men and women but the two above mentioned studies on the association between incident COPD and prevalent diabetes did not report gender-specific results.

We therefore conducted a large population-based study to evaluate the association of prevalent diabetes and the risk of developing a first-time diagnosis of COPD with a special focus on gender.

4.2.3 METHODS

For detailed information on the database and study design please refer to the general methods section here only the information on the study population, case validation and statistical analyses are repeated.

Study population: We identified in the GPRD all patients with a first-time diagnosis of COPD between January 1, 1995 and December 31, 2005 and who were aged 40-79 years. We excluded patients with less than 3 years of active recording history prior to the first COPD diagnosis. In addition, we identified at random from the GPRD one COPD-free comparison subject for each COPD patient, matched 1:1 on age (same year of birth), sex, general practice and calendar time (i.e. on the date of the first COPD diagnosis of the COPD patient). We applied the same exclusion criteria to the control group as to the COPD patients. Within this study population we assessed and compared the prevalence of diagnosed diabetes prior to the COPD diagnosis or the corresponding date in the comparison group.

Case validation: We identified patients with COPD based on recorded diagnoses. Soriano et al. validated the COPD diagnoses in the GPRD by sending questionnaires to the GPs and showed that the diagnoses are of high quality, with a concordance of κ=0.54.(114) Until March 2010, at least 11 studies on COPD have been done using GPRD data.(113) We identified patients with diabetes based on recorded diagnoses or administrative procedures used in diabetes care. We did not differentiate between diabetes typ I and typ II. To further ensure the validity of the diabetes diagnoses and as a surrogate marker for diabetes severity we stratified diabetic patients by exposure to oral antidiabetic treatment (metformin, sulfonylureas, thiazolidinediones and acarbose, glinides and guar gum), insulin treatment, a combination thereof and none thereof.

Statistical Analysis: We stratified the analyses by gender and adjusted the analyses for smoking status (none, current, past, unknown), body mass index (BMI; <18.5, 18.5-24.9, 25-29.9, 30-60 kg/m^2, or unknown), hypertension and hyperlipidemia. For each COPD patient

and each patient of the control group we assessed the exposure to oral antidiabetics (metformin, sulfonylureas, thiazolidinediones and acarbose) prior to the COPD diagnosis or the corresponding date in the comparison group. We stratified drug exposure by duration of use using the following categories: unexposed, 1-2 prescriptions, 3-11 prescriptions, 12-35 prescriptions or 36+ prescriptions.

4.2.4 RESULTS

We identified a total of 35,772 patients with a first-time COPD diagnosis between 1995 and 2005, and the same number of matched COPD-free patients in the comparison group. The total study population of 71,544 patients encompassed slightly more men (51.3 %) than women (48.7%), and 73.3 % of the study population were 60 years of age or older at the time of the first recording of a COPD diagnosis. Characteristics of the study population are displayed in Table 4.2.1.

The prevalence of diabetes in women was lower than in men and in patients with COPD lower than in patients without COPD, giving a crude odds ratio of 0.70 (95% CI, 0.65-0.76) in men and of 0.88 (95% CI, 0.80-0.96) in women; an observation made across all age groups except for the 40-49 years old, here the number of patients with diabetes was slightly higher in patients with a COPD diagnosis than in the COPD-free comparison group (data not shown). Women with COPD have a higher proportion of combined oral and insulin treatment (24%) than women without COPD (18%) or men with COPD (18%). In women diabetes with combined treatment with oral antidiabetics and insulin is associated with an increased number of COPD diagnoses when compared to women without diabetes (OR 1.42, 95% CI 1.11-1.83), adjusted for BMI, smoking status, hypertension and hyperlipidemia. In men it is associated with a lower number of COPD diagnoses (OR 0.78, 95% CI 0.62-0.98). Details on the prevalence of diabetes in men and women with COPD and the comparison group stratified by treatment are displayed in Tables 4.2.2 and 4.2.3.

TABLE 4.2.1 CHARACTERISTICS OF THE STUDY POPULATION

	COPD (%)	COPD-free (%)	Crude OR (95 % CI)
Male	18361 (51.3)	18361 (51.3)	--
Age groups (years)			
40-49	2432 (6.8)	2431 (6.8)	--
50-59	7101 (19.9)	7105 (19.9)	--
60-69	12075 (33.8)	12072 (33.8)	--
>70	14164 (39.6)	14164 (39.6)	--
Smoking status			
Non smoker	7722 (21.6)	18030 (50.4)	1.00 (ref)
Current smoker	15472 (43.3)	6428 (18.0)	6.27 (5.99-6.57)
Ex-smoker	9054 (25.3)	6431 (18.0)	3.65 (3.48-3.83)
Unknown	3524 (9.8)	4883 (13.7)	1.50 (1.41-1.60)
BMI (kg/m^2)			
15.0-18.4	1301 (3.6)	325 (0.9)	3.56 (3.14-4.03)
18.5-24.9	12026 (33.6)	10678 (29.9)	1.00 (ref)
25.0-29.9	9643 (27.0)	11647 (32.6)	0.74 (0.71-0.76)
30.0-60.0	5660 (15.8)	5690 (15.9)	0.89 (0.85-0.93)
Unknown	7142 (20.0)	7432 (20.8)	0.84 (0.80-0.88)
Co-morbidities			
Hyperlipidemia	3785 (10.6)	4324 (12.1)	0.85 (0.81-0.89)
Hypertension	9782 (27.4)	11353 (31.7)	0.80 (0.77-0.82)

Abbreviations: BMI: body mass index, ref: reference group, CI: confidence interval; OR: odds ratio; ref: reference; For all diseases each disease-free status is the reference.

TABLE 4.2.2 PREVALENCE OF TREATED AND UNTREATED DIABETES PRIOR TO THE INDEX DATE IN MEN

	Cases (%)	Controls (%)	Crude OR (95% CI)	Adj.* OR (95% CI)
No diabetes	**17072 (93.0)**	**16594 (90.4)**	**1.00 (ref)**	**1.00 (ref)**
Diabetes	**1289 (7.0)**	**1767 (9.6)**	**0.70 (0.65-0.76)**	**0.75 (0.69-0.82)**
Untreated	347 (1.9)	461 (2.5)	0.73 (0.63-0.84)	0.81 (0.69-0.94)
Treated	942 (5.1)	1306 (7.1)	0.69 (0.64-0.76)	0.73 (066-0.81)
Oral only	697 (3.8)	969 (5.3)	0.69 (0.63-0.77)	0.73 (0.65-0.82)
Insulin only	78 (0.4)	127 (0.7)	0.58 (0.44-0.78)	0.66 (0.48-0.90)
Combination	167 (0.9)	210 (1.1)	0.76 (0.62-0.94)	0.78 (0.62-0.98)

Abbreviations: ref: reference group, CI: confidence interval; OR: odds ratio; ref: reference, adj.* OR is adjusted for BMI, smoking status, hyperlipidemia and hypertension.

TABLE 4.2.3 PREVALENCE OF TREATED AND UNTREATED DIABETES PRIOR TO THE INDEX DATE IN WOMEN

	Cases (%)	Controls (%)	Crude OR (95% CI)	Adj.* OR (95% CI)
No diabetes	**16407 (94.2)**	**16275 (93.5)**	**1.00 (ref)**	**1.00 (ref)**
Diabetes	**1004 (5.8)**	**1136 (6.5)**	**0.88 (0.80-0.96)**	**0.96 (0.86-1.07)**
Untreated	268 (1.5)	284 (1.6)	0.93 (0.79-1.11)	0.99 (0.81-1.21)
Treated	736 (4.2)	852 (4.9)	0.86 (0.77-0.95)	0.95 (0.84-1.07)
Oral only	497 (2.9)	628 (3.6)	0.78 (0.69-0.88)	0.86 (0.75-0.99)
Insulin only	59 (0.3)	71 (0.4)	0.82 (0.58-1.16)	0.79 (0.53-1.18)
combination	180 (1.0)	153 (0.9)	1.17 (0.94-1.45)	1.42 (1.11-1.83)

Abbreviations: ref: reference group, CI: confidence interval; OR: odds ratio; ref: reference, adj.* OR is adjusted for BMI, smoking status, hyperlipidemia and hypertension.

The use of oral antidiabetics stratified by type of antidiabetic, duration of use and gender is displayed in Tables 4.2.4 and 4.2.5. Guar gum and glinides are not listed as less than 0.1% of the study population have been exposed. An increased duration of use of sulfonylurea preparations is associated with a decreased number of COPD diagnoses in men when compared to unexposed men; the odds ratio of 36 or more sulfonylurea prescriptions is 0.69 (95% CI 0.55-0.87). In women the use of sulfonylurea is not associated with a diagnosis of COPD. In a sensitivity analysis restricted to mutually exclusive use of sulfonylurea, 36 or

more prescriptions of sulfonylurea was associated with a decreased number of COPD diagnoses in women when compared to women not using oral antidiabetic treatment (OR 0.52, 95% CI 0.31-0.86).

TABLE 4.2.4 USE OF ORAL ANTIDIABETICS PRIOR TO THE INDEX DATE IN MEN

	Cases (%)	Controls (%)	Crude OR (95% CI)	Adj.* OR (95% CI)
Sulfonylurea				
Unexposed	17663 (96.2)	17394 (94.7)	1.00 (ref)	1.00 (ref)
1-2 P.	54 (0.3)	52 (0.3)	1.05 (0.71-1.55)	1.03 (0.67-1.61)
3-11 P.	142 (0.8)	158 (0.9)	0.90 (0.71-1.15)	0.93 (0.71-1.22)
12-35 P.	232 (1.3)	355 (1.9)	0.66 (0.55-0.80)	0.65 (0.53-0.81)
36+ P.	270 (1.5)	402 (2.2)	0.68 (0.55-0.83)	0.69 (0.55-0.87)
Biguanides				
Unexposed	17735 (96.6)	17544 (95.6)	1.00 (ref)	1.00 (ref)
1-2 P.	60 (0.3)	78 (0.4)	0.93 (0.65-1.32)	0.93 (0.63-1.38)
3-11 P.	127 (0.7)	188 (1.0)	0.82 (0.64-1.04)	0.82 (0.62-1.07)
12-35 P.	228 (1.2)	268 (1.5)	1.12 (0.91-1.38)	1.28 (1.02-1.62)
36+ P.	211 (1.2)	283 (1.5)	1.07 (0.85-1.34)	1.09 (0.85-2.73)
PPARs				
Unexposed	18314 (99.7)	18290 (99.6)	1.00 (ref)	1.00 (ref)
1-2 P.	11 (0.1)	17 (0.1)	0.72 (0.31-1.66)	0.56 (0.23-1.35)
3-11 P.	20 (0.1)	31 (0.2)	0.80 (0.45-1.43)	0.72 (0.38-1.36)
12-35 P.	12 (0.1)	21 (0.1)	0.75 (0.63-1.55)	0.68 (0.31-1.53)
36+ P.	4 (0.02)	2 (0.01)	2.64 (0.47-14.62)	2.83 (0.43-18.47)
Acarbose				
Unexposed	18309 (99.7)	18269 (99.5)	1.00 (ref)	1.00 (ref)
1-2 P.	16 (0.1)	16 (0.1)	1.46 (0.72-2.98)	1.24 (0.56-2.73)
3-11 P.	17 (0.1)	33 (0.2)	0.73 (0.40-.34)	0.63 (0.32-1.22)
12-35 P.	13 (0.1)	30 (0.2)	0.62 (0.32-1.22)	0.89 (0.43-1.85)
36+ P.	6 (0.03)	13 (0.1)	0.68 (0.25-1.84)	0.70 (0.23-2.13)

Adj.* OR is adjusted for BMI, smoking status, hyperlipidemia and hypertension, insulin use and all the variables in the table

TABLE 4.2.5 USE OF ORAL ANTIDIABETICS PRIOR TO THE INDEX DATE IN WOMEN

	Cases (%)	Controls (%)	Crude OR (95% CI)	Adj.* OR (95% CI)
Sulfonylurea				
Unexposed	16852 (96.8)	16790 (96.4)	1.00 (ref)	1.00 (ref)
1-2 P.	36 (0.2)	48 (0.3)	0.74 (0.47-1.15)	0.86 (0.51-1.43)
3-11 P.	124 (0.7)	110 (0.6)	1.12 (0.85-1.49)	1.32 (0.95-1.83)
12-35 P.	183 (1.1)	213 (1.2)	0.84 (0.66-1.06)	0.91 (0.69-1.19)
36+ P.	216 (1.2)	250 (1.4)	0.85 (0.66-1.08)	0.94 (0.71-1.25)
Biguanides				
Unexposed	16894 (97.0)	16840 (96.7)	1.00 (ref)	1.00 (ref)
1-2 P.	53 (0.3)	49 (0.3)	1.07 (0.71-1.62)	1.15 (0.70-1.88)
3-11 P.	119 (0.7)	124 (0.7)	0.96 (0.72-1.27)	1.06 (0.76-1.47)
12-35 P.	162 (0.9)	171 (1.0)	0.97 (0.76-1.24)	0.94 (0.70-1.24)
36+ P.	183 (1.1)	227 (1.3)	0.80 (0.62-1.04)	0.82 (0.61-1.10)
PPARs				
Unexposed	17360 (99.7)	17355 (99.7)	1.00 (ref)	1.00 (ref)
1-2 P.	8 (0.1)	10 (0.1)	0.82 (0.32-2.14)	0.48 (0.16-1.48)
3-11 P.	21 (0.1)	20 (0.1)	1.10 (0.58-2.08)	1.17 (0.57-2.42)
12-35 P.	21 (0.1)	26 (0.2)	0.92 (0.50-1.67)	0.95 (0.48-1.87)
36+ P.	1 (0.01)	0 (0.0)	--	--
Acarbose				
Unexposed	17335 (99.6)	17354 (99.7)	1.00 (ref)	1.00 (ref)
1-2 P.	20 (0.1)	25 (0.1)	1.03 (0.55-1.91)	0.94 (0.45-1.92)
3-11 P.	26 (0.2)	14 (0.1)	2.07 (1.05-4.09)	2.82 (1.27-6.25)
12-35 P.	22 (0.1)	10 (0.1)	2.55 (1.18-5.52)	3.57 (1.49-8.52)
36+ P.	8 (0.1)	8 (0.1)	1.26 (0.47-3.42)	1.17 (0.35-3.88)

Adj.* OR is adjusted for BMI, smoking status, hyperlipidemia and hypertension, insulin use and all the variables in the table

As smoking is the most important risk factor for COPD and might confound associations between diabetes and COPD we ran a sensitivity analysis stratified by smoking and the presence of diabetes. Comparing non-smokers with diabetes with non-smokers without diabetes the adjusted relative risk of COPD in men was 0.88 (95% CI 0.76-1.03) and in

women 1.10 (95% CI 0.94-1.28). Smokers with diabetes and ex-smokers with diabetes had lower odds ratios than smokers and ex-smokers without diabetes (data not shown). Testing for interaction showed that there is a statistically significant interaction between smoking and diabetes (p=0.05).

4.2.5 DISCUSSION

The prevalence of diabetes we observed is in the range reported by national statistics in the UK, which in men aged 45 to 74 years ranges between 6% and 16% and in women aged 45-74 ranges between 4% and 10%.(139) Cross-sectional studies have shown that diabetes mellitus and COPD are often coexisting. A study using the Italian 'Health Search Database' found a higher prevalence of diabetes mellitus in patients with COPD compared to COPD-free patients, prevalences were 18.7% and 10.5%, respectively.(127) The prevalence of diabetes in US veterans with and without COPD in 1992 was both 15.1% while in 1998 the prevalence of diabetes in veterans with COPD was 21.1% and in veterans without COPD 20.7%, thus there was no significant difference in diabetes prevalence between veterans with and without COPD.(129) We report a lower prevalence of diabetes in patients with COPD compared to patients without COPD. As the diabetes incidence is increased in patients with COPD the difference in our results compared to the results of the first study might be due to different timing of the analysis. There is, however, also a study measuring the lung function in a community-based cohort of diabetes patients over a period of 7 years, which showed that the lung function decreased over time.(136) This is opposite to our results. Another study from the GPRD studying 1927 COPD patients registered in 1996, however, also reported a protective association between diabetes and COPD (OR 0.57, 95% CI 0.44-0.72) when compared to COPD-free patients, which is even slightly lower than the odds ratios we found. They, however, did not stratify their analysis by gender.(137) Whether there is indeed a causal association between diabetes and COPD cannot be clarified by this observational study we simply report an interesting observation which may for example at least in part be confounded by differences in smoking intensity and duration, as indicated by our results in

non-smokers. Patients with diabetes might have a greater incentive to stop smoking than patients without as smoking puts diabetic patients at a higher risk of complications. Smoking cessation is the single most effective procedure in COPD prevention.(27) If this was the real explanation behind this observation it would demonstrate how potent smoking cessation - even of a few years – is in the prevention or at least delay of COPD development. Residual differences in smoking intensity and duration might also explain the difference observed between men and women as more women without a smoking history develop COPD and women usually also smoked less. We also tested whether the observed association between COPD and diabetes might be explained by exposure to antidiabetic drugs. We found that men exposed to sulfonylurea were underrepresented in patients with COPD when compared to patients without COPD. Whether there is really an association between sulfonylurea use and COPD must be clarified in other studies. We are not aware of any mechanism which would explain this association. It is possible that sulfonylurea are just a marker for a special subgroup of COPD patients.

The results are based on GP-diagnosed COPD and diabetes. While the GPRD has been extensively validated in previous studies and has proven to be of high quality, including studies on COPD and diabetes,(114, 140) we cannot rule out the possibility that a certain proportion of patients with these disease diagnoses may have been missed, particularly those with mild forms of the disease. By matching cases and controls on practice, we controlled to some degree for socioeconomic status, as social deprivation shows a geographical pattern and therefore people from the same area are more likely to see the same GP. We, however, cannot exclude residual confounding by socioeconomic status or smoking as we only assessed smoking status but not smoking intensity. Further studies are necessary to determine whether there is indeed an association between COPD and diabetes and whether there is a real difference between men and women.

4.3 COPD AND THE RISK OF CARDIOVASCULAR OUTCOMES

4.3.1 ABSTRACT

Previous large epidemiological studies reporting an association between chronic obstructive pulmonary disease (COPD) and cardiovascular diseases, rather focussed on prevalent diseases than on the incidence of newly diagnosed cardiovascular outcomes.

We used the UK-based General Practice Research Database (GPRD) to assess incidence of cardiovascular diseases in COPD patients aged 40-79 years between 1995 and 2005, and we randomly matched COPD-free comparison patients to COPD patients. In nested-case control analyses, we compared the risks of developing an incident diagnosis of cardiac arrhythmias, venous thromboembolism, myocardial infarction, or stroke between patients with and without COPD, stratifying the analyses by COPD-severity, using COPD-treatment as a proxy for disease severity.

We identified in total 2646 cardiovascular outcomes, incidence rates of most cardiovascular disease were higher in men than in women. The overall relative risk estimates of developing an incident diagnosis of cardiac arrhythmia (OR 1.19, 95% CI 0.98-1.43), deep vein thrombosis (OR 1.35, 95% CI 0.97-1.89), pulmonary embolism (OR 2.51, 95% CI 1.62-3.87), myocardial infarction (OR 1.40, 95% CI 1.13-1.73), or stroke (OR 1.13, 95% CI 0.92-1.38), tended to be increased for patients with COPD as compared to COPD-free controls. Relative risks of arrhythmia, pulmonary embolism and deep vein thrombosis were similar in men and women. The relative risk estimates for myocardial infarction and stroke / TIA in women were increased in comparison to men.

The findings of this large observational study provide further evidence that men and women with COPD are at increased risk for most cardiovascular diseases. COPD increased the risk of stroke / TIA in women but not in men.

4.3.2 INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is increasingly recognized as a respiratory disease with an important systemic component.(27, 65) Persistent low-level systemic inflammation is present in COPD, reflected for example by elevated levels of C-reactive protein.(141) Systemic inflammation has also been associated with atherosclerosis, ischemic heart disease and stroke.(142) Cardiovascular events are an important cause of morbidity and mortality among COPD patients.(143, 144) Apart from a possible direct association between COPD and adverse cardiovascular outcomes, COPD therapy with beta-agonists is of concern (145) due to the potential of increasing the risk for cardiac arrhythmia and myocardial infarction. In addition, COPD patients may require treatment with macrolides and quinolone antibiotics (146) which themselves may also cause adverse cardiovascular effects, and COPD and cardiovascular diseases also share smoking as an important risk factor.(122)

Regardless of the underlying mechanism, various studies indicate an association between COPD and the risk of cardiovascular diseases.(147-149) According to the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation, supraventricular arrhythmias are common in patients with COPD,(150) and pulmonary embolism has frequently been observed during exacerbations of COPD.(151, 152) Patients with COPD who experienced a myocardial infarction were at a two-fold increased risk of dying within one-year after the myocardial infarction compared to patients without COPD,(153) and in another study COPD patients were at an increased risk of fatal strokes when compared to COPD-free patients.(154) A Canadian study based on data from Saskatchewan assessed the period prevalence of cardiovascular events and incidence of hospitalisations and mortality from cardiovascular outcomes in COPD patients (155, 156) and a study based on the Kaiser Permanente Medical Care Program (157) provided additional information on the incidence of hospitalisations for cardiovascular outcomes.

In the current study, we quantified the risks of developing an incident diagnosis of cardiac arrhythmia, myocardial infarction (MI), deep vein thrombosis (DVT), pulmonary embolism

(PE), stroke or transient ischemic attack (TIA) in relation to COPD using primary-care data from the United Kingdom (UK) between 1995 and 2005 and assessed whether there are gender differences.

4.3.3 METHODS

For detailed information on the database and study design please refer to the general methods section here only the information on the exclusion criteria, case validation and statistical analyses are repeated.

Exclusion Criteria: We excluded all patients from the COPD group and from the comparison group who had a recorded history of congestive heart failure, MI, DVT, pulmonary embolism (PE), stroke, TIA, cardiac arrhythmia, prior to the first COPD diagnosis (or the corresponding date in the COPD-free group).

Case definition: All patients with a recorded first-time diagnosis of cardiac arrhythmia, PE, DVT, MI or stroke / TIA were identified using specific disease codes recorded by the GP. We validated potential cases according to the pharmacological treatment recorded after the cardiovascular diagnosis. In order to be eligible, cases with DVT or PE had to have been hospitalised within 30 days after the diagnosis or had to die within 30 days after the diagnosis, and/or had to start treatment with heparin, vitamin K antagonists, platelet aggregation inhibitors, direct thrombin inhibitors or fibrinolytic enzymes within 90 (DVT) or 180 (PE) days after the diagnosis. If potential cases had one or more prescriptions for heparin, vitamin K antagonists, platelet aggregation inhibitors, direct thrombin inhibitors or fibrinolytic enzymes recorded more than 90 days prior to the DVT diagnosis, the potential case was excluded from the analysis. Patients with an incident MI diagnosis had to have been hospitalised within 30 days of the MI diagnosis, or had to die within 30 days after the diagnosis, and/or they had to start a new treatment with ACE antagonists, beta blockers, statins, vitamin K antagonists, platelet aggregation inhibitors, or aspirin within 90 days after the diagnosis. Patients with heart surgery or with prescriptions for heparin, vitamin K

antagonists, platelet aggregation inhibitors, direct thrombin inhibitors or fibrinolytic enzymes more than 30 days prior to the diagnosis date were excluded. Stroke or TIA patients had to be hospitalised within 30 days of the stroke diagnosis, had to die within 30 days after the diagnosis, and/or had to have a new treatment with aspirin, heparin, vitamin K antagonists, platelet aggregation inhibitors, direct thrombin inhibitors or fibrinolytic enzymes within 180 days after the diagnosis.

Statistical Analyses: Arrhythmia analyses are adjusted for smoking status, hypertension, use of beta agonists, xanthines, quinolones, macrolides, vitamin K antagonists, beta blockers, calcium channel blockers, diuretics, cardiac glycosides and coronary dilatators. PE and DVT analyses are adjusted for smoking status, BMI, hypertension and NSAID use. MI analyses are adjusted for smoking status, BMI, hypertension, hyperlipidemia, diabetes and NSAID use. Stroke / TIA analyses are adjusted for smoking status, BMI, hypertension, diabetes and use of aspirin.

For the mortality analyses we followed all patients with a diagnosis of myocardial infarction or stroke / TIA until they died, left the practice, or the study ended, whatever came first. We then did a logistic regression analysis stratified by COPD status to evaluate the crude impact of gender on mortality.

4.3.4 RESULTS

After excluding patients with prevalent cardiovascular diseases, cancer, HIV, alcoholism or drug abuse, we identified among the remaining study population 1191 cases with an incident cardiac arrhythmia diagnosis, 136 cases with an incident pulmonary embolism, 210 cases with an incident DVT, 511 cases with an incident MI, and 598 cases with an incident stroke / TIA diagnosis. In absolute terms there were more cardiovascular outcomes in men than in women, although women outnumbered men with regard to DVT diagnoses and in COPD patients also with regard to stroke diagnoses. Incidence rates of all cardiovascular endpoints were higher among COPD patients than among patients without COPD; the incidence rate of

PE was more than twice as high (12.8 / 10,000 py among COPD patients vs. 5.4 / 10,000 py in the comparison group). In absolute terms, the incidence rates were highest for arrhythmia (91.1 / 10,000 py among COPD patients and 66.7 / 10,000 py in the comparison group), and lowest for PE. The various incidence rates, stratified by gender, are displayed in detail in Table 4.3.1. Patients with COPD, both men and women, develop most cardiovascular outcomes slightly younger than patients without COPD an exception to this phenomena is the diagnosis of stroke in men. Figure 4.2 displays the age distribution at the time of the cardiovascular diagnosis stratified by gender for patients with and without COPD. Smoking prevalence was generally higher in COPD patients compared to COPD-free patients as well as in patients developing a cardiovascular outcome compared to patients not developing a cardiovascular outcome independent of COPD status. The percentage of current smokers was generally smaller in women compared to men. Men with COPD and MI had the highest current smoker percentage 51% (data not shown).

TABLE 4.3.1 INCIDENCE RATES OF CARDIOVASCULAR DISEASES IN COPD AND CONTROL PATIENTS

	Cases	Person-time (years)	IR per 10,000 py (95 %CI)	IRR (95% CI)
Arrhythmia				
COPD-Free	**563**	**84435.2**	**66.7 (61.4-72.4)**	
Men	288	39532.0	72.9 (64.9-81.7)	1.19 (1.01 - 1.40)
Women	275	44903.3	61.2 (54.4-68.9)	1.00 (ref)
COPD	**628**	**68958.5**	**91.1 (84.3-98.4)**	
Men	334	32432.2	103.0 (92.6-114.6)	1.28 (1.09 - 1.49)
Women	294	36526.2	80.5 (71.8-90.2)	1.00 (ref)
PE				
COPD-Free	**46**	**85765.1**	**5.4 (4.0-7.2)**	
Men	23	40260.6	5.7 (3.8-8.6)	1.13 (0.63 - 2.02)
Women	23	45504.4	5.1 (3.4-7.6)	1.00 (ref)
COPD	**90**	**70233.0**	**12.8 (10.4-15.8)**	
Men	48	33258.3	14.4 (10.9-19.1)	1.27 (0.84 - 1.92)
Women	42	36974.8	11.4 (8.4-15.4)	1.00 (ref)

TABLE 4.3.1 INCIDENCE RATES OF CARDIOVASCULAR DISEASES IN COPD AND CONTROL PATIENTS

	Cases	Person-time (years)	IR per 10,000 py (95 %CI)	IRR (95% CI)
DVT				
COPD-Free	**96**	**85765.1**	**11.2 (9.2-13.7)**	
Men	39	40260.6	9.7 (7.1-13.2)	0.77 (0.52 - 1.15)
Women	57	45504.4	12.5 (9.7-16.2)	1.00 (ref)
COPD	**114**	**70233.0**	**16.2 (13.5-19.5)**	
Men	53	33258.3	15.9 (12.2-20.8)	0.97 (0.67-1.39)
Women	61	36974.8	16.5 (12.9-21.2)	1.00 (ref)
MI				
COPD-Free	**224**	**85538.9**	**26.2 (23.0-29.8)**	
Men	147	39990.9	36.8 (31.3-43.2)	2.17 (1.67 - 2.82)
Women	77	45548.0	16.9 (13.5-21.1)	1.00 (ref)
COPD	**287**	**70055.2**	**41.0 (36.5-46.0)**	
Men	174	33000.8	52.7 (45.5-61.1)	1.73 (1.37 - 2.17)
Women	113	37054.3	30.5 (25.4-36.7)	1.00 (ref)
Stroke / TIA				
COPD-Free	**298**	**84586.7**	**35.2 (31.5-39.5)**	
Men	165	39554.0	41.7 (35.8-48.6)	1.41 (1.12 - 1.77)
Women	133	45032.7	29.5 (24.9-35.0)	1.00 (ref)
COPD	**300**	**69510.2**	**43.2 (38.6-48.3)**	
Men	134	32857.9	40.8 (34.5-48.3)	0.90 (0.72 - 1.13)
Women	166	36652.2	45.3 (38.9-52.7)	1.00 (ref)

Abbreviations: IR: incidence rate, CI: confidence interval; py: person years

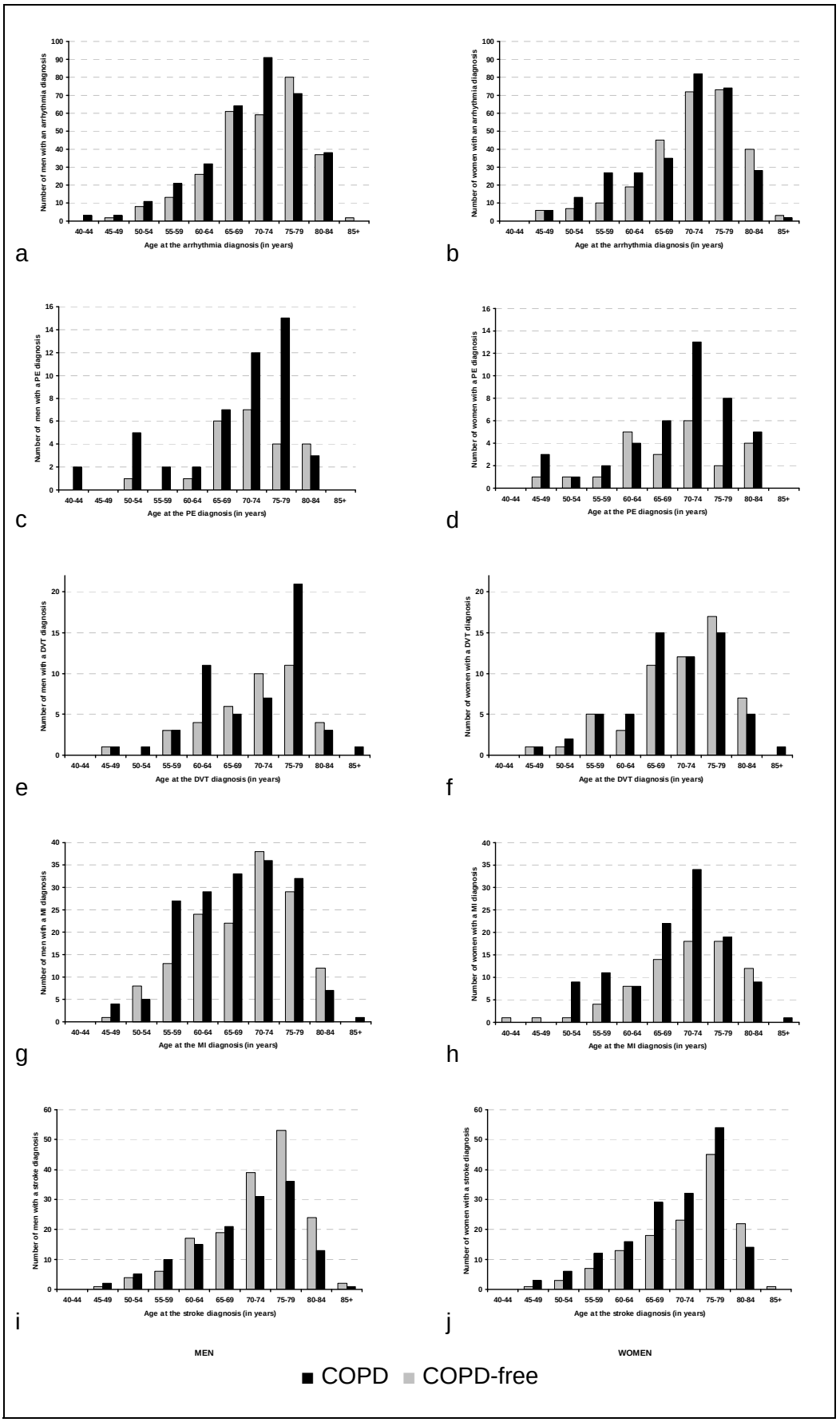


FIGURE 4.2 AGE AT THE DIAGNOSIS OF THE CARDIOVASCULAR OUTCOME IN PATIENTS WITH AND WITHOUT COPD STRATIFIED BY GENDER

In order to evaluate the effect of COPD severity on the risk of developing a study outcome of interest, we conducted a nested case-control analysis, where we stratified COPD patients according to their treatment pattern into mild, moderate or severe COPD. The relative risk of developing arrhythmia overall was similar for patients with or without COPD (OR 1.19, 95% CI 0.98-1.43), and COPD severity did not alter the risk estimate substantially. The arrhythmia risk was similar in men and women. The overall association between COPD and the risk of stroke / TIA was 1.13 (95% CI 0.92-1.38) for COPD patients as compared to patients without COPD, however stratification by gender revealed that there is no association in men (OR 0.91, 95% CI 0.69-1.21) while the association in women was 1.41 (95% CI 1.06-1.88). This difference in men and women was only seen for mild and moderate COPD while men and women with severe COPD did not have an increased risk of stroke / TIA. For MI, the relative risk estimate was highest for patients with severe COPD (OR 3.00, 95% CI 1.53-5.86) and tended to be slightly higher in women than in men. The relative risk of PE was increased across all categories of COPD severity with a particularly high risk for patients with severe COPD, based on only 8 cases and 6 controls (OR 7.47, 95% CI 2.35-23.7). The PE risk was similar in men and women. Overall, the risk of DVT was 1.35 (95% CI 0.97-1.89) for COPD patients compared to COPD-free controls. The risk of developing DVT was similar in men and women. The findings for the various cardiovascular outcomes, stratified by COPD severity, are displayed in Table 4.3.2.

The total mortality of patients with myocardial infarction was higher in patients who had COPD (38%) than in the COPD-free patients (29%), with almost no difference between men and women. Most of the patients died within the first 30 days after a diagnosis of myocardial infarction with a slightly higher percentage of death in men than in women in this 30 days period: 22% of all women with COPD and myocardial infarction died within the first 30 days compared to 27% of all men with COPD and myocardial infarction, yielding a crude odds ratio of 0.77 (95% CI, 0.44-1.34), the percentages in men and women without COPD were 19% and 17%, respectively. The overall mortality in patients with stroke and COPD was 36% compared to 25% in COPD-free patients with stroke. The mortality within the first 30 days

after a stroke diagnosis was similar in men and women with COPD, 18% and 19% respectively. In men and women without COPD the 30 days-mortality in women was higher than in men, 19% and 9%, respectively, yielding a crude odds ratio of 2.50 (95% CI 1.24-5.02).

TABLE 4.3.2 RISK OF CARDIOVASCULAR DISEASES STRATIFIED BY COPD SEVERITY IN MEN AND WOMEN

	Cases	Controls	Crude OR (95% CI)	Adj.[a] OR (95% CI)
Arrhythmia				
No COPD	**563**	**3116**	**1.00 (ref)**	**1.00 (ref)**
Men	288	1598	1.00 (ref)	1.00 (ref)
Women	275	1518	1.00 (ref)	1.00 (ref)
Any COPD	**628**	**2418**	**1.42 (1.25-1.61)**	**1.19 (0.98-1.43)**
Men	334	1300	1.43 (1.20-1.71)	1.18 (0.90-1.55)
Women	294	1118	1.41 (1.18-1.68)	1.19 (0.91-1.56)
Mild	**48**	**191**	**1.42 (1.01-2.00)**	**1.64 (1.14-2.34)**
Men	30	112	1.54 (0.99-2.38)	1.82 (1.15-2.89)
Women	18	79	1.27 (0.74-2.18)	1.42 (0.80-2.55)
Moderate	**548**	**2146**	**1.39 (1.22-1.59)**	**1.07 (0.86-1.32)**
Men	287	1148	1.39 (1.16-1.67)	1.00 (0.74-1.35)
Women	261	998	1.40 (1.16-1.68)	1.14 (0.84-1.54)
Severe	**32**	**81**	**2.10 (1.36-3.23)**	**1.29 (0.79-2.11)**
Men	17	40	2.35 (1.29-4.26)	1.49 (0.75-2.95)
Women	15	41	1.86 (1.00-3.47)	1.11 (0.55-2.25)
PE				
No COPD	**46**	**314**	**1.00 (ref)**	**1.00 (ref)**
Men	23	157	1.00 (ref)	1.00 (ref)
Women	23	157	1.00 (ref)	1.00 (ref)
Any COPD	**90**	**230**	**2.57 (1.74-3.78**)	**2.51 (1.62-3.87)**
Men	48	127	2.47 (1.44-4.24)	2.58 (1.38-4.81)
Women	42	103	2.67 (1.53-4.64)	2.79 (1.44-5.42)
Mild	**7**	**18**	**2.61 (1.03-6.64)**	**3.58 (1.32-9.70)**
Men	6	14	2.81 (1.00-7.88)	3.59 (1.15-11.23)

TABLE 4.3.2 RISK OF CARDIOVASCULAR DISEASES STRATIFIED BY COPD SEVERITY IN MEN AND WOMEN

	Cases	Controls	Crude OR (95% CI)	Adj.[a] OR (95% CI)
Women	1	4	1.59 (0.15-16.56)	3.63 (0.31-42.55)
Moderate	**75**	**206**	**2.39 (1.60-3.58)**	**2.23 (1.42-3.50)**
Men	37	109	2.24 (1.27-3.96)	2.17 (1.13-4.20)
Women	38	97	2.55 (1.45-4.48)	2.67 (1.36-5.23)
Severe	**8**	**6**	**8.58 (2.88-25.6)**	**7.47 (2.35-23.7)**
Men	5	4	8.25 (2.10-32.49)	8.79 (1.93-40.03)
Women	3	2	9.08 (1.46-56.32)	6.15 (0.82-45.91)
DVT				
No COPD	**96**	**454**	**1.00 (ref)**	**1.00 (ref)**
Men	39	186	1.00 (ref)	1.00 (ref)
Women	57	268	1.00 (ref)	1.00 (ref)
Any COPD	**114**	**386**	**1.38 (1.02-1.86)**	**1.35 (0.97-1.89)**
Men	53	182	1.36 (0.87-2.13)	1.33 (0.80-2.22)
Women	61	204	1.39 (0.93-2.08)	1.36 (0.86-2.15)
Mild	**10**	**26**	**1.78 (0.84-3.77)**	**1.73 (0.78-3.80)**
Men	5	15	1.55 (0.55-4.39)	1.49 (0.49-4.55)
Women	5	11	2.09 (0.70-6.26)	2.19 (0.68-7.07)
Moderate	**100**	**334**	**1.41 (1.03-1.91)**	**1.37 (0.97-1.94)**
Men	47	160	1.38 (0.87-2.19)	1.33 (0.78-2.26)
Women	53	174	1.42 (0.94-2.16)	1.37 (0.85-2.22)
Severe	**4**	**26**	**0.70 (0.24-2.06)**	**0.79 (0.26-2.39)**
Men	1	7	0.64 (0.07-5.56)	0.74 (0.08-6.81)
Women	3	19	0.72 (0.21-2.53)	0.76 (0.21-2.84)
MI				
No COPD	**224**	**1082**	**1.00 (ref)**	**1.00 (ref)**
Men	147	666	1.00 (ref)	1.00 (ref)
Women	77	416	1.00 (ref)	1.00 (ref)
Any COPD	**287**	**813**	**1.70 (1.39-2.06)**	**1.40 (1.13-1.73)**
Men	174	534	1.47 (1.15-1.87)	1.25 (0.96-1.63)
Women	113	279	2.18 (1.57-3.03)	1.77 (1.24-2.53)
Mild	**33**	**64**	**2.43 (1.56-3.81)**	**1.79 (1.12-2.86)**

TABLE 4.3.2 RISK OF CARDIOVASCULAR DISEASES STRATIFIED BY COPD SEVERITY IN MEN AND WOMEN

	Cases	Controls	Crude OR (95% CI)	Adj.[a] OR (95% CI)
Men	17	49	1.52 (0.85-2.73)	1.12 (0.61-2.07)
Women	16	15	5.55 (2.63-11.71)	4.46 (2.03-9.80)
Moderate	**238**	**726**	**1.58 (1.29-1.94)**	**1.30 (1.04-1.62)**
Men	149	474	1.42 (1.10-1.83)	1.21 (0.92-1.60)
Women	89	252	1.91 (1.36-2.69)	1.56 (1.08-2.27)
Severe	**16**	**23**	**3.11 (1.62-5.95)**	**3.00 (1.53-5.86)**
Men	8	11	2.96 (1.18-7.45)	2.80 (1.06-7.38)
Women	8	12	3.53 (1.40-8.89)	3.36 (1.31-8.63)
Stroke / TIA				
No COPD	**298**	**1256**	**1.00 (ref)**	**1.00 (ref)**
Men	165	614	1.00 (ref)	1.00 (ref)
Women	133	642	1.00 (ref)	1.00 (ref)
Any COPD	**300**	**1004**	**1.25 (1.05-1.49)**	**1.13 (0.92-1.38)**
Men	134	510	0.98 (0.76-1.26)	0.91 (0.69-1.21)
Women	166	494	1.61 (1.25-2.08)	1.41 (1.06-1.88)
Mild	**20**	**66**	**1.28 (0.77-2.15)**	**1.21 (0.70-2.09)**
Men	10	34	1.13 (0.55-2.33)	1.05 (0.49-2.26)
Women	10	32	1.49 (0.72-3.10)	1.47 (0.68-3.16)
Moderate	**271**	**900**	**1.26 (1.05-1.51)**	**1.13 (0.92-1.38)**
Men	118	454	0.97 (0.75-1.25)	0.90 (0.67-1.21)
Women	153	446	1.64 (1.27-2.13)	1.42 (1.06-1.90)
Severe	**9**	**38**	**0.98 (0.47-2.05)**	**1.00 (0.47-2.15)**
Men	6	22	1.01 (0.40-2.53)	0.94 (0.36-2.45)
Women	3	16	0.89 (0.25-3.10)	1.01 (0.28-3.66)

[a]Arrhythmia analyses are adjusted for smoking status, hypertension, beta agonist use, xanthine use, quinolone use, macrolide use, vitamin K antagonist use and use of beta blockers, calcium channel blockers, diuretics, cardiac glycosides and coronary dilatators; PE and DVT analyses are adjusted for smoking status, BMI, hypertension and NSAID use; MI analyses are adjusted for smoking status, BMI, hypertension, hyperlipidemia, diabetes and NSAID use; Stroke / TIA analyses are adjusted for smoking status, BMI, hypertension, aspirin use and diabetes.

Abbreviations: OR: odds ratio, ref: reference value, CI: confidence interval.

4.3.5 DISCUSSION

In this large observational study, we explored the association between COPD and the risk of developing an incident diagnosis of cardiac arrhythmia, DVT, PE, MI, or stroke / TIA. We quantified the prevalence of these diseases prior to the first COPD diagnosis, and we compared their incidence rates between COPD patients and a matched comparison group free of COPD. In general, the findings for the association between cardiovascular diseases and COPD in our study are comparable to results from studies in other health care settings and/or other countries.

PE is a relatively rare outcome, but the association between COPD and PE was rather strong (OR 2.51, 95% CI 1.62-3.87) with incidence rates increased both in men and women with COPD compared to COPD-free controls. It is difficult to tell whether this association is a causal one or possibly the result of some diagnostic bias, since PE has been reported to be frequently observed during exacerbations of COPD.(151, 152) The authors of a French prospective cohort study investigated PE in COPD patients with unexplained exacerbations and reported a prevalence of PE of 25%.(151) Sidney et al. (157) reported an age-adjusted case patient rate per 100,000 py for hospitalized PE of 129.4 among COPD patients and a 2.74 (95% CI 1.99-3.76)-fold increased relative risk of hospitalisation due to PE among COPD patients compared to control patients, adjusted for age, gender and cardiovascular risk morbidities. The RR in women of 2.32 (95% CI 1.58-3.41) is closely similar to the crude IRR 2.25 (1.38-3.66) which we found, however, their RR in men was slightly higher than in our analysis. A study based on Saskatchewan data reported a 5.46 (95% CI 4.25-7.02)-fold increased relative risk of PE for COPD patients when compared to control patients.(156) DVT, often preceding pulmonary embolism, was not associated with a substantially altered relative COPD risk when compared to the COPD-free comparison group in our study.

In absolute terms, cardiac arrhythmia was the most frequent cardiovascular outcome observed in our study population. COPD patients – both men and women - were slightly more likely to have an incident arrhythmia diagnosis recorded than patients without COPD.

Part of this association might be explained by a higher exposure to arrhythmogenic drugs such as beta agonists, a mainstay in COPD therapy,(145) and quinolone or macrolide antibiotics for bacterial infections.(146) Hypoxemia and hypercapnia in COPD patients may also contribute to an increased risk of cardiac arrhythmias as they increase the QTc dispersion (QTcD).(158) The authors of a Danish study focussed on atrial fibrillation among COPD patients and observed an increased risk associated with reduced lung function during a five-year follow-up.(159) Previously reported baseline prevalences of arrhythmia in COPD vary; Sidney et al. (157) reported that 4.7 % of COPD patients had atrial fibrillation and 2.7% other arrhythmias, while a study in American Veterans found a prevalence of arrhythmias of 14.2%.(129) A comparison of the prevalence of arrhythmias in a Canadian study found an OR of 1.76 (95% CI 1.64-1.89) when comparing COPD patients with COPD-free patients. This study did not exclude patients with a history of cardiovascular events, but the authors adjusted the analysis for cardiovascular co-morbidities.(156) The authors of another observational study stratified by COPD severity and reported relative risk estimates associated with various levels of COPD severity ranging from 0.92 (mild COPD) to 1.27 (severe COPD).(154)

We observed a rather strong association between severe COPD and the risk of developing an incident MI (OR 3.00, 95% CI 1.53-5.86], after adjusting for smoking, a common risk factor of COPD and MI. Persistent low-level systemic inflammation, reflected by increased levels of the C-reactive protein (CRP), is often present in patients with COPD,(141) and increased levels of CRP are associated with an increased MI risk. Several previous observational studies have reported an association between COPD and MI,(156, 157) while Engström et al. (160) did not detect an association between low FEV_1 and cardiac events, defined as fatal or non-fatal MI or death from chronic ischemic heart disease. The association between COPD and risk of MI was higher in women than in men, an observation which was also reported by Sydney et al..(157)

We found only a weak association between COPD and the risk of stroke / TIA with an OR of 1.13 (95% CI 0.92-1.38). While the crude incidence rates in men with or without COPD were

closely similar, COPD was associated with a 1.5-fold increased risk in women. Sidney et al. also reported a RR of 1.50 (95% CI 1.30-3.41) in women with COPD. (157) Truelsen et al. (161) explored the association between reduced lung function and the risk of stroke, resulting in ORs ranging between 1.00 and 1.38 for FEV_1 values below 80% when compared to FEV_1 values ≥100%. Hozawa et al. (162) did not find a significant association between airway obstruction and ischemic stroke. Engström et al. (160) did not observe a statistically significantly altered risk when they studied the association between low FEV_1 and stroke. Two other longitudinal studies found only weak associations between COPD and stroke.(156, 157) In COPD-free patients the 30-days mortality was greater in women than in men, a common observation which is often contributed to older age and more severe strokes in women.(163, 164) It is an interesting observation that the presence of COPD leads to similar rates of 30-days mortality in men and women, which needs to be further investigated in other studies. Whether the slightly different findings for MI and stroke / TIA incidence in association with COPD indeed reflect a greater vulnerability of women, or whether this is due to residual confounding e.g. by smoking needs further investigation.

Several limitations of our study need to be addressed. As this study is based on data from the primary-care setting, there is a possibility that we might have missed some cases with COPD, especially patients with milder forms of COPD who have not yet been diagnosed. Thus, our results only apply to GP-diagnosed COPD diagnoses, and the same holds true for the cardiovascular outcomes. However, as most of the cardiovascular outcomes in this study represent acute and rather severe diseases, we can assume that few cases with an outcome of interest would have been missed. We decided a priori to analyze only the first cardiovascular event during follow-up; the various cardiovascular outcomes are highly related to each other and their treatment and management is similar, thus a first episode of a cardiovascular outcome materially alters the risk of developing a second. It would have been desirable to have (more) information on potential risk factors for the outcomes such as immobility, disease severity or socioeconomic status. We assessed COPD severity using medication as a proxy in the nested case-control analysis, and we stratified the analyses by

this parameter. However, we were not able to classify the large group of patients with moderate COPD (i.e. those with some pharmacological treatment) in more detail with these data. By matching cases and controls on practice, we controlled to some degree for socioeconomic status, as social deprivation shows a geographical pattern and therefore people from the same area are more likely to see the same GP. On the other hand, it is a strength of the this high-quality data source that it encompassed a large population with a considerably long follow-up of up to 10 years, and this database has already proven to be of high validity for studies of COPD and various cardiovascular outcomes. Another advantage of the GPRD, for example compared with other settings such as the study from the Kaiser Permanente Medical Care Program, is the availability of information on lifestyle factors, in this case particularly on smoking. Collecting information from different settings is important as the pattern and the impact of factors, such as smoking or the health care system, may vary.

4.4 COPD AND RISK OF REFLUX DISEASE OR PEPTIC ULCER

4.4.1 ABSTRACT

Peptic ulcer disease and gastro-oesophageal reflux disease (GORD) have been associated with chronic obstructive pulmonary disease (COPD). Many studies, especially on peptic ulcer are cross-sectional or were done back in the 1960s or 1970s. Our purpose was to learn more about GORD and peptic ulcer in relation to COPD during long-term follow-up in recent years. We conducted a case-control and a follow-up study using the UK-based General Practice Research Database to assess and compare the incidence of GORD and peptic ulcer in patients with COPD and in COPD-free patients during the period 1995-2005. We identified 35,772 patients with COPD and the same number of COPD-free patients. Incidence rates of GORD and peptic ulcer in COPD patients were 59.2 and 14.8 per 10,000 person years, respectively. Incidence rates of GORD were higher in women while incidence rates of peptic ulcer were higher in men. In patients with COPD the risk of GORD was (OR 1.19, 95% CI 1.00-1.40) and of peptic ulcer was (OR 1.24, 95% CI 0.92-1.66) compared to COPD-free patients. Current use of long-acting beta agonists was associated with a decreased risk of peptic ulcer (OR 0.38, 95% CI 0.16-0.93). The results provide further evidence that there is no materially increased risk for ulcer or GORD associated with COPD. The observed association between use of long-acting beta agonists and peptic ulcer needs further investigation.

4.4.2 INTRODUCTION

As indicated in the recent update of the GOLD definition,(27, 65) chronic obstructive pulmonary disease (COPD) has increasingly been recognized to have systemic involvement such as depression, cardiovascular diseases or weight loss.(65)

Gastro-oesophageal reflux disease (GORD) is a disease of considerable prevalence often seen in COPD patients, and it has been reported to be increasingly diagnosed in the past years.(165, 166) There are several hypotheses to explain the association between COPD and GORD, and it is important to distinguish between two temporally and thus causally differing approaches. According to approach one, GORD is a risk factor for developing COPD; GORD is thought to facilitate the development or exacerbation of COPD by irritation of the airways through microaspiration of gastric contents and/or by vagally mediated reflex bronchoconstriction.(167, 168) On the other hand, bronchial obstruction in asthma has been reported to affect lower oesophageal sphincter motility,(169) which may promote GORD, so COPD would be a risk factor for GORD.

Another explanation for a possible association between COPD and GORD focuses on smoking as a common risk factor for both diseases.(170) Smoking is thought to be the most important common factor for COPD and gastric or duodenal ulcer, as reported in the past.(123, 171, 172) Only few recent studies have investigated this association despite the fact that both diseases have seen opposing time trends;(173, 174) the incidence of gastrointestinal ulcers has been decreasing, while the burden of COPD has been projected to increase.(31, 175)

Proton pump inhibitors and histamine H_2 receptor antagonists and *Helicobacter pylori* eradication are the mainstay of ulcer and GORD therapy.(176) Another - so far only experimental - strategy, targets the beta adrenergic system. In the 1980s and 1990s there were some reports on the role of a novel type of beta receptor, the beta 3 receptor, in the regulation of gastric acid secretion. In the following, selective beta-3-agonists have been developed against gastric ulcers and shown promising results in rats (SR 58611A, ZD 7114,

CGP 12177A, CL 316243, BRL 37344). (177-179) Comparisons between selective beta 3 agonists and other beta agonists and studies prior to the development of selective beta 3 agonists, suggest that also beta 2 agonists and even the unselective agonist isoprenaline have protective effects against gastric ulcer.(180-182)

It was the goal of the current observational study to assess the incidence of new onset GORD and gastrointestinal ulcer disease in patients with COPD compared to patients without COPD stratified by gender, thereby focusing on COPD severity and treatment as a risk factor for these outcomes.

4.4.3 METHODS

For detailed information on the database and study design please refer to the general methods section here only the information on the exclusion criteria, case validation and statistical analyses are repeated.

Exclusion Criteria: For the analysis of GORD we excluded patients with a history of GORD, or gastric or duodenal ulcer; for the analysis of gastric or duodenal ulcer we excluded patients with a history of these ulcers prior to the COPD diagnosis date or prior to the corresponding date in the COPD-free group.

Case definition: We identified all patients with a first-time recorded diagnosis of GORD, or peptic ulcer based on computer-recorded codes. In a computer-aided algorithm we then excluded all patients who had been treated with proton pump inhibitors or H_2- antagonist prior to the COPD diagnosis to ensure that we included only incident GORD or ulcer cases. We also excluded patients who had no records of proton pump inhibitor use within one year after the GORD or ulcer diagnosis since proton pump inhibitors are recommended as a first-line treatment for GORD and gastrointestinal ulcer disease. (176)

Statistical Analyses: GORD analyses were adjusted for smoking status, BMI, systemic steroid use and NSAID use; further adjustment for COX-2 inhibitor use did not have a major

impact on the results. Peptic ulcer analyses were adjusted for smoking status, BMI, NSAID use, GORD and vitamin K antagonist use.

We assessed drug exposure prior to the index date for both cases and controls. We conducted conditional logistic regression analyses to compare the type of exposure (long-acting beta 2 agonists, short-acting beta 2 agonists or no exposure) and the timing of exposure (current, recent or past). Current users had a last prescription for a study drug recorded within 60 days, recent users between 60 and 364 days, and past users ≥ 365 days prior to the index date. We adjusted these analyses for body mass index (BMI) (15.0 -18.4, 18.5-24.9, 25-29.9, 30+ kg/m^2, unknown) smoking status (non, current, past, unknown), use of NSAIDs, vitamin K antagonists, xanthines, inhaled steroids, inhaled short-acting anticholinergics or tiotropium and for the presence of diagnosed GORD prior to the index date.

4.4.4 RESULTS

After excluding patients with prevalent GORD, ulcer, cancer, alcoholism, drug abuse or HIV, we identified among the remaining study population 961 patients who had a pharmacologically treated incident GORD-diagnosis and 247 patients who had a treated incident ulcer diagnosis of the stomach or duodenum. Fifty-five percent of the GORD patients were women and they were slightly younger at their diagnosis than men 65.7 ± 9.8 years compared to 67.1 ± 9.5 years. Characteristics of the GORD study population are displayed in Table 4.4.1. The proportion of women among patients with a peptic ulcer diagnosis was 43% and again women were slightly younger than men when they received their ulcer diagnosis, the mean ages were 69.9 ± 9.6 years and 71.8 ± 8.0 years, respectively. Women with COPD received their diagnosis at a younger age than women without COPD, 68.5 ± 9.5 years and 71.4±9.6 years respectively; in men the mean age was almost similar 72.1±7.6 years and 71.5±8.5 years, respectively. Characteristics of the peptic ulcer study population are displayed in Table 4.4.2.

TABLE 4.4.1 CHARACTERISTICS OF CASES WITH INCIDENT GORD AND THEIR CONTROLS

	MEN			WOMEN		
	Cases (%) n=433	**Controls (%) n=1608**	**OR (95% CI)**	**Cases (%) n=528**	**Controls (%) n=2020**	**OR (95% CI)**
Mean age (years) ± sd	67.1±9.5	66.9±9.3	--	65.7±9.8	65.7±9.7	--
BMI (kg/m^2)						
<17.5	2 (0.5)	14 (0.9)	0.52 (0.12-2.30)	6 (1.1)	42 (2.1)	0.50 (0.21-1.20)
17.5-24.9	134 (31.0)	485 (30.2)	1.00 (ref)	195 (36.9)	672 (33.3)	1.00 (ref)
25.0-29.9	156 (36.0)	555 (34.5)	1.03 (0.80-1.34)	155 (29.4)	606 (30.0)	0.88 (0.69-1.11)
≥30	69 (15.9)	272 (16.9)	0.93 (0.67-1.29)	103 (19.5)	395 (19.6)	0.89 (0.68-1.18)
unknown	72 (16.6)	282 (17.5)	0.92 (0.65-1.30)	69 (13.1)	305 (15.1)	0.74 (0.54-1.03)
Smoking status						
Non-smokers	145 (33.5)	496 (30.9)	1.00 (ref)	234 (44.3)	868 (43.0)	1.00 (ref)
Smokers	101(23.3)	430 (26.7)	0.81 (0.61-1.07)	119 (22.5)	531 (26.3)	0.83 (0.65-1.07)
Ex-smokers	163 (37.6)	542 (33.7)	1.07 (0.82-1.40)	146 (27.7)	468 (23.2)	1.18 (0.92-1.50)
unknown	24 (5.5)	140 (8.7)	0.54 (0.32-0.90)	29 (5.5)	153 (7.6)	0.61 (0.38-0.99)
Drug exposure						
NSAIDs	349 (80.6)	1218 (75.8)	1.33 (1.02-1.74)	439 (83.1)	1546 (76.5)	1.53 (1.19-1.98)
Vitamin K antagonists	29 (6.7)	125 (7.8)	0.84 (0.55-1.28)	13 (2.5)	72 (3.6)	0.67 (0.37-1.23)
Systemic steroids	199 (46.0)	617 (38.4)	1.38 (1.11-1.72)	271 (51.3)	843 (41.7)	1.50 (1.23-1.82)

Abbreviations: OR – odds ratio, CI – confidence interval, sd – standard deviation,

TABLE 4.4.2 CHARACTERISTICS OF CASES WITH INCIDENT PEPTIC ULCER AND THEIR CONTROLS

	MEN			WOMEN		
	Cases (%) n=140	**Controls (%) n=560**	**OR (95% CI)**	**Cases (%) n=107**	**Controls (%) n=428**	**OR (95% CI)**
Mean age (years) ± sd	71.8±8.0	71.5±7.8	--	69.9±9.6	69.7±9.4	--
BMI (kg/m^2)						
<17.5	5 (3.6)	12 (2.1)	1.67 (0.57-5.00)	6 (5.6)	15 (3.5)	2.09 (0.73-6.02)
17.5-24.9	41 (29.3)	169 (30.2)	1.00 (ref)	26 (24.3)	139 (32.5)	1.00 (ref)
25.0-29.9	56 (40.0)	197 (35.2)	1.15 (0.74-1.80)	38 (35.5)	119 (27.8)	1.71 (0.97-3.02)
≥30	19 (13.6)	93 (16.6)	0.84 (0.45-1.56)	18 (16.8)	82 (19.2)	1.20 (0.62-2.32)
unknown	19 (13.6)	89 (15.9)	0.87 (0.46-1.63)	19 (17.8)	73 (17.1)	1.39 (0.68-2.85)
Smoking status						
Non-smokers	50 (35.7)	191 (34.1)	1.00 (ref)	37 (34.6)	195 (45.6)	1.00 (ref)
Smokers	40 (28.6)	109 (19.5)	1.41 (0.87-2.29)	38 (35.5)	107 (25.0)	1.94 (1.14-3.30)
Ex-smokers	44 (31.4)	223 (39.8)	0.73 (0.46-1.18)	27 (25.2)	87 (20.3)	1.61 (0.91-2.84)
unknown	6 (4.3)	37 (6.6)	0.55 (0.20-1.53)	5 (4.7)	39 (9.1)	0.34 (0.07-1.58)
GORD	16 (11.4)	50 (8.9)	1.34 (0.72-2.47)	12 (11.2)	52 (12.2)	0.90 (0.45-1.83)
Drug exposure						
NSAIDs	113 (80.7)	424 (75.7)	1.38 (0.58-2.23)	88 (82.2)	331 (77.3)	1.39 (0.79-2.44)
Vitamin K antagonists	10 (7.1)	44 (7.9)	0.90 (0.44-1.84)	11 (10.3)	22 (5.1)	2.19 (1.00-4.80)
Systemic steroids	54 (38.6)	235 (42.0)	0.87 (0.59-1.27)	51 (47.7)	193 (45.1)	1.12 (0.72-1.74)

Abbreviations: OR – odds ratio, CI – confidence interval, sd – standard deviation,

Incidence rates of GORD and ulcer were higher among COPD patients (59.2 and 14.8 per 10,000 py, respectively) than among patients in the COPD-free comparison group (44.4 and 10.8 per 10,000 py, respectively). Incidence rates of GORD were higher in women compared to men in COPD and COPD-free patients while incidence rates of peptic ulcer were higher for men. The IRs and IRRs for the two outcomes of interest, stratified by sex, are displayed in Table 4.4.3.

TABLE 4.4.3 INCIDENCE RATES OF GORD AND PEPTIC ULCER IN COPD AND COPD-FREE PATIENTS

	Cases	Person-time (years)	IR per 10,000 py (95% CI)	IRR IRR 95% CI
GORD				
COPD-free	**450**	**101361.7**	**44.4 (40.5-48.7)**	
Men	195	50697.5	38.5 (33.4-44.2)	0.77 (0.64-0.92)
Women	255	50664.2	50.3 (44.5-56.9)	1.00 (ref)
COPD	**511**	**86305.9**	**59.2 (54.3-64.6)**	
Men	238	42795.5	55.6 (49.0-63.1)	0.89 (0.75-1.05)
Women	273	43510.4	62.7 (55.8-70.6)	1.00 (ref)
ULCER				
No COPD	**114**	**105781.0**	**10.8 (9.0-12.9)**	
Men	63	51251.6	12.3 (9.6-15.7)	1.31 (0.91-1.90)
Women	51	54529.4	9.4 (7.1-12.3)	1.00 (ref)
COPD	**133**	**89946.2**	**14.8 (12.5-17.5)**	
Men	77	43159.0	17.8 (14.3-22.3)	1.49 (1.06-2.09)
Women	56	46787.1	12.0 (9.2-15.5)	1.00 (ref)

Abbreviations: IR: incidence rate, CI: confidence interval; py: person years

In order to evaluate the effects of COPD severity on the study outcomes we conducted a nested case-control analysis where we stratified COPD patients according to treatment into mild, moderate or severe COPD. Differences in the risk of developing GORD or ulcer in relation to COPD severity were small. The relative risk of developing GORD was not

materially altered in women with COPD compared to women without COPD and did not show a significant association with COPD severity. In men the GORD risk was highest in patients with mild COPD. The peptic ulcer risk was statistically significantly increased in male patients with moderate COPD while in female patients there was a tendency towards an increased risk in severe COPD although it was not statistically significant and based on only 6 women. The detailed findings for the various associations between COPD and gastrointestinal outcomes, stratified by COPD severity, are displayed in Table 4.4.4.

In order to evaluate the effects of beta agonists on the risk of peptic ulcer we compared COPD patients using beta agonist with patients not using them. In total 125 COPD patients used long-acting beta 2 agonists and 21 of them developed an ulcer yielding a crude risk estimate of 0.62 (95% CI 0.37-1.05). Risks in men and women were closely similar. Stratified by the timing of long-acting beta agonist exposure we found a protective association between current exposure within the last 60 days and the risk of an ulcer diagnosis of 0.38 (0.16-0.93), again the risk estimates in men and women were closely similar but the stratified analysis was not statistically significant. Current exposure to short-acting beta agonists was not associated with a protective effect. The detailed findings stratified by gender and timing of exposure are displayed in Table 4.4.5.

TABLE 4.4.4 RISK OF GORD AND PEPTIC ULCER STRATIFIED BY COPD SEVERITY IN MEN AND WOMEN

	GORD				Ulcer disease			
	Cases	Controls	Crude OR (95% CI)	Adj. * OR (95% CI)	Cases	Controls	Crude OR (95% CI)	Adj. * OR (95% CI)
No COPD	**450**	**1931**	**1.00 (ref)**	**1.00 (ref)**	**114**	**533**	**1.00 (ref)**	**1.00 (ref)**
Men	195	833	1.00 (ref)	1.00 (ref)	63	301	1.00 (ref)	1.00 (ref)
Women	255	1098	1.00 (ref)	1.00 (ref)	51	232	1.00 (ref)	1.00 (ref)
Any COPD	**511**	**1697**	**1.27 (1.11-1.46)**	**1.19 (1.00-1.40)**	**133**	**455**	**1.34 (1.02-1.76)**	**1.24 (0.92-1.66)**
Men	238	775	1.29 (1.05-1.59)	1.29 (1.00-1.67)	77	259	1.38 (0.97-1.97)	1.41 (0.96-2.07)
Women	273	922	1.26 (1.05-1.52)	1.14 (0.90-1.43)	56	196	1.28 (0.85-1.94)	1.01 (0.63-1.62)
Mild	**41**	**116**	**1.52 (1.05-2.21)**	**1.66 (1.13-2.44)**	**8**	**41**	**0.89 (0.41-1.94)**	**0.82 (0.37-1.83)**
Men	26	56	2.01 (1.23-3.28)	2.25 (1.35-3.77)	6	27	1.04 (0.42-2.62)	0.99 (0.38-2.58)
Women	15	60	1.07 (0.60-1.92)	1.16 (0.64-2.11)	2	14	0.64 (0.14-2.83)	0.44 (0.09-2.16)
Moderate	**453**	**1528**	**1.25 (1.09-1.45)**	**1.14 (0.95-1.35)**	**119**	**397**	**1.37 (1.04-1.82)**	**1.26 (0.93-1.71)**
Men	205	695	1.24 (1.00-1.54)	1.20 (0.92-1.56)	68	218	1.45 (1.00-2.11)	1.84 (1.18-2.87)
Women	248	833	1.27 (1.05-1.54)	1.13 (0.89-1.43)	51	179	1.28 (0.84-1.96)	1.07 (0.62-1.86)
Severe	**17**	**53**	**1.36 (0.78-2.37)**	**1.22 (0.68-2.18)**	**6**	**17**	**1.62 (0.61-4.32)**	**1.66 (0.60-4.61)**
Men	7	24	1.25 (0.53-2.96)	1.17 (0.48-2.86)	3	14	0.96 (0.26-3.56)	1.57 (0.39-6.40)
Women	10	29	1.45 (0.70-3.01)	1.40 (0.64-3.03)	3	3	4.41 (0.88-22.10)	3.78 (0.61-23.40)

* GORD analyses are adjusted for smoking status, BMI, systemic steroid use and NSAID use; further adjustment for cox-2 inhibitor use did not have a major impact on the results; ulcer analyses are adjusted for smoking status, BMI, NSAID use, GORD, vitamin K antagonist use; Adj.: adjusted; CI: confidence interval; OR: odds ratio; ref: reference

TABLE 4.4.5 USE OF BETA AGONISTS AND THE RISK OF PEPTIC ULCER IN MEN AND WOMEN

	Cases #	Controls #	Crude OR (95% CI)	Adj. OR (95% CI)	P-value
Controls					
all	**114**	**533**	**0.54 (0.35-0.83)**	**0.58 (0.37-0.91)**	**0.02**
Men	63	301	0.45 (0.27-0.77)	0.48 (0.27-0.83)	0.01
Women	51	232	0.75 (0.35-1.61)	0.85 (0.37-1.95)	0.69
Long-acting beta agonists					
unexposed	**112**	**351**	**1.00 (ref)**	**1.00 (ref)**	**--**
Men	64	194	1.00 (ref)	1.00 (ref)	--
Women	48	157	1.00 (ref)	1.00 (ref)	--
<60 days	**7**	**54**	**0.41 (0.17-0.97)**	**0.38 (0.16-0.93)**	**0.03**
Men	3	32	0.35 (0.10-1.27)	0.33 (0.09-1.25)	0.10
Women	4	22	0.51 (0.16-1.69)	0.39 (0.11-1.46)	0.16
60-364 days	**9**	**23**	**1.35 (0.59-3.12)**	**1.35 (0.57-3.18)**	**0.50**
Men	6	16	1.26 (0.42-3.80)	1.40 (0.45-4.38)	0.57
Women	3	7	1.45 (0.33-6.35)	1.42 (0.28-7.37)	0.67
≥ 1 year	**5**	**27**	**0.59 (0.21-1.70)**	**0.63 (0.21-1.87)**	**0.40**
Men	4	17	0.94 (0.26-3.39)	1.11 (0.30-4.18)	0.87
Women	1	10	0.22 (0.02-2.11)	0.20 (0.02-1.94)	0.16
Short-acting beta agonists					
unexposed	**43**	**112**	**1.00 (ref)**	**1.00 (ref)**	**--**
Men	31	74	1.00 (ref)	1.00 (ref)	--
Women	12	38	1.00 (ref)	1.00 (ref)	--
<60 days	**52**	**193**	**0.85 (0.47-1.55)**	**0.82 (0.44-1.52)**	**0.52**
Men	25	106	0.87 (0.39-1.94)	0.91 (0.40-2.11)	0.83
Women	27	87	1.06 (0.39-2.87)	0.96 (0.33-2.77)	0.94
60-364 days	**21**	**78**	**0.68 (0.34-1.36)**	**0.65 (0.32-1.34)**	**0.25**
Men	12	35	0.88 (0.36-2.11)	0.97 (0.39-2.43)	0.94
Women	9	43	0.56 (0.17-1.84)	0.54 (0.15-1.92)	0.34
≥ 1 year	**17**	**72**	**0.61 (0.30-1.25)**	**0.58 (0.28-1.22)**	**0.15**
Men	9	44	0.52 (0.20-1.33)	0.49 (0.18-1.32)	0.16
Women	8	28	0.73 (0.23-2.32)	0.68 (0.20-2.34)	0.54

Crude ORs are adjusted for all variables in the table, short-acting anticholinergics, tiotropium, xanthines and inhaled steroids use. Adj ORs are in addition adjusted for all variables in the table and BMI, smoking status, NSAID use, GORD and vitamin K antagonist use.

4.4.5 DISCUSSION

The GORD incidence rates we found are similar to incidence rates reported in two other studies investigating the frequency of GORD in the general population.(183, 184) Our GORD incidence in the COPD population, however, is lower than recently reported by Garcia Rodriguez et al.. Different case definitions might explain this difference, for example, we excluded patients with a history of PPI or histamine 2 receptor antagonists use.(185) We did not observe an increasing risk of GORD with increasing COPD severity, which is in contrast to previous reports of a higher risk of reflux oesophagitis among patients with severe COPD and a higher GORD prevalence in more severe COPD.(186-189) Ruigomez et al., who investigated the natural history of GORD, also reported that COPD was only weakly associated with GORD (OR: 1.3 [1.0-1.8] 95% CI), which is similar to our results.(183) They also found slightly higher incidence rates in women than in men in COPD patients. Other settings not restricted to COPD reported inconclusive results with respect to gender differences.(190, 191)

There was only a weak association between COPD and ulcer disease, a smaller association than was reported in studies analysing the association between ulcer and COPD back in the 1960s and 1970s. Most of these studies investigated the association between 'emphysema' and ulcer, and it was hypothesized that pulmonary emphysema may change the 'blood acid balance', thereby increasing the 'acid attack factors' and causing peptic ulceration.(171, 172) Since then, a decrease in peptic and duodenal ulcer cases was observed (175, 192). Currently, *Helicobacter pylori* infection, NSAID use and tobacco smoking are thought to be the main risk factors for ulcer.(123, 176) Only a few recent studies investigated the association between COPD and ulcer. A Danish study assessed the association between COPD and 30-day mortality of severe peptic ulcer (i.e. hospitalization-requiring perforated or bleeding ulcers) and reported that COPD was associated with less favourable outcomes.(173) A recent, cross-sectional, American study based on self-reported data

reported a crude increased risk of GI ulcer disease in patients with COPD compared to COPD-free patients (OR: 2.34 [2.21-2.47] 95% CI).(174)

We found an incidence rate of ulcer disease of 14.8 / 10,000 person-years (py) among COPD patients, which was slightly higher than the 10.8 / 10,000 py among COPD-free patients. Incidence rates in men were slightly higher than incidence rates in women in both patients with and patients without COPD. Male sex has also before been reported to be a risk factor for peptic ulcer.(193) Kang et al. analysed the period prevalence of peptic ulceration in England and Wales between 1994 and 1998 and reported falling age-standardized rates from 3.3 and 1.8 / 1000 male or female patients, respectively, in 1994 to 1.5 and 0.9 / 1000 in male and female patients, respectively, in 1998.(175) In Belgium, incidence rates of duodenal and gastric ulcer were also reported to be decreasing between 1994 and 2003; the age-standardized rates for gastric ulcer decreased from 2.22 (1.94-2.50) in 1994/95 to 0.85 (0.70-1.00) in 2002/03 (per 1000 patient years), and rates for duodenal ulcer decreased from 1.75 (1.50-2.00) to 1.01 (0.84-1.18) (per 1000 patient years) in the same period.(192) Women, however, seem to be slightly younger at their first peptic ulcer diagnosis than men.

Current exposure to long-acting beta agonists was associated with a decreased risk of an ulcer diagnosis (OR 0.38, 95% CI 0.16-0.93) with similar results in men and women while current short-acting beta agonist exposure was not associated with the risk of an ulcer diagnosis. Animal studies suggested that the beta adrenergic system might be involved in the control of gastric acid secretion. The receptor involved is, however, not a beta 2 adrenergic receptor but a beta 3 adrenergic receptor. Selective agonists of beta 3 receptor have shown promising effects in animal studies of gastric ulcer.(177-179) Beta 2 agonists have also proven some protective effects in rats and cats. In a study in cats clenbuterol, a beta 2 agonist, and SR58611A have been compared, both had gastro-protective effects but the effects of clenbuterol could be prevented by the addition of propanolol, a beta blocker.(180) Animal studies in rats showed that terbutaline, a beta 2 agonist, reduced indomethacin-induced gastric ulceration.(182) Salbutamol has also been reported to confer

protective effects.(181) To our knowledge this is the first study showing this effect in humans. Why this effect is only observed with long-acting beta agonists is not clear but might be explained by the longer half life. The analysed study population, however, is small and thus the results need to be interpreted with caution. Further research is needed to evaluate whether beta 2 agonist indeed have a protective effect in humans.

We adjusted all analyses on the risk of developing GORD or ulcer for the potential confounders smoking and NSAID use. We accounted for the possible role of alcohol abuse by excluding patients with known alcoholism from the analysis. We also tried to adjust for *Helicobacter pylori* infections but had only limited information so that we could not include this factor in the analyses. Despite these efforts we cannot fully exclude residual confounding by smoking, *Helicobacter pylori* infection and/or drinking when reporting the results for the analyses on COPD and ulcer risk.

It is both a strength and a limitation of the current study that diagnoses were based on GP-recorded diagnoses. It is a strength because all diagnoses in the GPRD are recorded on a routine basis and independently from any study hypothesis, which is superior to interview-based assessments of diagnoses with a particular study hypothesis in mind. On the other hand, we cannot rule out a certain amount of misclassification for both COPD and the gastrointestinal outcomes of interest. Some diagnoses may have been missed due to underreporting of symptoms to the GP (e.g. for mild forms of COPD), or because patients may have treated themselves (e.g. antacids for GORD, which are available over the counter). Thus, reported incidence rates for these outcomes might be underestimated to some degree. This might also affect the comparison of incidence rates between men and women if there is a difference in reporting symptoms to their GP. Other diagnoses may be slightly overrepresented in COPD patients, for example because COPD patients may have a higher likelihood of getting a diagnosis recorded because they may see the GP more often. Thus, these results represent incidence rates of GP-recorded GORD in ulcer in the UK primary-care setting based on a large, well validated database which has been used for previous published studies on COPD, ulcer and GORD.(84, 175, 183)

4.5 CANCER RISK IN PATIENTS WITH COPD

4.5.1 ABSTRACT

The aim of this study was to compare the risk of developing cancer between patients with or without COPD, and to assess the role of gender on the risk of developing lung cancer in COPD patients. We used the UK-based General Practice Research Database to conduct a follow-up study with a nested case-control analysis. We identified all patients with an incident COPD diagnosis aged 40-79 years between 1995 and 2005 and a matched COPD-free comparison group. We then identified all patients who received an incident cancer diagnosis during follow-up. Among 35,772 COPD patients and 35,772 COPD-free patients, we identified 4506 patients with an incident cancer diagnosis, of whom 2585 (57.4%) had a previous COPD diagnosis, yielding a crude incidence rate ratio of 1.64 (95% CI 1.55-1.74). The increased risk was mainly driven by a high lung cancer risk among COPD patients. In the nested case-control analysis, the odds ratio (OR) for lung cancer associated with COPD was higher for women (OR 5.26, 95% CI 3.64-7.61) than for men (OR 2.10, 95% CI 1.70-2.60). Our findings provide further evidence that COPD is associated with an elevated lung cancer risk, and that women with COPD may be more susceptible to developing lung cancer than men.

4.5.1 INTRODUCTION

According to the 'Global Initiative for Obstructive Lung Diseases' (GOLD), chronic obstructive pulmonary disease (COPD) is associated with an abnormal inflammatory response of the lungs which is accompanied by a not fully reversible airflow limitation.(27) The pronounced chronic inflammatory process is thought to increase the risk for lung cancer due to constant tissue damage and exposure to substances with mutagenic potential such as reactive oxygen species.(194, 195) For other organ systems, similar associations between chronic inflammation and cancer have been discussed, such as inflammatory bowel disease (IBD) and colon cancer,(196) chronic hepatitis and liver cancer,(197) or human papilloma virus (HPV-16 and HPV-18) infection and anogenital carcinoma.(198) Asthma is another major obstructive lung disease with substantial inflammation; although studies on the association between asthma and lung cancer reported conflicting results, pooled estimates did not provide evidence for an association between asthma and an increased cancer risk.(199-201)

Previous studies on the association between COPD and cancer risk mainly focused on lung cancer, suggesting that COPD increases the risk for lung cancer materially.(202, 203) COPD patients and lung cancer patients share an important risk factor, which is smoking. Men have been reported to have higher COPD rates than females, which may be attributed to higher smoking rates in males compared to females in the past, but smoking rates as well as COPD rates in females have been reported to rise.(84) In addition, studies indicated that female smokers might be more susceptible to developing COPD than male smokers, as women with COPD tended to suffer from a greater reduction in FEV_1.(99)

In this study we explored the association between COPD and the risk of developing cancer stratified in men and women.

4.5.3 METHODS

For detailed information on the database and study design please refer to the general methods section here only the information on the exclusion criteria, case validation and statistical analyses are repeated.

Exclusion Criteria: All patients with a history of cancer except for non-melanoma skin cancer were excluded.

Case definition: All patients with a code for cancer were identified.

Statistical Analyses: We provided the risks estimates stratified for different cancer sites and adjusted for patient characteristics such as body mass index (BMI (<18.5, 18.5-25, 25-29.9, 30-60 kg/m^2, or unknown), smoking history (no, current, past, unknown), as well as for various cancer type specific confounders (breast cancer: contraceptive use, hormone replacement therapy use, benign neoplasms, non-melanoma skin cancer, and NSAID use; lymphoma: benign neoplasms, use of carcinogenic drugs; gastro-oesophageal cancer: gastro-oesophageal reflux disease, benign neoplasms, non-melanoma skin cancer; colorectal cancer: NSAID use, constipation, benign neoplasms, non-melanoma skin cancer; female reproductive system cancer: contraceptive use, hormone replacement therapy use, benign neoplasm, non-melanoma skin cancer, NSAID use; urinary system cancers: hypertension, benign neoplasms, use of diuretics, use of carcinogenic drugs, urinary dysfunction).

4.5.4 RESULTS

Within the study population, we identified a total of 4506 cancer cases during follow-up, 2585 among the COPD patients and 1921 among the COPD-free patients. The incidence rates (IR) were 27.8 / 1000 person-years (py) among COPD-patients, and 16.8 / 1000 py among COPD-free patients. IR were higher among men than among women, but the incidence rate ratio (IRR) associated with COPD was slightly higher in females than in males. The cancer IR increased with age. Details on cancer IRs are displayed in Table 4.5.1.

TABLE 4.5.1 INCIDENCE RATES OF CANCER IN COPD AND COPD-FREE PATIENTS

	Cases	Person-time (years)	IR per 1000 py (95% CI)	IRR (95% CI)
COPD-free	**1921**	**114441.4**	**16.8 (16.1 – 17.5)**	
Men	1207	56919.3	21.2 (20.1 – 22.4)	1.00 (ref)
Women	714	57522.1	12.4 (11.5 – 13.4)	1.69 (1.55-1.85)
COPD	**2585**	**92923.9**	**27.8 (26.8 – 28.9)**	
Men	1526	45642.3	33.4 (31.8 – 35.1)	1.00 (ref)
Women	1059	47281.7	22.4 (21.1 – 23.8)	1.48 (1.37-1.59)

IR: incidence rate; IRR: incidence rate ratio; CI: confidence interval; py: person years

In the nested case-control analysis we explored the association between a history of COPD and the risk of developing various types of cancer, stratified by gender. The results are displayed in Tables 4.5.2 and 4.5.3. The relative risk was highest for developing lung cancer and it was particularly high in women; OR 5.26 (95% CI 3.64-7.61), compared to men: OR 2.10 (95% CI 1.70-2.60) (P<0.001). The risks were highest in patients with severe COPD receiving oxygen therapy OR 4.96 (95% CI 3.05-8.07) in men and OR 7.54 (95% CI 3.78-15.05) in women. The risk of developing urinary / kidney cancer (in both men and women) was also increased, while the relative risk of developing one of the other cancer types was not or only marginally altered in association with a previous COPD diagnosis.

To further analyze the association between COPD and lung cancer we did an analysis stratified by smoking status. The presence of COPD increased the risk of being diagnosed with lung cancer in non-smokers OR 4.21 (95% CI 2.65-6.69), OR 9.45, (95% CI 3.87-23.07) in women compared to 3.00 (95% CI 1.71-5.24) in men. The results of this analysis stratified by gender are provided in detail in Table 4.5.4.

TABLE 4.5.2 CANCER RISK IN MEN STRATIFIED BY CANCER LOCALIZATION

	Cases (N=1643)	Controls (N=6572)	OR (95% CI)	Adj. OR (95% CI)
Gastro-oesophageal cancers				
No COPD	63	264	1.00 (ref)	1.00 (ref)
COPD	58	220	1.09 (0.75-1.60)	1.03 (0.69-1.54)
Intestinal cancers				
No COPD	90	390	1.00 (ref)	1.00 (ref)
COPD	93	342	1.17 (0.85-1.60)	1.24 (0.88-1.74)
Lymphoma				
No COPD	34	137	1.00 (ref)	1.00 (ref)
COPD	38	151	1.01 (0.61-1.68)	1.01 (0.61-1.68)
Male genital cancers				
No COPD	270	1066	1.00 (ref)	1.00 (ref)
COPD	231	938	0.97 (0.81-1.18)	1.01 (0.83-1.24)
Urinary / Kidney cancers				
No COPD	95	444	1.00 (ref)	1.00 (ref)
COPD	121	420	1.34 (0.99-1.80)	1.08 (0.75-1.57)
Lung cancer				
No COPD	146	1172	1.00 (ref)	1.00 (ref)
COPD	404	1028	2.93 (2.40-3.59)	2.10 (1.70-2.60)

Abbreviations: OR – odds ratio, CI – confidence interval, OR adjusted for potential confounders as stated in the methods.

TABLE 4.5.3 CANCER RISK IN WOMEN STRATIFIED BY CANCER LOCALIZATION

	Cases (N=1007)	Controls (N=4028)	OR (95% CI)	Adj. OR (95% CI)
Gastro-oesophageal cancers				
No COPD	19	93	1.00 (ref)	1.00 (ref)
COPD	26	87	1.44 (0.75-2.76)	0.92 (0.43-1.98)
Intestinal cancers				
No COPD	51	233	1.00 (ref)	1.00 (ref)
COPD	63	223	1.28 (0.85-1.91)	1.14 (0.73-1.77)
Lymphoma				
No COPD	24	89	1.00 (ref)	1.00 (ref)
COPD	18	79	0.86 (0.45-1.65)	0.86 (0.45-1.65)
Breast cancer				
No COPD	170	687	1.00 (ref)	1.00 (ref)
COPD	167	661	1.02 (0.81-1.28)	1.06 (0.82-1.38)
Female genital cancers				
No COPD	53	184	1.00 (ref)	1.00 (ref)
COPD	35	168	0.74 (0.47-1.17)	0.82 (0.48-1.37)
Urinary / Kidney cancers				
No COPD	22	125	1.00 (ref)	1.00 (ref)
COPD	38	115	1.86 (1.04-3.33)	1.88 (0.83-4.27)
Lung cancer				
No COPD	41	733	1.00 (ref)	1.00 (ref)
COPD	280	551	8.35 (5.90-11.8)	5.26 (3.64-7.61)

Abbreviations: OR – odds ratio, CI – confidence interval, OR adjusted for potential confounders as stated in the methods.

TABLE 4.5.4 LUNG CANCER RISK STRATIFIED BY SMOKING STATUS

	Cases	Controls	Crude OR (95% CI)	Adj. OR (95% CI)
No COPD				
Non-smoker	**32**	**959**	**1.00 (ref)**	**1.00 (ref)**
Men	25	525	1.00 (ref)	1.00 (ref)
Women	7	434	1.00 (ref)	1.00 (ref)
Current Smoker	**85**	**281**	**9.23 (6.00-14.21)**	**9.04 (5.87-13.94)**
Men	62	187	7.27 (4.42-11.95)	7.02 (4.26-11.58)
Women	23	94	15.03 (6.17-36.61)	15.69 (6.40-38.47)
Ex-smoker	**60**	**446**	**3.99 (2.55-6.24)**	**4.13 (2.63-6.46)**
Men	54	326	3.48 (2.12-5.73)	3.59 (2.18-5.92)
Women	6	120	2.72 (0.89-8.32)	2.94 (0.97-8.95)
COPD				
Non-smoker	**52**	**339**	**4.26 (2.69-6.76)**	**4.21 (2.65-6.69)**
Men	30	195	3.02 (1.735.27)	2.99 (1.71-5.24)
Women	22	144	9.18 (3.79-22.25)	9.45 (3.87-23.07)
Current Smoker	**337**	**545**	**17.19 (11.77-25.09)**	**16.25 (11.10-23.78)**
Men	186	325	11.37 (7.32-17.65)	10.59 (6.79-16.50)
Women	151	220	40.61 (18.46-89.35	40.61 (18.30-90.10)
Ex-smoker	**248**	**581**	**11.48 (7.81-16.86)**	**11.62 (7.90-17.09)**
Men	158	438	6.96 (4.48-10.80)	6.95 (4.47-10.81)
Women	90	143	35.52 (18.80-79.84)	39.50 (17.78-89

Abbreviations: OR – odds ratio, CI – confidence interval, OR adjusted for BMI and all variables in the table.

4.5.5 DISCUSSION

In this large population-based study, the overall cancer risk was increased in COPD patients as compared to COPD-free patients. This increased risk was mainly driven by the increased lung cancer risk. There was also a suggestion of an increased cancer risk for cancers of the urinary and the gastrointestinal tract, but after adjusting for smoking and other covariates the risk estimates no longer reached statistical significance. Smoking is the most important risk factor for both COPD and lung cancer, and it is likely that most of the observed lung cancer risk is due to smoking. However, stratification by smoking status showed that COPD

increased the risk in non-smokers, when comparing non-smoking COPD patients with non-smoking patients without COPD, which indicates an independent contribution of COPD on the lung cancer risk. This proposition is consistent with findings from previous studies reporting risk estimates ranging from 1.5 to 2.7 for various levels of COPD severity.(202, 203) Nevertheless our results can still be biased by residual confounding, for example, driven by a potential misclassification of tobacco exposure, i.e. a patient being recorded as non-smoker although he or she is an ex-smoker.

Overall the distribution of various cancer types in the current study population reflects what is known from cancer statistics: in men, lung cancer and cancer of the reproductive system (mainly prostate cancer) are the most frequent cancer types, followed by colorectal cancer; in women, lung, breast and colorectal cancer are the most common malignancies. We observed higher relative lung cancer risk estimates associated with a history of COPD for women than for men; whether this finding points towards a greater susceptibility for women, or whether it is due to other factors needs to be further explored.

An important limitation of this study is the limited follow-up time between the first COPD diagnosis and the incident cancer diagnosis. Both COPD and cancer are chronic diseases, which develop and are present for some time before first symptoms become clinically manifest. Thus, we may have missed a certain proportion of patients with mild COPD who had not yet been diagnosed by the GP. Further, the proportion of patients with severe COPD may be small due to limited follow-up. Thus, the current study population may reflect a patient population with a relatively high proportion of moderate COPD. In addition it would have been desirable to have more information on potential risk factors or protective factors for certain cancers, such as former use of oral contraceptives or human papilloma virus infections. We assessed OC use prior to the index date for women in the nested case-control analysis and adjusted the analyses for this parameter, but for elderly women the likelihood of having previous OC use recorded on computer was of course low. By matching cancer cases and controls on practice, we made an attempt to take socioeconomic status into account to

some degree, as social deprivation shows a geographical pattern and therefore people from the same neighbourhood are more likely to see the same GP.

A strength of this study is that the GPRD is a well-validated data source with a high validity of recorded drug exposure. In addition, all drug use was recorded prior to these analyses and in the absence of any study hypothesis. Further we classified drug use in all patients (i.e. cases or controls, or patients with or without COPD) in the same way, so that any exposure misclassification should be non-differentially distributed across users of various COPD medications.

In summary, this observational study provides further evidence that COPD is only marginally or not at all associated with most cancers except lung cancer. The risk of developing lung cancer is substantially increased for COPD patients, which can be in part explained by smoking as major common underlying risk factor, but an independent association between chronic lung inflammation due to COPD and an increased cancer risk beyond the effect of smoking is also possible. In our study population, the risk of developing lung cancer in association with COPD was higher in women than in men.

4.6 COPD AND RISK OF DEPRESSION

4.6.1 ABSTRACT

Chronic co-morbidities are often associated with depression. Most previous studies exploring the association between COPD and depression were rather small and based on a cross-sectional study design. We conducted a large population-based study on the risk of developing an incident depression diagnosis in association with a previous COPD diagnosis.

We used the UK-based General Practice Research Database to assess and compare the prevalence of a history of depression, and to quantify the risk of developing incident depression in patients with COPD and COPD-free patients between 1995 and 2005. We conducted a nested case-control analysis, matching up to four patients who did not develop depression for each case patient with depression, to further analyze the impact of COPD severity. In a study population of 35,722 COPD patients and 35,722 COPD-free patients, the prevalence of diagnosed depression prior to the first COPD diagnosis was higher in the COPD population (23.1%) than among COPD-free patients (16.8%). The incidence rate of a new onset diagnosis of depression after the first COPD diagnosis was 16.2 / 1000 person-years (py) in the COPD group, while it was only 9.4 / 1000 py in the COPD-free comparison group. In the nested case-control analysis, patients with severe COPD had the highest risk of developing depression (OR 2.01, 95% CI 1.45-2.78). This large observational study provides further evidence that patients with COPD are at an increased risk of developing depression.

4.6.2 INTRODUCTION

Depression is an important public health problem worldwide.(204) The disease is often associated with chronic co-morbidities, which is of particular and increasing relevance in an ageing polymorbid society.(205) Chronic obstructive pulmonary disease (COPD) has a high prevalence in the elderly, and the burden of disease is expected to increase.(31)

Observational studies investigating the association between COPD and depression reported a wide range of depression prevalences in COPD patients from 7% with a forced expiratory volume in 1 second (FEV_1) <80%, up to 79.1% in COPD patients with chronic respiratory failure.(206, 207) The cumulative incidence has recently been reported to be 6.1%.(126) The risk of depression seems to be associated with COPD severity,(208, 209) but the wide range of depression prevalence reported in previous studies may also be related to differences in disease definitions and inclusion criteria. Methods used to define depression ranged from self-reports to diagnoses made by general practitioners (GPs) to diagnoses made by psychiatrists after detailed assessments, and the case classification was based on various coding systems such as ICD-10, DSM-III or Beck Depression Inventory.(207)

Depression has been associated with adverse health outcomes and increased mortality,(210) though not all studies have found such an association.(210, 211) Authors of previous studies which reported an increased mortality suggested that suicide may account in part for the increased mortality among depressive patients.(212) The assessment of the impact of depression in COPD is complicated by a two-sided association; depression is thought to contribute indirectly to the development of COPD as depressed people are less likely to quit smoking, but depression can also develop as a direct or indirect consequence of a COPD diagnosis.(124)

Most previous studies investigating the association between COPD and depression were rather small and/or based on a cross-sectional design.(207, 213) We conducted a large observational study using data from a primary-care setting in the UK to quantify the prevalence of depression in COPD patients at the time of the first COPD diagnosis and to

compare this prevalence to a COPD-free population, and to assess the incidence rate of newly diagnosed depression among COPD-patients and among a COPD-free comparison group.

4.6.3 METHODS

For detailed information on the database and study design please refer to the general methods section here only the information on the exclusion criteria, case validation and statistical analyses are repeated.

Exclusion Criteria: All patients with a diagnosis of depression or suicidal ideation prior to the start of follow-up (i.e. the date of the first COPD diagnosis or the corresponding date in the controls) were excluded.

Case definition: All patients with a recorded depression were identified. For a sensitivity analysis we identified patients with a recorded depression, who received at least 1 prescription for selective serotonin reuptake inhibitors (SSRI), monoamine reuptake inhibitors (MNRI), monoaminooxidase A inhibitors (MAOA) or other antidepressive drugs within half a year around the depression diagnosis and who did not have prescriptions for the above mentioned drugs prior to the COPD index date.

Statistical Analyses: Depression analyses were adjusted for smoking status, BMI, serious infections, sleeping disorders and cardiovascular diseases (deep vein thrombosis, pulmonary embolism, ischemic heart disease, or stroke / TIA). In addition to analyzing all cases with an incident diagnosis of depression, we also conducted sensitivity analyses in which we only included cases with an incident depression diagnosis followed by specific pharmacological treatment, i.e. those who received at least one prescription for selective serotonin reuptake inhibitors (SSRI), monoamine reuptake inhibitors (MNRI), monoaminooxidase A inhibitors (MAOA), or another antidepressive agent within 6 months of the depression diagnosis (and who had no such treatment prior to the index date). We further assessed the time between the first COPD diagnosis and the first depression diagnosis in two-year intervals and

explored whether the risk of developing a depression diagnosis was dependent on the duration of COPD. We stratified this conditional regression analysis by gender and adjusted for smoking status, BMI, cardiovascular diseases (pulmonary embolism, deep vein thrombosis, ischemic heart disease, stroke / TIA), a history of serious infections, sleeping disorders, and for COPD treatment (oxygen use, beta agonist use, anticholinergic use and use of xanthines), which have been associated with depression in univariate analyses. Statistical significance was set at $p < 0.05$.

In addition, we assessed among patients with COPD the proportion of cases who developed depression and who died within one year after the depression diagnosis. We compared this proportion to the proportion of COPD patients who died within a year after the index date without having developed depression in order to assess the impact of depression on mortality among COPD-patients.

4.6.4 RESULTS

After excluding patients with prevalent depression, previous suicidal ideation, cancer, human immunodeficiency virus (HIV), drug abuse or alcoholism, we identified 2027 patients with an incident diagnosis of depression (65 had a diagnosis of suicidal ideation or suicide), of whom 1174 came from the COPD group and 853 from the COPD-free comparison group. The incidence rates of diagnosed depression were 16.2 / 1000 person-years (py) in the COPD group, and 9.4 / 1000 py in the COPD-free comparison group, yielding a crude incidence rate ratio (IRR) of 1.72 (95% CI 1.58-1.88). Incidence rates in women were higher than in men in both patients with COPD and patients without COPD. The incidence rates stratified by gender are displayed in Table 4.6.1.

TABLE 4.6.1 INCIDENCE RATES OF DEPRESSION IN COPD AND COPD-FREE PATIENTS

	Cases	Person-time (years)	IR per 1000 py (95% CI)	IRR (95% CI)
COPD-free	**853**	**91214.0**	**9.4 (8.7-10.0)**	
Men	338	48457.3	7.0 (6.3-7.8)	0.58 (0.51-0.67)
Women	515	42756.7	12.0 (11.1-13.1)	1.00 (ref)
COPD	**1174**	**72310.0**	**16.2 (15.3-17.2)**	
Men	528	39473.5	13.4 (12.3-14.6)	0.68 (0.61-0.77)
Women	646	32836.5	19.7 (18.2-21.2)	1.00 (ref)

Abbreviations: IR: incidence rate, IRR: incidence rate ratio, CI: confidence interval; py: person years

The nested case-control analysis included 2027 cases and 8108 matched controls from the study population; 42.7% of them were men. Their characteristics are presented in Table 4.6.2 stratified by gender. Compared to the reference group of COPD-free patients, the relative risk estimate (OR) of developing an incident depression diagnosis for patients with COPD was 1.44 (95% CI 1.30-1.60), 1.32 (95% CI 1.15-1.52) in women and 1.62 (95% CI 1.37-1.90) in men, after adjusting for smoking status, BMI, serious infections, sleeping disorders and cardiovascular diseases (deep vein thrombosis, pulmonary embolism, ischemic heart disease, or stroke / TIA). The relative risk of developing depression was highest for severe COPD patients receiving oxygen therapy (OR 2.01, 95 % CI 1.45-2.78), the risk being markedly increased in men (adj. OR 2.68, 95% CI 1.61-4.47) and slightly increased in women (adj. OR 1.63, 95% CI 1.06-2.51). Risks were almost the same in mild and moderate COPD in men adj. OR 1.52, 95% CI 1.05-2.20 and adj. OR 1.58, 95% CI 1.34-1.87) while the risk in mild COPD was not increased in women (adj. OR 0.95, 95% CI 0.65-1.37) and slightly increased in moderate COPD (adj. OR 1.34, 95% CI1.16-1.55).

TABLE 4.6.2 CHARACTERISTICS OF CASES WITH INCIDENT DEPRESSION AND THEIR CONTROLS

	MEN			WOMEN		
	Cases (%) n=866	**Controls (%) n=3464**	**OR (95% CI)**	**Cases (%) n=1161**	**Controls (%) n=4644**	**OR (95% CI)**
Mean age (years) ± sd	66.3 ± 10.3	66.3 ± 10.0	--	66.3 ± 10.5	66.3 ± 10.2	--
BMI (kg/m^2)						
<17.5	13 (1.5)	28 (0.8)	1.69 (0.87-3.31)	35 (3.0)	76 (1.6)	1.70 (1.12-2.57)
17.5-24.9	294 (34.0)	1055 (30.5)	1.00 (ref)	430 (37.0)	1587 (34.2)	1.00 (ref)
25.0-29.9	254 (29.3)	1195 (34.5)	0.76 (0.63-0.92)	308 (26.5)	1370 (29.5)	0.83 (0.71-0.98)
≥30	142 (16.4)	513 (14.8)	0.99 (0.79-1.24)	194 (16.7)	814 (17.5)	0.88 (0.73-1.06)
Unknown	163 (18.8)	673 (19.4)	0.86 (0.69-1.08)	194 (16.7)	797 (17.2)	0.89 (0.73-1.09)
Smoking status						
Non-smokers	218 (25.2)	1164 (33.6)	1.00 (ref)	428 (36.9)	2210 (47.6)	1.00 (ref)
Smokers	273 (31.5)	899 (26.0)	1.64 (1.34-2.00)	371 (32.0)	1071 (23.1)	1.82 (1.55-2.14)
Ex-smokers	301 (34.8)	1050 (30.3)	1.55 (1.27-1.89)	269 (23.2)	936 (20.2)	1.49 (1.25-1.77)
Unknown	74 (8.6)	351 (10.1)	1.09 (0.80-1.49)	93 (8.0)	427 (9.2)	1.09 (0.83-1.44)
COPD						
COPD (all)	528 (61.0)	1532 (44.2)	1.91 (1.65-2.22)	646 (55.6)	1997 (43.0)	1.62 (1.43-1.84)
Mild	47 (5.4)	147 (4.2)	1.79 (1.26-2.53)	39 (3.4)	170 (3.7)	1.15 (0.80-1.65)
Moderate	451 (52.1)	1342 (38.7)	1.86 (1.60-2.17)	573 (49.4)	1745 (37.6)	1.65 (1.45-1.88)
Severe	30 (3.5)	43 (1.2)	3.85 (2.37-6.24)	34 (2.9)	82 (1.8)	2.10 (1.38-3.17)

TABLE 4.6.2 CHARACTERISTICS OF CASES WITH INCIDENT DEPRESSION AND THEIR CONTROLS

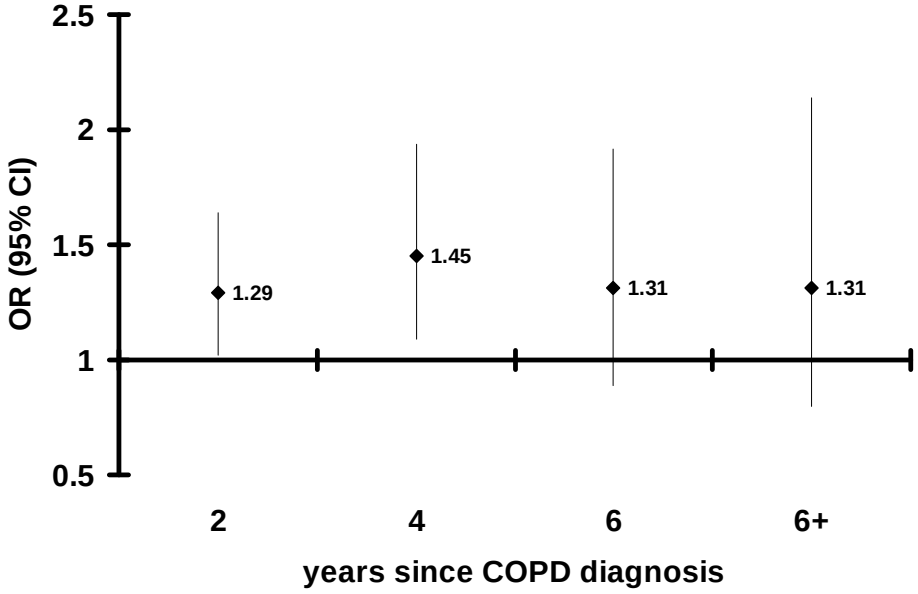
	MEN			WOMEN		
	Cases (%) n=866	Controls (%) n=3464	OR (95% CI)	Cases (%) n=1161	Controls (%) n=4644	OR (95% CI)
Co-morbidities						
Cardiovascular diseases	324 (37.4)	968 (27.9)	1.62 (1.37-1.91)	299 (25.8)	1007 (21.7)	1.29 (1.10-1.50)
Serious infections	52 (6.0)	111 (3.2)	2.00 (1.39-2.76)	64 (5.5)	135 (2.9)	1.96 (1.44-2.66)
Sleeping disorder	206 (23.8)	337 (9.7)	3.37 (2.73-4.17)	284 (24.5)	611 (13.2)	2.29 (1.93-2.70)
Diabetes	96 (11.1)	306 (8.8)	1.30 (1.01-1.66)	76 (6.6)	306 (6.6)	0.99 (0.77-1.29)
Hypertension	263 (30.4)	1041 (30.1)	1.02 (0.86-1.20)	399 (34.4)	1584 (34.1)	1.01 (0.88-1.17)

Abbreviations: OR – odds ratio, CI – confidence interval, sd – standard deviation, cardiovascular disease - pulmonary embolism, congestive heart failure, ischemic heart disease, stroke / TIA. For all diseases each disease-free status is the reference.

In the analysis in which we assessed the duration of a previous history of COPD among cases with depression and their controls (stratified by gender), the relative risk of developing depression was stable over time in men, i.e. independent of the duration of a previous COPD history. On the other hand, it tended to increase slightly with increasing COPD duration in women (Figure 4.3).

Among patients with COPD, the proportion of those who died within a year of the index date was higher for patients with depression (9.5%) than for those who did not develop depression (5.4%). This difference was larger in men (12.7% vs. 5.1%) than in women (7.0% vs. 5.7%). In men, the increased mortality was apparent in all stages of COPD (Figure 4.4).

a



b

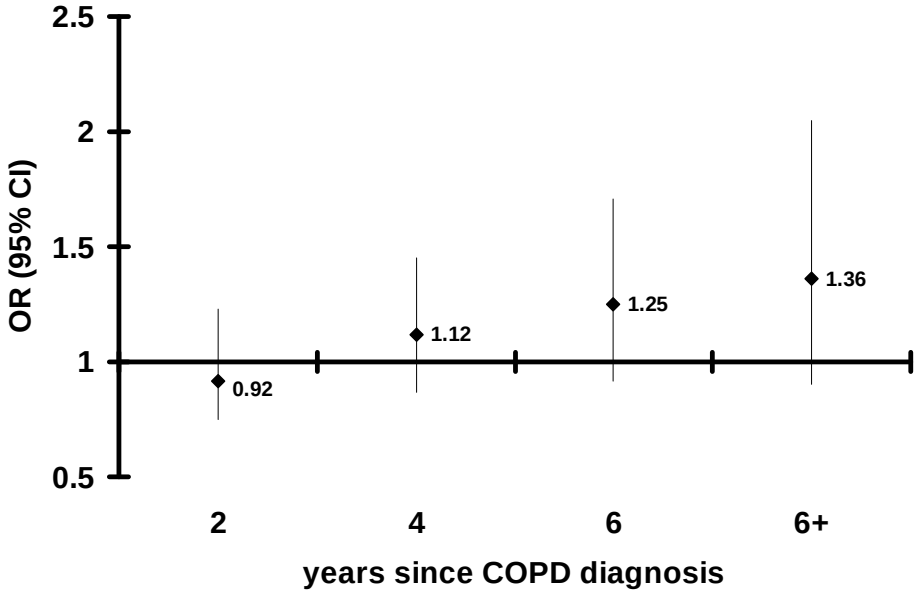
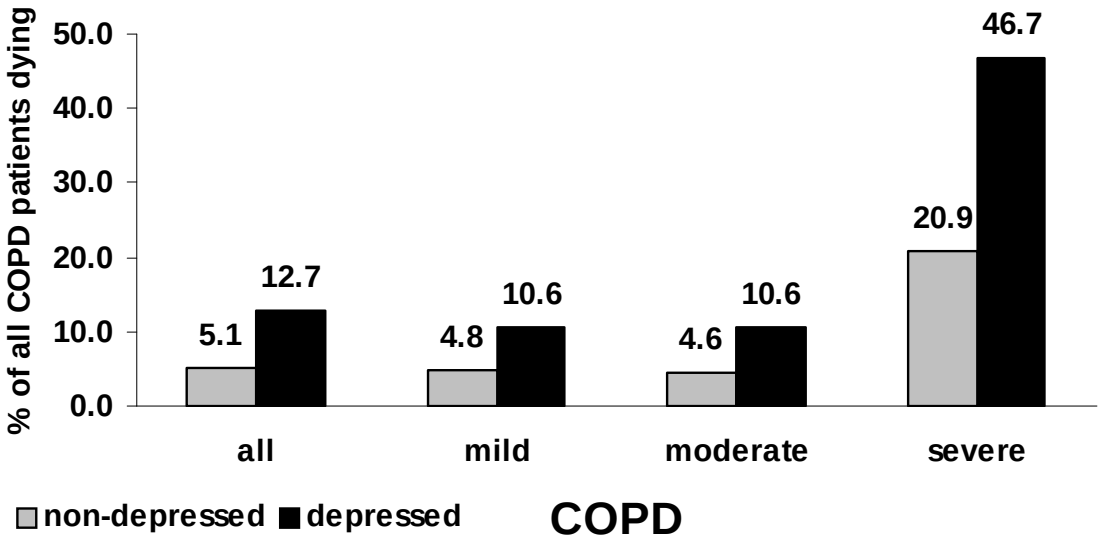


FIGURE 4.3. RISK OF DEPRESSION STRATIFIED BY TIME SINCE COPD DIAGNOSIS

a) male, b) female. The graph shows ORs (·) and 95% confidence intervals (|). The ORs are adjusted for smoking status, BMI, cardiovascular diseases and serious infections, oxygen use, beta agonist use, anticholinergics and xanthine use. Abbreviations: OR –odds ratio

a



b

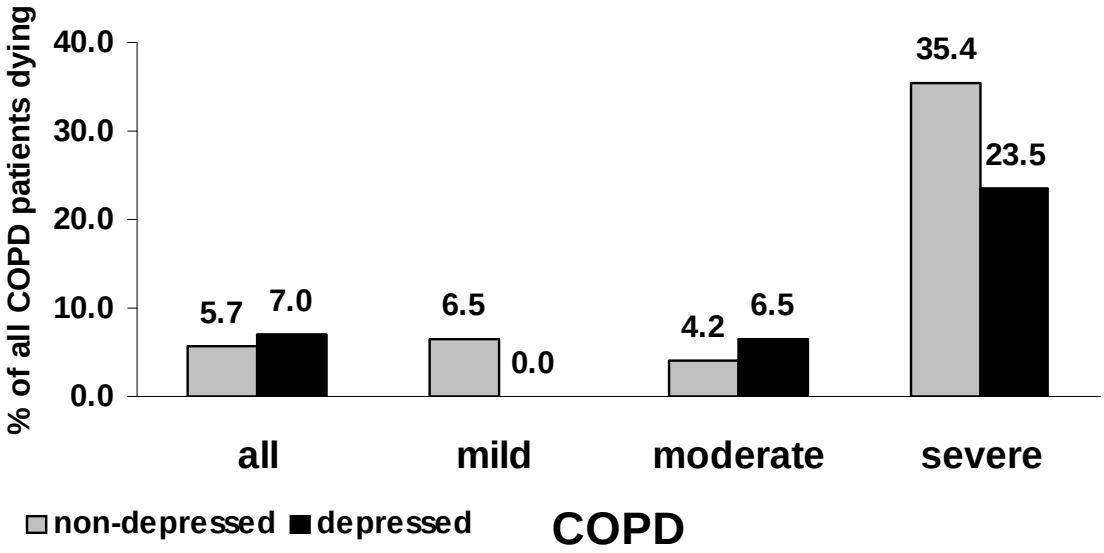


FIGURE 4.4 1-YEAR MORTALITY OF COPD PATIENTS STRATIFIED BY DEPRESSION; COPD SEVERITY AND GENDER

a) shows the 1-year mortality of all male COPD patients at the end of follow-up in percents stratified by COPD severity. b) shows the 1-year mortality of all female COPD patients at the end of follow-up in percents stratified by COPD severity

4.6.5 DISCUSSION

In the follow-up analysis, we found an increased risk of developing an incident diagnosis of depression among COPD patients as compared to COPD-free patients, particularly in women, which is in line with reports from the literature showing that the lifetime prevalence of depression is twice as high in women as in men.(125, 126) In women we also found some evidence for an increasing depression risk with increasing COPD duration, while this was not the case in men. One possible explanation for this observation may be that men and women react differently to a COPD diagnosis, but it is also possible that women tend to get diagnosed with COPD at an earlier disease stage than men, which may lead to a longer lag time between the first COPD diagnosis and the first depression diagnosis.

In our study population, depression was associated with an increased risk of mortality which is consistent with some reports from the literature, documenting that depression is associated with poorer survival after hospitalisation for COPD.(210, 214) However, not all previous studies reported an association between depression and mortality in COPD patients. A study in 137 outpatients with symptomatic disabling COPD stated no association between depression or quality of life and mortality in this group.(211) In contrast to a study by Fan et al.(215) who found an increased 3-year mortality risk, we saw an increased mortality in the first year after the depression diagnosis. Yohannes et al., found that in an univariate analysis depression was an independent predictor of 1 year mortality in patients after an acute exacerbation of COPD.(216) We found a difference between men and women with regard to the 1 year mortality which may point to differences in coping with the disease, or to differences in disease severity. The finding is at odds with the results of Crockett et al., who investigated the association between quality of life and mortality in patients with severe COPD, and reported that higher emotional distress was associated with mortality in women but not in men.(217)

Our results are based on GP-diagnosed COPD and depression. While the GPRD has been extensively validated in previous studies and has proven to be of high quality, including

studies on COPD and depression,(218, 219) we cannot rule out the possibility that a certain proportion of patients with these diagnoses may have been missed, particularly those with mild forms of these diseases. A survey in private UK homes conducted by the 'Office for National Statistics' in 2000 reported that only 62% of people with symptoms of a depressive episode had spoken to their GP about it within the last year.(220) Furthermore, we could not classify patients with COPD and/or depression according to the disease severity with high reliability because scores for disease severity are not routinely recorded. However, we categorized COPD severity based on treatment patterns, as done in previous GPRD-based studies on COPD. (114)

Discussion

In recent years the awareness of gender differences in medicine in general and in particular in reaction on drugs has increased. However, systematic analyses are still scarce, although international guidelines on drug development incorporated the requirement of sex-specific analyses. It was the aim of this PhD thesis to contribute to the understanding of the natural history of COPD from a gender perspective. Detailed discussions of the findings can be found in the discussion sections of each study. In the following, I will put the results of this thesis in a gender perspective and discuss more general aspects of database research.

5.1 COPD AND GENDER MEDICINE

Coronary heart disease has long been regarded as primary male disease, even women themselves were long not aware that they are at risk of this disease. In 1993 a study asked women to estimate their risk of coronary heart disease at the age of 70, 73% estimated their risk to be less than one percent and 39% even estimated it to be less than 0.1%.(221) In the UK in 2008, 87,392 women died of circulatory system diseases and 80,846 men.(222) Data from the 2006 Health Survey for England suggest that “more than 1 in 3 men and around 1 in 4 women aged 75 or older live with coronary heart disease”.(223) However, women are on average 10-15 years older than men at their first diagnosis of a coronary heart disease, in men 45 years of age or older is considered as risk factor while in women it is 55 of age or older. (21) We found a higher incidence of myocardial infarction in men, compared to women but the presence of COPD decreased the difference between men and women.

The incidence of stroke is higher in men than in women and women tend to be older than men at their first stroke diagnosis.(163, 164, 224) Women have often more severe strokes than men, they have a higher degree of disability and a higher likelihood to die within 28 days of the stroke diagnosis than men.(163, 164) It is not known why there are gender differences. Smoking, diabetes, hypertension, obesity and reduced mobility are important risk factors in

men and women. It is discussed that differences in smoking and alcohol abuse might explain part of the differences. However, women are thought to have a greater susceptibility to the effects of smoking than men. Hormones have also been discussed as a reason for gender differences as within 10 years after the menopause women have similar rates of stroke than men.(21) Studies on HRT, however, showed inconclusive results.(225) We found a higher incidence of stroke in men compared to women in the COPD-free population, however women were more likely to die within 30 days than men. This gender difference is lost in patients with COPD. While the presence of COPD had no impact on the risk to develop stroke in men, COPD increased the risk of stroke in women by 1.41 (95% CI, 1.06-1.88). The presence of COPD increased the overall mortality, in particular the mortality in men which was as high as the mortality in women with and without COPD.

Whether there is a gender difference in incidence and prevalence of VTE is controversially discussed.(21, 226) A systemic review of studies on the incidence of DVT published in 2003 did not find a difference between men and women.(227) There are, however, sex-specific risk factors for the development of a VTE, which might explain small differences observed at certain age-groups. Pregnancy, use of oral contraceptives and hormone replacement therapy are associated with VTE in women.(226) The incidence rates of pulmonary embolism of men and women were closely similar in the COPD-free group and slightly higher in men with COPD than in women with COPD, also statistically non-significant. The incidence rates of DVT in the COPD-free group were slightly higher in women than in men while they were closely similar in men and women with COPD. Overall the impact of COPD on the incidence of a VTE was more important than a potential gender difference.

Atrial fibrillation is the most common cardiac arrhythmia in developed countries, with a prevalence in a general population of about 0.7%, increasing up to 9% in patients over the age of 80 years. (228, 229) Atrial fibrillation is a major independent risk factor for thromboembolic events, mainly stroke and transient ischemic attacks.(230) The incidence in women is higher than in men but as women outnumber men in the older age-groups the prevalence of atrial fibrillation is almost the same in men and women.(21) We found slightly

higher incidence rates in men than in women in both patients with and without COPD. The incidence of arrhythmia was increased in patients with COPD, however, in an analysis adjusted for other potential risk factors we found only a non-significant association of 1.19 in both men and women. Women, however, tended to be slightly older than men at the diagnosis and patients with COPD, in particular men, tended to be slightly younger at the diagnosis of arrhythmia.

There are tumours which are only found in women or men because they are localized in sex-specific organs such as the ovary, uterus, prostate or penis. Brest cancer is mainly affecting women, but can also affect men. Tobacco-smoke associated tumours, such as lung cancer, oesophagus, kidney and bladder cancer are more often seen in men than in women but women are catching up. Gall bladder and thyroid cancer are more common in women while liver cancer is more common in men. Most other tumours have a similar distribution in men and women.(21) We observed a higher number of cancer cases in men, both with and without COPD when compared to women. COPD, however, seemed to have a greater impact on the risk of a cancer diagnosis in women than in men. For most cancers the risk was materially unchanged except for lung cancer which was materially increased in men and women. This association was even seen in non-smokers. Associations in women were much stronger than in men. In women in addition the risk of urinary and kidney cancers was increased although, results were statistically not significant.

Men have historically higher numbers of peptic ulcer (231, 232) The reason for this gender difference is not clear. It might be due to a different risk factor profile (*H.pylori* infection, NSAID exposure, smoking status) or sex hormones. Ulcer rates in younger men are declining while they are increasing in the older population, particularly in women. (233) Recent numbers on gender differences are scarce. Men had higher incidence rates of peptic ulcer than women, in both patients with and without COPD. COPD did not have a strong impact on the risk of peptic ulcer.

Whether there is a gender difference in the prevalence and incidence of GORD is controversial.(190, 191) It might be important to distinguish erosive reflux disease from non-

erosive reflux disease. Non-erosive reflux disease is more commonly observed in women, although part of this difference (if not all) might be attributed to pregnancy. Erosive reflux disease and Barrett's oesophagus are more common in men.(234) We found slightly higher incidence rates of GORD in women than in men but we could not stratify this analysis into erosive and non-erosive reflux disease. Differences were slightly smaller in COPD patients than in COPD-free patients but neither COPD nor gender had a significant impact in the risk of GORD.

Women are twice as likely to develop depression as men. This difference is strongest in early and middle adulthood, while during childhood and in elderly, men and women are more equally affected by the disease. Explanations for these observed differences are diverse ranging from hormonal or genetic differences, over diagnostic bias to differences in social status. The truth might be a mixture of all of them but it is not clear. This difference is restricted to a first-time diagnosis of depression, recurrence is observed at similar rates in men and women.(21) We observed higher incidence rates of depression in women, in both patients with and without COPD. The impact of COPD on the risk of depression seemed to be slightly higher in men than in women and was highest for patients with severe COPD. In addition the presence of both COPD and depression had a negative impact on survival in men but not in women, a phenomenon which needs further investigation.

5.2 NATURAL HISTORY OF DISEASE STUDIES

Natural history of disease studies not only provide valuable information about background incidence rates and co-morbidities for the introduction of a new drug on the market but are also valuable tools for hypothesis generation regarding potential new indications of drugs. In this project sulfonylurea have been negatively associated with the incidence of COPD (study 2) and long-acting beta agonists have been negatively associated with the incidence of

peptic ulcer (study 4). As diabetes itself is associated with a lower incidence of COPD in men, the association between sulfonylurea and COPD might just be a marker for the diabetes-COPD association. The increase of the association with increasing duration of use as well as the fact that no such observation is made for biguanides, however, favour a direct association between sulfonylurea and COPD. The fact that this association is rather seen in men could either mean that there is a gender-specific effect or sulfonylurea are just a marker for residual confounding. In the case of long-acting beta blockers the disease itself (COPD) had rather been positively associated with the incidence of peptic ulcer. Thus this favours a real association between the drug and the disease. The fact that animal studies have reported similar effects further supports this observation. The fact that more selective agonists the beta 3 agonists are in development, however, limits the importance of this observation. Nevertheless, it might be important for health care providers to trade the risk:benefit ratios of different respiratory drugs in COPD treatment, and in case this effect is true patients at an increased risk of ulcer might favour beta agonists. Further research is needed to answer the question whether there are true protective associations.

5.3 LIMITATIONS AND STRENGTH

As COPD patients experience symptoms differently they might be diagnosed in different stages of the disease. In addition patients might experience differences in disease progression. In a sensitivity analysis, where we stratified COPD patients according to therapy into mild, moderate and severe cases, we tried to account for the influence of disease severity. We used the therapy as a proxy for severity classification as there is only limited information on FEV_1 values available. Although this leaves room for misclassification we feel that this method is a useful indicator in the absence of more specific measures, as treatment guidelines are oriented on FEV_1 values. Soriano et al.(114) who validated a classification

scheme based on treatment found good correlation between FEV_1 and treatment classification.

As smoking is the most important risk factor for COPD it would be desirable to have complete smoking information for the analysis. There is the potential that COPD patients are more likely to be asked about their smoking status than controls and thus there might be some selective misclassification of smoking status. In the analysis this may have led to some dilution of potential COPD risk estimates towards 0. Additionally, it has been shown that smoking intensity might influence the risk of developing lung cancer or cardiovascular diseases, a factor we cannot account for in our analysis.

In spite of these (small) limitations database research is in general a powerful tool to support pharmacovigilance. It is able to depict a picture of the real world, shows the effectiveness rather than the efficacy of drugs at affordable costs. Database research is much less affected by selection bias, which is a huge problem in clinical trials, which are often not conducted in the patients finally taking the drugs. The population of the GPRD is representative of the general UK population. (107) Database research does not replace clinical trials but adds important information to the safety profile of drugs and provides information on the clinical presentation of the underlying diseases. This research can even be conducted when clinical trials are considered unethical or are impossible to do. Compared to other epidemiological studies database research is less affected by selection and recall bias, as all information are entered at the time they are identified.

Conclusion & Outlook

6.1 CONCLUSION

Evidence based medicine requires that decisions about the management of an individual case are based on “conscientious, explicit, and judicious use of current best evidence” and “individual clinical expertise.(235) This thesis provided further evidence that sometimes the important information is hidden in details and that best evidence can only be provided by specific guidance. COPD is no risk factor for stroke in men but it increases the risk in women. The following list summarises the most important findings of this thesis. Some of them confirm older findings from the literature, others rather present a hypothesis all of them apply to a situation in the GPRD between 1995 and 2005. Research in other settings, other countries and at other times will have to confirm or disprove these associations.

- Patients with COPD have more co-morbidities and a higher mortality than COPD-free patients.

- Diabetes is underrepresented in men at the time of the first COPD diagnosis. This observation is at least in part contributed to higher proportion of ex-smokers among diabetic patients. Whether there is an association between sulfonylurea and the subsequent risk of COPD needs further investigation.

- Patients with COPD have in general a higher risk of depression, lung cancer, pulmonary embolism and myocardial infarction.

- Gender differences were observed for the risk of cancer (urinary cancer and lung cancer), myocardial infarction, stroke, depression, peptic ulcer, survival and respiratory drug utilization.

- Severity of COPD seemed to increase the risk of depression, myocardial infarction, pulmonary embolism and lung cancer.

- The proposition that patients using long-acting beta agonists have a decreased risk of peptic ulcer needs further investigation.

- Smoking is a strong risk factor, therefore smoking stratified analysis are important.

6.2 OUTLOOK

6.2.1 COPD PROJECT

The answer yes there are gender differences in the natural history of COPD opens another whole array of new questions. This thesis suggested that patients with diabetes are underrepresented in patients at the time of their COPD diagnosis mainly in male patients. To further investigate this association one could follow diabetes patients from their diagnosis until they develop COPD or loss of follow-up. It is important that this study has detailed information on smoking history and intensity. MI and stroke showed gender different incidences in men and women with COPD. Further research is needed to identify whether this is due to a different exposure to known risk factors in this case it might be smoking, a higher susceptibility of women to the effects of COPD or an artefact of the study design used. There was no difference in the risk of arrhythmia. As women have been shown to be particularly at risk of Q-T prolongation it would be interesting to investigate the association stratified by arrhythmia type and see whether there are any differences. Depression negatively influenced survival in men with COPD but not women. An open question is whether this difference arises from different COPD staging in men and women with men

being more advanced in COPD than women and thus more likely to die. A study adequately addressing disease severity at the time of the depression diagnosis and then following patients until death or loss of follow-up might contribute new insights. A clinical study with direct patient contact might be more suitable than database research or validated markers of disease severity have to be identified.

Women still have a higher life expectancy than men and catch up with smoking behaviours; therefore it is likely that the future typical COPD patient will be women even if women are not more susceptible to smoking than men. Gender difference in susceptibility to smoking is one of the unanswered questions when dealing with COPD but also other tobacco-associated diseases. Future research is needed adequately addressing differences in lung biology and exposure to environmental tobacco smoke. An important problem is that women smoke for different reasons than men and they are less likely to quit. (236)

6.2.2. GENDER

Natural history of disease studies are important to identify and quantify gender differences. They have to sensitize researchers, health care providers and regulators and last but not least the public. However, they usually cannot answer the question why there are differences. The identification of a difference is only the first step in a chain of events which will hopefully lead to the identification of the underlying mechanism and finally to effective treatment or even prevention strategies.

In women a further level of complexity when studying disease associations is introduced by changing hormonal status. Menopause marks a turning point after which the risk of many diseases increases and becomes similar to risks seen in men, an example is hypertension. In addition women on HRT might experience different risks for diseases than women not taking hormones (237) and to further complicate this HRTs are not alike.(238) The results of the „WHI“-trial (Women’s Health Initiative) have intensified the debate about the safety of

HRT preparations and thus also started intense research in this area so that in the future we might gain more information on this topic. Much less is known on women using oral contraceptives (OC) except maybe for their risk of venous thromboembolism.(239) Both HRTs and OCs might interact with other drugs. Pregnancy puts women requiring drugs at an immense psychological burden, they want the best for their babies but not much is known about drug effects and the comparison between effects of the disease itself and drug effects. Pregnant women are excluded from official clinical trials due to worries about teratogenic effects to the baby. Nevertheless, about two thirds of women delivering a baby have taken at least one prescription medication during their pregnancy. Thus pregnant women take part in uncontrolled and unmonitored experiments – one by one and most of their data were never assessed. There are now efforts to close this knowledge gap. The FDA and collaborators launched a program called the 'Medical Exposure in Pregnancy Risk Evaluation Program' to fund research on effects of prescription medications used during pregnancy. Therefore health care information from mothers and babies born between 2001-2007 will be linked and analysed providing information on about 1 million births.(240) There have been efforts to use the GPRD for investigating the effects of medication used during pregnancy, (241) however, these analyses are complicated because records of mothers and their children were not routinely linked.

There is even less information on paternal drug exposure and pregnancy outcomes, although many fathers used drugs around the time of conception (242) and teratology information services are addressed by concerned future parents.(243, 244) Linking not only mothers with their children but also fathers in administrative database would enable us top learn more about the effects of paternal drug exposure on pregnancy outcomes. In case paternal drug exposure poses a risk this should also be considered in clinical trials by ensuring that men and women both take effective measures to prevent a pregnancy while they are participating in a clinical trial.

Although this thesis mainly focussed on differences it is as important to identify equalities between gender, even if at first glance the assumption is that there is a difference. It is

always important to question an observation, same numbers might still present different underlying mechanism and different numbers might be due to diagnostic bias. Equalities have to be identified to avoid double standards and ensure that men and women receive the same therapy when they need it. Research on differences but also equalities between men and women is important to offer best care to the patient. Integration into medical guidelines and of course daily practice has to follow.

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