A STUDY OF THE IMPACT OF STATINS, ACE INHIBITORS AND GASTRIC ACID SUPPRESSANTS ON PNEUMONIA RISK AND MORTALITY USING THE HEALTH IMPROVEMENT NETWORK DATABASE

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Abstract

Pneumonia is a common diagnosis in general practice and is associated with significant morbidity and mortality. Current estimates of pneumonia incidence in the UK are based on studies more than a decade ago and little is known about longer term outcomes in pneumonia patients. Though much is known about the aetiology of pneumonia and predictors of mortality, an emerging area for research is the relationship between commonly prescribed drugs in general practice and pneumonia.

The aims of this thesis were first, to determine overall incidence and mortality for pneumonia and how these vary by socio-demographic characteristics like age, sex, deprivation; and second, to investigate whether statins, angiotensin converting enzyme inhibitors (ACEIs) and gastric acid suppressants like proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RAs) modify the risk of acquiring pneumonia and its prognosis.

This study used data from The Health Improvement Network (THIN) database, a longitudinal database of anonymised computerised medical patient records from 330 United Kingdom (UK) general practices at the time of data extraction in 2006. A cohort design was used to determine pneumonia incidence and mortality in the UK. Case-control, case-series and cohort study designs were used to investigate associations between the various drug exposures and pneumonia. The overall incidence of pneumonia was 237 per 100,000 person-years (95 % confidence interval (CI): 235 to 239) and this rate was stable between 1991 and 2003. Pneumonia was more common in men and in

children under the age of four years and adults over the age of 65 years. There was an increased incidence of pneumonia with higher levels of socioeconomic disadvantage. Pneumonia cases showed much higher all-cause mortality as compared to the general population, both in the short and long-term and this increase was independent of underlying comorbidity. After adjusting for potential confounders, current prescriptions for statins and ACE inhibitors were associated with a significant reduction in the risk of acquiring pneumonia. Current prescriptions for PPIs were associated with an increased risk of pneumonia. With regards the impact on mortality: the use of statins was associated with a lower risk of short and long-term mortality following pneumonia whereas the use of ACEIs was associated with a decreased mortality risk only in the short-term. No relationship was observed between prescriptions for PPIs, H2RAs and pneumonia mortality. This study shows that caution must be exercised while prescribing proton pump inhibitors especially in patients known to be at high risk of pneumonia. There is also a potential role for statins in preventing pneumonia in at-risk patients and improving pneumonia outcomes but this will necessitate clinical trials to determine adequate dose, duration and safety profiles before any prescribing policy recommendations are made.

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List of Abbreviations

ACEI	Angiotensin converting enzyme inhibitor
AHD	Additional Health Data
ALRI	Acute Lower Respiratory Infection
ASCII	American Standard Code for Information Interchange
BNF	British National Formulary
BTS	British Thoracic Society
CAP	Community Acquired Pneumonia
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
EPIC	Epidemiology and Pharmacology Information Core
FDC	Full Data Collection
GPRD	General Practice Research Database
HR	Hazard Ratio
H2RA	Histamine 2 Receptor Antagonist
ICD-9	International Classification of Disease- 9th Revision
IHD	Ischaemic Heart Disease
InPS	In Practice Systems
IR	Incidence Rate
IRR	Incidence Rate Ratio
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
NHS	National Health Service
OPCS-4	Surgical Operations and Procedures Fourth Revision
OR	Odds Ratio
OXMIS	Oxford Medical Information Systems
PPI	Proton Pump Inhibitor
PSI	Pneumonia Severity Index
THIN	The Health Improvement Network
VAMP	Value Added Medical Products

1 Introduction

1.1 Introduction to thesis and aims

Pneumonia is a common diagnosis in general practice and is associated with significant morbidity and mortality. While considerable research has been carried out into the aetiology and prognosis of pneumonia in the past, an emerging area for research is the relationship between commonly prescribed drugs in general practice and pneumonia. The aims of this thesis are:

1) To determine overall incidence and mortality for pneumonia in general practice;
2) To determine how incidence and mortality vary by socio-demographic characteristics like age, sex and deprivation
3) To investigate whether statins, angiotensin converting enzyme inhibitors (ACEIs) and gastric acid suppressants like proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RAs) modify the risk of acquiring pneumonia and its prognosis.

This introductory chapter provides a brief overview of pneumonia, detailed objectives of the thesis and an outline of subsequent chapters. More detailed background to the incidence, mortality and pharmacoepidemiology of pneumonia will be provided in the individual chapters addressing these study aims.

1.2 Background: Introduction to pneumonia

1.2.1 Definition and diagnosis

Pneumonia is an acute lower respiratory tract infection that is usually bacterial in origin. Clinical symptoms of pneumonia may include pleuritic chest pain, shortness of breath, cough, sputum production, night sweats and confusion. Signs of pneumonia present on examination include fever, increased respiratory rate, focal chest signs (dullness on percussion, decreased chest expansion, crackles, bronchial breathing and decreased entry of air).[1] Though chest x-rays are advised for making a diagnosis of pneumonia,[1-3] according to the British Thoracic Society (BTS) guidelines these are not necessary for the majority of patients with suspected community-acquired pneumonia (CAP) managed in primary care.[4] The BTS guidelines definition of CAP is:

- Symptoms of an acute lower respiratory illness (cough and at least one other lower respiratory tract symptom)
- New focal chest signs
- At least one systemic feature (either a symptom complex of sweating, fever, shivers, aches and pains and/or temperature of 38° C or more)
- No other explanation for the illness, which is treated as CAP with antibiotics

1.2.2 Incidence

The annual incidence of pneumonia diagnosed in the community is estimated to be between 5 and 11 per 1000 adult population.[4] Incidence varies by age from about 6 per 1000 population in the 18-39 age-group to 34 per 1000 population in those aged 75 years and above.[2] Chapter 3 includes a detailed literature review on the incidence of pneumonia. Risk factors for pneumonia include increasing age, male sex, comorbidities, cigarette smoking, pre-existing chronic obstructive pulmonary disease, heart disease and occupational dust exposure.[2]

1.2.3 Aetiology

The most common cause of CAP both in developed and developing countries is *Streptococcus pneumoniae* (pneumococcus) with its incidence ranging from 3 to 76 percent of all pneumonia cases.[2 3 5-7] Pneumococcal infection tends to be more common in those aged 60 years and above, as well as in people with underlying chronic disease; accounting for about 40 percent of the infection in these patient groups.[5] Other bacterial agents include *Haemophilus influenzae, Staphylococcus aureus, Klebsiella pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumoniae* and *Legionella spp.*[2 3] In developing countries *Mycobacterium tuberculosis* is an important cause of pneumonia following *Streptococcus pneumoniae.*[7] In children up to 60% of lower respiratory infections are caused by viruses with superimposed bacterial infection. Paramyxovirus is an important respiratory tract pathogen and is a cause of pneumonia in both adults and children.[2] In adults the major viral cause of

pneumonia is influenza and other less common viral pathogens include: respiratory synctial virus, parainfluenza virus, adenovirus, hantavirus, varicella and herpes simplex.[3]

1.2.4 Pathophysiology and clinical course

Pulmonary pathogens reach the lungs using one of the following routes:[8]

- Direct inhalation of infectious respiratory droplets
- Aspiration of oropharyngeal contents
- Direct spread along the mucosal membrane surface from the upper to the lower respiratory system
- Haematogenous spread

The invasion of the pulmonary tissue by the pathogenic agent triggers an acute inflammatory reaction. This reaction comprises first, an exudation of fluid and polymorphonuclear leukocytes and second, the deposition of fibrin within the alveoli. This is followed over the next few days by the appearance of macrophages in the alveoli. The accumulation of fluid in the lobe of the lung leads to the characteristic lobar consolidation visible on chest radiographs.[9] Resolution of fever in ambulatory pneumonia patients occurs in a median time of 3 days whereas median resolution times for other symptoms are as follows:[10]

- Myalgia- 5 days
- Dyspnoea- 6 days
- Cough- 14 days
- Fatigue- 14 days

1.2.5 Prognosis

The mortality in adults with pneumonia managed in the community is estimated to be less than 1% whereas in hospitalised patients it ranges from 5 to 14%.[4] Chapter 5 includes a detailed review of the evidence on pneumonia mortality estimates. Previous research suggests that approximately half of pneumonia deaths could be attributed to a worsening of pre-existing conditions.[11] Factors predicting poor prognosis in pneumonia patients include the following:[3]

- Age over 65 years
- Underlying comorbidity including diabetes, renal failure, congestive heart failure, lung disease, malignancy
- Immunosuppression
- Alcoholism
- Hospitalisation or residence in a nursing home in the previous year
- Severity of pneumonia

Infection due to *S. pneumoniae, Legionella spp.*, Gram-negative bacilli or *S. aureus*

- Initiation of antimicrobial therapy that is not active against the pathogen or is delayed

1.2.6 Management

In the UK, between 22 to 42 percent of pneumonia patients require hospitalisation while the remainder are managed in the community.[2 4] The decision to hospitalise a patient is based on a combination of factors: severity

of illness, associated comorbidity, adequacy of home support and probability of compliance.[3] Two scoring systems for assessing the severity of pneumonia have been used widely: the pneumonia severity index (PSI) score and the CURB-65 criteria. The PSI stratifies patients into severity categories based on age, presence of comorbid conditions, vital signs, mental status and abnormal laboratory tests. The CURB-65 is an acronym for five indicators of increased mortality:[3]

- Confusion
- Urea levels (<7mmol/l or 20mg/dl)
- Respiratory rate >30 breaths per minute
- Blood pressure (systolic <90 mmHg or diastolic ≤60 mmHg)
- Age ≥65 years

The mainstay of pneumonia treatment is appropriate antimicrobial therapy to eradicate the infecting organism with supportive care including maintenance of oxygenation and other vital functions in more severe cases. The selection of appropriate antimicrobials is based on the following considerations:[3]

- Predicting the most likely pathogen
- Presence of medical comorbidities that may influence the pathogen
- Spectrum of activity
- Potential for inducing drug-resistance
- Efficacy
- Safety profile
- Cost

1.2.7 Prevention

The polysaccharide pneumococcal vaccine (PPV) and the influenza vaccine have been recommended in the Centres for Disease Control (CDC) guidelines as prevention measures for pneumonia.[10] In addition, the pneumococcal conjugate vaccine has been shown to be effective in reducing serious pneumococcal infections and colonisation of vaccine strains in children.[10] In the UK under current immunisation policy children are offered the pneumococcal conjugate vaccine (PCV) at two, four and thirteen months, with people over 65 years of age being routinely offered pneumococcal polysaccharide vaccine (PPV) to protect against pneumococcal disease.[12] The PCV was introduced as part of the routine childhood immunisation programme in September 2006. In 2003 the PPV vaccination for older adults was introduced in a phased manner over a three year period. In August 2003, the first phase was implemented and the PPV was recommended for those aged 80 and over. Phase 2 started in April 2004 with anyone age 75 or over being offered the PPV. This included those aged 80 or more who did not receive their vaccine in the first phase. In April 2005 the policy was fully implemented and all those aged 65 and over were included in the recommendation to have the Pneumococcal polysaccharide vaccine.[13]

1.3 Chapter outlines

A brief overview of subsequent chapters is as follows:

Chapter 2: Methods: Database, variables and overview of study designs

This chapter describes the database used in the study, as well as how exposure, outcome, and covariates were defined. It also provides an overview of the study designs used and the methods used in the analyses. Detailed methods relevant to the individual studies are included in subsequent chapters.

Chapters 3-7:

Each of these chapters addresses one of the thesis objectives and starts with a review of the existing studies on the given topic area and then goes on to describe the detailed methods for the specific study. Results are presented followed by a discussion of the findings.

These chapters deal with the following topics:

Chapter 3: Incidence of pneumonia in the UK general practice population

This chapter deals with the specific study objective to calculate the overall incidence of pneumonia in UK general practice for the period 1991-2003 and incidence stratified by calendar year, age group (five year age bands), gender and deprivation.

Chapter 4: Case-control study: The impact of statins, ACEIs, PPIs and H2RAs on pneumonia risk

This chapter considers the study objective to investigate the effect of exposures to statins, angiotensin converting enzyme inhibitors (ACEI), proton pump inhibitors (PPI) and histamine 2 receptor antagonists (H2RA) on pneumonia risk.

Chapter 5: Self-controlled case-series analysis: The impact of statins, ACEIs, PPIs and H2RAs on pneumonia risk

This chapter explores a different methodological approach, the self-controlled case-series analysis to investigate the effect of exposures to statins, ACEIs, PPIs and H2RAs on pneumonia risk.

Chapter 6: Cohort study: Mortality from pneumonia in general practice compared to general population

This chapter is devoted to the specific study objective: to calculate all-cause mortality in people with pneumonia in UK general practice as compared to the general population at discrete time-periods following pneumonia diagnosis: short-term mortality within 30 days of a pneumonia diagnosis, medium-term mortality between 31-90 days post-pneumonia and long-term mortality that occurs more than 90 days.

Chapter 7: Cohort study: The impact of statins, ACEIs, PPIs and H2RAs on pneumonia mortality

This chapter considers the study objective: to investigate whether statins, ACEIs, PPIs and H2RAs have an impact on short-term and long-term mortality in pneumonia cases.

Chapter 8: Conclusions and recommendations

This chapter summarises the main findings and then goes on to describe the clinical and public health implications. The chapter concludes with a section on recommendations for future studies.

2 Methods: Database, variables and overview of study designs

2.1 Introduction

This chapter describes the database used in the study, as well as how exposure, outcome, and covariates were defined. It also provides an overview of the study designs used and the methods used in the analyses. As this research was carried out in stages using more than one study design, detailed methods relevant to the individual studies are included in subsequent chapters.

2.2 The health improvement network (THIN) database

2.2.1 Background to THIN

The health improvement network (THIN) is a longitudinal database of anonymised computerised medical records from 330 UK general practices across England, Scotland, Wales and Northern Ireland.[14-16] In 2006 when the data for this study were extracted, THIN covered 4% of the UK population with representation from all sections of the population.[15] The THIN database currently includes data on a total of 5.7 million patients of whom more than 2.5 million patients are actively registered with practices and can be followed prospectively. This is equivalent to more than 30 million person years with diagnostic and prescribing data.[16] The database was set up in 2002 through the collaboration of the medical database research company known as Epidemiology and Pharmacology Information Core (EPIC), which had

previously managed the General Practice Research Database until 1999. Data collection was started in 2003. All contributing general practices are required to use the latest version of Vision Software, a practice management software programme from In Practice Systems (InPS), for their prospective recording.[15] The use of computers to record patient data in general practice, including medical diagnoses and prescriptions, started in the 1980s. A feasibility study conducted by the directors of THIN showed a high level of completeness of clinical information, including the prevalence of pregnancies and prescriptions, when compared with national data.[14]

Prior to joining THIN most general practices were previously using the Value Added Medical Products (VAMP) system[17] to enter patient data, which was used in the well established General Practice Research Database (GPRD).[18 19] The GPRD like THIN is an anonymised longitudinal database of primary care records from the UK and is currently managed by the Medicines and Healthcare products Regulatory Agency (MHRA), the UK's medicines and devices regulator. It has 3.6 million active patient records and 46 million patient-years of data from 450 general practices.[20] The use of routine primary care databases like the General Practice Research Database (GPRD) appears to be valid for primary care epidemiological studies including respiratory epidemiology and is advantageous in terms of large size, a longer time period covered, and ability to link prescriptions with diagnoses.[21] In 2004 fifty two percent (141 out of 268) of the practices contributing to THIN also contributed data to the GPRD.[22] A more recent independent publication of several validation studies in THIN demonstrated that data from non-GPRD practices

have the same high standard of validity as data collected for GPRD practices.[23] THIN and GPRD are essentially similar in nature but there are some differences in the way raw data is presented. In theory, similar studies carried out separately in GPRD and THIN should yield similar results.

Upon joining THIN an initial Full Data Collection (FDC), including all retrospective data, is carried out for the contributing practice. Following this Incremental Data (IDC) are collected each month.[15] Information for each patient is contained in 4 separate tables, which are linked by a unique identification number (Table 2.1).[15] Medical conditions and symptoms are recorded in the Medical and Additional Health Data (AHD) tables using the Read clinical classification version 2 and the codes may be cross-referenced to the International Classification of Diseases Ninth Revision (ICD-9).[15] Procedures and interventions can be mapped onto the classification of Surgical Operations & Procedures Fourth Revision (OPCS-4).[15] Drug prescription codes are based on the chapters in the British National Formulary chapters.[24]

Table 2.1 Structure of the health improvement network (THIN) database

THIN Data Table	Information contained
Patient	Basic demographic information (e.g. registration date, transfer-out date, date of birth/death, sex, family number)
Medical	Medical symptoms, disease diagnoses, hospital admissions, medical procedures and investigations
Therapy	Drug prescriptions (including frequency, quantity, dose, and formulation of medication)
Additional Health Data	Additional information such as lifestyle and preventative health care (e.g. smoking habit, weight, height, blood pressure, vision, hearing, perinatal monitoring, birth details, physical/mental child development, immunisations, biological test results) N.B. Read medical codes will also be attached to some additional health data tables

2.2.2 Data anonymity and ethical approval

All patient records in THIN are anonymised to ensure that researchers cannot identify individuals. Each record in THIN has a unique identification number for the individual as well as unique identification numbers for the individual's family (or household) and the general practice that the individual attends. The broad geographic location of a THIN general practice is available as one of 12 regions across England, Scotland, Wales and Northern Ireland. The location of a patient's household, however, is not provided to researchers to protect the identity of the individual. The study protocol was reviewed and approved by the Nottingham Research Ethics Committee.

2.3 Data management

In February 2006, the September 30th, 2005 update of the database was supplied by THIN in the form of flat ASCII (American Standard Code for Information Interchange) files. Data management and cleaning of the entire THIN database was initially conducted by Chris Smith in the Division of Epidemiology & Public Health at the University of Nottingham. The author of this thesis provided a list of Read codes for pneumonia (as per the case definition adopted for this study; see Table 2.2) so that data on pneumonia cases could be extracted. The THIN data was provided as four separate files as outlined in Table 2.1 for all patients with a Read code for pneumonia in the period 1991 to 2003. In addition a denominator file was provided for the THIN population, stratified by age group, sex, region, Townsend score and year. The author of this thesis then used the Read code dictionary and the BNF code dictionary to create separate files for the covariates and the exposure variables. The Charlson Comorbidity Index (CCI) was adapted and constructed by the author for this thesis. The author finally extracted a sample of cases to be used for the case-control and survival studies. Chris Smith then provided 6 controls matched to each case on age, sex and general practice.

2.4 Building the dataset: Description of key variables

The following section describes the key variables that are used throughout the research. Other variables will be discussed in the individual chapters dealing with each of the four studies separately.

2.4.1 Definition of pneumonia

Pneumonia was one of the main outcomes of interest for this research. The author of this thesis identified all recorded diagnoses of pneumonia and acute lower respiratory tract infection (ALRI) using a look-up table of specific medical Read Codes. The list included the code for ALRI to ensure that all undiagnosed cases of pneumonia categorised in this way were captured. Read codes signifying working diagnoses, symptoms, signs and ill-defined conditions were excluded.[15] The list of codes used to define pneumonia is given in Table 2.2.

Table 2.2: Read codes for pneumonia

Read code	Description	Percent
H26..00	Pneumonia due to unspecified organism	35.8
H25..00	Bronchopneumonia due to unspecified organism	24.1
H062.00	Acute lower respiratory tract infection	18.9
H21..00	Lobar (pneumococcal pneumonia)	7.6
H2z..00	Pneumonia or Influenza NOS	3.7
H2...00	Pneumonia and influenza	1.7
H261.00	Basal pneumonia due to unspecified organism	1.3
H28..00	Atypical pneumonia	1.2
H260.00	Lobar pneumonia due to unspecified organism	0.96
H231.00	Pneumonia due to mycoplasma pneumoniae	0.68
H20..00	Viral pneumonia	0.54
H20z.00	Viral pneumonia NOS	0.46
H22z.00	Bacterial pneumonia NOS	0.46
H540000	Hypostatic pneumonia	0.43
SP13100	Other aspiration pneumonia as a complication of care	0.21
H56y100	Interstitial pneumonia	0.19
H540100	Hypostatic bronchopneumonia	0.15
H22..00	Other bacterial pneumonia	0.14
H23..00	Pneumonia due to other specified organisms	0.12
H470312	Aspiration pneumonia due to vomit	0.12
H223.00	Pneumonia due to streptococcus	0.10
H201.00	Pneumonia due to respiratory syncitial virus	0.09
H2y..00	Other specified pneumonia or influenza	0.09
H22..11	Chest infection- other bacterial pneumonia	0.08
H22y200	Pneumonia-legionella	0.08
H25..11	Chest infection- unspecified bronchopneumonia	0.08
H270000	Influenza with bronchopneumonia	0.08
A3BXA00	Mycoplasma pneumoniae (PPLO) cause/dis classifd/oth	0.05
H224.00	Pneumonia due to staphylococcus	0.05
H270.00	Influenza with pneumonia	0.04
H20..11	Chest infection- viral pneumonia	0.03
H220.00	Pneumonia due to klebsiella pneumoniae	0.03
H23z.00	Pneumonia due to specified organism NOS	0.03
A3BXB00	Klebsiella pneumoniae/cause/disease classifd/oth chapt	0.02
A789300	HIV disease resulting in Pneumocystis carinii pneumonia	0.02
H060A00	Acute bronchitis due to mycoplasma pneumoniae	0.02
H221.00	Pneumonia due to pseudomonas	0.02
H233.00	Chlamydial pneumonia	0.02
H24y200	Pneumonia with pneumocystis carinii	0.02
H262.00	Postoperative pneumonia	0.02
H270.11	Chest infection- influenza with pneumonia	0.02
A116.00	Tuberculous pneumonia	0.01
A380300	Septicaemia due to streptococcus pneumoniae	0.01
AB24.11	Pneumonia- candidal	0.01
H06z112	Acute lower respiratory tract infection	0.01
H20y.00	Viral pneumonia NEC	0.01
H222.00	Pneumonia due to haemophilus influenzae	0.01
H22y000	Pneumonia due to Escherichia coli	0.01
H22yz00	Pneumonia due to bacteria NOS	0.01
H24..00	Pneumonia with infectious disease EC	0.01
H24y700	Pneumonia with varicella	0.01

2.4.2 Definition of drug exposures

Data were extracted for all recorded prescriptions of statins, ACE inhibitors, PPIs and H2RAs. A search was conducted within the THIN database for all the drugs in a given drug family that were available as prescription drugs in the National Health Service (NHS) as listed in the most recent British National Formulary (Table 2.3).[24]

Table 2.3: Drug exposures considered

Drug family	Generic drug name
Statins	Simvastatin Pravastatin Cerivastatin Atorvastatin Fluvastatin Rosuvastatin
Ace inhibitors	Ramipril Captopril Enalapril Lisinopril Quinapril Trandolapril Fosinopril Cilazapril Perindopril Imidapril Moexipril
Proton pump inhibitors	Omeprazole Lansoprazole Pantoprazole Esomeprazole Rabeprazole
Histamine 2 receptor antagonists	Cimetidine Ranitidine Nizatidine Famotidine Ranitidine bismuth citrate

2.4.3 Definitions of covariates

2.4.3.1 Smoking status

Subjects were categorised as non-smokers, ex-smokers or current smokers. If subjects had more than one record for smoking status, the most recent record of smoking status was used. This would imply that for people who changed status from smokers to non-smokers, the most recent record should read 'ex-smoker'.

2.4.3.2 Comorbidity: Charlson's comorbidity index score

The Charlson Index, a combined weighted comorbidity index was adapted for use with ICD-9 codes (list of codes included in Appendix 2).[25-28] Charlson et al (1987) developed this index based on a medical record review of diagnoses and procedures associated with 1-year mortality among hospital inpatients.[25] The index is calculated using a list of 17 comorbidities including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, liver disease, diabetes, hemiplegia, renal disease, neoplasms and AIDS. Each of these comorbidities is assigned a weighted score and the sum of the scores is an indicator of disease burden (Appendix 2).[25]

2.4.3.3 Socio-economic disadvantage: Townsends deprivation index score

Socio-economic disadvantage was measured using the Townsend index score (in quintiles) derived from 2001 census data at output area level (approximately 150 households in a homogeneous socioeconomic area).[16] The Townsend index is an area-based measure of deprivation and aims to represent the extent of material disadvantage.[29] Townsend's own description of material

disadvantage includes, “the material apparatus, goods, services, resources, amenities and physical environment and location of life”.[30] The Townsend score is calculated using the following data:[31]

- percentage of potentially economically active residents over 16 years of age who are unemployed
- percentage of households with ≥1 person per room
- percentage of households without car ownership
- percentage of households in which the occupier is not the owner

In THIN, the Townsend deprivation index is derived from patients’ home postcodes and then grouped into quintiles of deprivation. The first quintile corresponds to the least deprived and the fifth quintile corresponds to the most deprived. At the time of data collection for this thesis, Townsend deprivation index quintile was available for 256 (78%) general practices as the process of integrating this variable into the database for research purposes was in development.[16] There was about 8% missing data for this variable and a separate dummy category called ‘missing’ has been created for inclusion in the logistic regression and Cox regression models.

2.4.3.4 Individual comorbid conditions

The following conditions were included in the analyses because of their recognition as risk factors for pneumonia: [32 33] ischaemic heart disease (IHD) and chronic pulmonary disease [including chronic obstructive pulmonary disease (COPD) and asthma]. Identification of these conditions was done using search terms that mapped onto the relevant ICD-9 codes (Apendix 2).[34]

2.4.3.5 Other drugs

Drug prescriptions for nitrates, ACE-2 inhibitors, beta blockers, calcium channel blockers, diuretics, fibrates, antacids and oral and inhaled steroids were treated as proxy indicators for underlying comorbidity and considered as potential confounders. As in the case of the primary drug exposures, a search was conducted within the THIN database for all the drugs in a given drug family that were available as prescription drugs in the National Health Service (NHS) as listed in the most recent British National Formulary (Appendix 1).

2.5 Overview of study designs and analyses

This section provides a brief overview of study designs and analyses used. Detailed methods for the individual studies are included in the relevant chapters (Chapters 3-6).

2.5.1 Pneumonia incidence cohort study

All recorded diagnoses in THIN of pneumonia and acute lower respiratory tract infection from 1991 to 2003 were identified. The denominator population was the total population active and contributing data to THIN on the first of July of each year. The overall incidence of pneumonia was calculated for the study period and results were further stratified by calendar year, age group (five year age bands), gender and deprivation. The main outcome measures were incidence rates (IR) per 100,000 person-years, adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI).

2.5.2 Pneumonia case-control study

A population-based matched case-control study nested within THIN was conducted to investigate the effect of exposures to statins, ACEIs, PPIs and H_2RAs on pneumonia. Since data on exposure and outcome are recorded prospectively in THIN, it could be argued that a cohort analysis would be as easy to implement as a case-control analysis. Smeeth at al[35] point out that a case-control study carried out in primary care databases is essentially nested within a cohort study and separate studies on the risk of developing atopic diseases in children registered with GPRD showed that cohort and case-control approaches to analysing primary care data produce very similar findings.[35] A case-control study design was selected for this research question because it would be the most efficient design using pneumonia cases occurring within a year. Moreover, it would get over the problem of time-varying exposures arising with a cohort design. Cases were patients aged 40 years and above (because there were few drug exposures in those below this age) in the database with a diagnosis of pneumonia occurring between 1st July 2001 and 1st July 2002. For each case, six controls were matched by practice, sex and age at index date (within three years). Conditional multiple logistic regression was used to assess the strength of the association between current treatment with the different drugs and the risk of pneumonia. Main outcome measures were adjusted odds ratios (OR) and 95% CI.

2.5.3 Pneumonia self-controlled case-series analysis

The case-series analysis was conducted in all individuals (aged 40 years and above) with a recorded diagnosis of pneumonia during a one-year study

period. The aim of this study was to provide some degree of verification of the case-control analysis results by eliminating the bias introduced by the selection of controls. More importantly, this design controls for the effects of fixed (per individual) confounding factors by only using data on cases.[36] In this study this involved a comparison of pneumonia incidence rates in cases within exposed periods (period covered by prescription as well as periods following end of medication when there is a likely residual influence of the drug) compared to pneumonia incidence rates occurring within unexposed periods (periods not covered by prescription which are out of the influence of the drug). Main outcome measures were incidence rate ratios (IRR) and 95 % CI.

2.5.4 Pneumonia mortality study

This was a cohort study design conducted in two parts. The first part of the study looked at all-cause mortality in people with pneumonia in UK general practice as compared to the general population at discrete time-periods following pneumonia diagnosis: short-term mortality within 30 days of a pneumonia diagnosis, medium-term mortality between 31-90 days post-pneumonia and long-term mortality that occurs more than 90 days following a pneumonia diagnosis. Cases were patients of all ages in the THIN database with a diagnosis of pneumonia occurring between 1st July 2001 and 1st July 2002. For each case, a general population sample of similar characteristics was determined by matching six controls by practice, sex and age at index date i.e. pneumonia diagnosis date of case (within three years). Follow-up data on these patients was available till 5th July 2005 at the time of analysis.

The second part of the study investigated whether statins, ACEIs, PPIs and H2RAs have an impact on short-term and long-term mortality in pneumonia cases. Cases were patients aged 40 years and above in the THIN database with a diagnosis of pneumonia occurring between 1st July 2001 and 1st July 2002. These patients were followed up till 5th July 2005. Main outcome measures for both studies were adjusted hazard ratios (HR) and 95% CI.

All data management and analyses were carried out in Stata SE10 (StataCorp. 2007. Stata Statistical Software: Stata/SE 10.0 for Windows; Stata Corporation, College Station, TX, USA).

3 Incidence of pneumonia in the UK general practice population

3.1 Introduction

This chapter reviews the existing studies on pneumonia incidence and then goes on to describe the detailed methods for the incidence study. It describes the demographic details of the cohort of General Practice registered patients that was used for the analysis. It then presents the results for the incidence of pneumonia overall (including acute lower respiratory tract infection) as well as for each of the following codes individually: acute lower respiratory infection, bronchopneumonia, pneumonia unspecified and lobar pneumonia. This chapter also looks at incidence of pneumonia by gender, age group, deprivation and region. The chapter concludes with a discussion of how the results fit in with the literature. The findings described in this chapter have been published in a peer-reviewed journal and the paper is included in Appendix 4 for reference.[37]

3.2 Background to study

Pneumonia is widely recognised as an important public health problem but there are surprisingly few data on the current incidence of pneumonia in the UK and how this varies with calendar time and demographic factors such as age, gender and socio-economic status. Potential sources of data on pneumonia incidence include Hospital Episode Statistics (HES), death

registrations and computerised general practice databases. Clearly the estimates obtained using these different approaches will vary, but all provide information on the impact of pneumonia in the UK and how incidence rates vary with demographic factors. Previous evidence suggests that less than a third of people with a diagnosis of pneumonia in the UK are admitted to hospital,[38] and so the majority of cases of pneumonia in the UK are diagnosed and managed by general practitioners. This suggests that data from Hospital Episodes Statistics will underestimate the true incidence of pneumonia markedly and for this reason it is useful to study pneumonia incidence using a computerised general practice database. The main aims of this study were to estimate the overall incidence of pneumonia and current trends in the UK, to determine how the incidence of pneumonia varies with age, gender and socio-economic status and to compare these findings with those of studies in other settings.

3.3 Literature review: Incidence of pneumonia

A search was carried out using the terms 'pneumonia' AND 'incidence' OR 'cohort' OR 'longitudinal' in the PubMed database. Additional studies were identified from the reference lists of relevant papers. No language or setting restrictions were applied. In their guidelines the British Thoracic Society quote annual pneumonia incidence figures of 6 per 1000 in the 18-39 age group and 34 per 1000 in people of 75 years and above.[4 39 40] These figures are based on the research of Foy et al in the late 1970s in the US and Jokinen et al in the early 1990s in Finland.[41 42] More recently Almirall et al reported a lower annual incidence rate of 1.6 per 1000 for people over the age of 14 years in Spain with

a diagnosis of pneumonia confirmed radiologically.[43] Table 3.1 summarises studies to date on pneumonia incidence and their findings as incidence rates per 1000 person-years (IR/1000 py). Some of the specific features and limitations of the reviewed studies are discussed in Section 3.6.3 of this chapter where findings of this study are compared with the existing literature.

Table 3.1: Studies of pneumonia incidence

Study	Study period	Population	Identification of pneumonia cases	Pneumonia cases (n)	Age/age group	Incidence rate per 1000 person-years
Foy et al. (1979)[41]	1964-1975	Seattle, US: 64,000-180,000 Group Health Cooperative (prepaid primary care group) registered population	Physician reported diagnosis	15,141	<5 5-9 10-14 15-59 60-69 ≥70 All ages	34 16 8 5-8 10 18 12
Foy et al. (1979)[41]	1965 (non-influenza epidemic period)	Seattle, US: 64,000-180,000 Group Health Cooperative (prepaid primary care group) registered population	Physician reported diagnosis	(not specified)	<5 5-9 10-14 15-19 20-29 30-39 40-49 50-59 >60	12 5.4 1.4 0.7 1.3 1.3 1.8 2.0 3.6
Woodhead et al. (1987)[44]	1984-1985	Nottingham, England: 53,137 (15-79 yrs)	General practitioner diagnosed	251	15-79	4.7
Jokinen et al. (1993)[42]	1981-1982	Four municipalities in Finland: population 46,979	Patients reported by all physicians working in the area or at referral hospitals, autopsy diagnoses and cause of death on death certificates	546	<5 5-9 10-14 15-59 60-69 70-79 ≥80 All ages	36 17 16 6 15 21 42 12
Houston et al. (1995)[45]	1987	Minnesota, US: population 8,100 (≥65 years)	Recorded physician diagnoses in primary care, hospital diagnoses, autopsy diagnoses and cause of death on death certificates	243	≥65	30
Almirall et al. (1993)[46]		Barcelona, Spain: population 39,733 (above 13 years)	Diagnosis by primary care physicians and from A&E attendances	105	>13	2.6
Almirall et al. (2000)[43]	1993-1995	Barcelona, Spain: population 4,368 (≥14 yrs)	Diagnosis by primary care physicians	241	≥14	1.62
Present study (2008)	1991-2003	England and Wales: General Practice registered population	General practitioner diagnosed	56,332	All ages	2.37

3.4 Methods

The source population included all patients registered with THIN general practices who had at least one year of recorded data. Therefore for each patient satisfying this criterion, data were extracted from this point onwards i.e. one year after the computerised record start. When patients register with a new general practice or the practice converts from paper-based records to computerised patient databases, past diagnoses may be inadvertently recorded by using the date of entry into the new system.[47] Excluding the first year of a patient's record would ensure that no prevalent cases were included and is an adequate exclusion period as median resolution times for pneumonia are well within a month.[10] For these patients all recorded diagnoses of pneumonia and acute lower respiratory tract infection from 1991 to 2003 were identified using a look-up table of specific medical Read Codes (Chapter 2, Table 2.2). Read codes signifying working diagnoses, symptoms, signs and ill-defined conditions were excluded.[15] The total population active and contributing data to THIN on the first of July of each year served as the denominator. The overall incidence of pneumonia was calculated for the study period and results were further stratified by calendar year, age group (five year age bands), gender, geographical region and deprivation. An investigation was carried out to determine whether there was effect modification by age group and gender in the association between pneumonia incidence and socio-economic deprivation. The Townsend index score (in quintiles) derived from the 2001 census at output area level (approximately 150 households) was used as a marker of deprivation. In order to determine whether the use of specific pneumonia codes had changed over time the

analyses were repeated for each of the four most commonly used pneumonia codes. Poisson regression was used to compare rates between different populations and adjusted analyses were conducted to allow for confounding variables such as age and sex. The main outcome measures were incidence rates (IR) per 100,000 person-years, adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI). A series of post-hoc sensitivity analyses was also conducted:

- Pneumonia incidence by varying assumptions of disease episode length (7 days, 15 days and 30 days) i.e. any records of pneumonia within the specified episode length were treated as a single episode and only counted once
- Overall pneumonia incidence trends by geographical area to assess any geographical variations in coding uptake over time
- Incidence of lobar pneumonia and acute lower respiratory tract infection to identify geographical variations in the usage of codes (only these two sub-types were examined in the sensitivity analysis because 'lobar pneumonia' was considered a more stable code in terms of validity and reliability, whereas 'acute lower respiratory infection' was considered a 'broad' category with the greatest degree of variability).
- Pneumonia incidence by deprivation quintile and age-group to examine interactions between age and deprivation.

3.5 Results

The THIN database cohort included 56,322 recorded diagnoses of pneumonia between the years 1991-2003, inclusive. The mean age of people at pneumonia diagnosis was 61.9 years. 79% of cases had only a single recorded diagnosis of pneumonia.

3.5.1 Overall incidence

Figure 3.1 presents the trends in pneumonia incidence for the period 1991-2003. The overall crude incidence rate (IR) of pneumonia in the study cohort between 1991 and 2003 was 237 per 100,000 person-years (95% confidence interval (CI) 235 to 239), and remained stable during the study period (incidence rate ratio (IRR) 1.01, 95% CI 1.01 to 1.01) (Figure 3.1). Adjusting these crude incidence rates for age and gender did not alter this pattern (IRR 1.01, 95% CI 1.01 to 1.02).

Figure 3.1: Trends in pneumonia incidence, 1991-2003

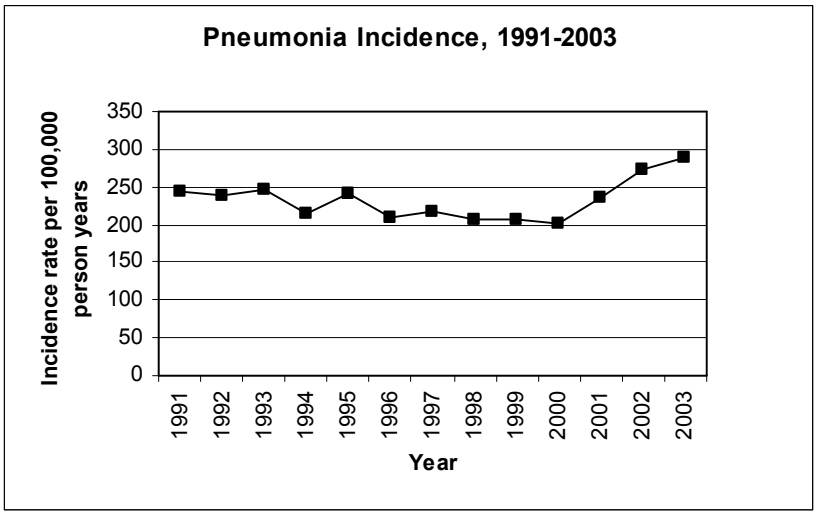


Table 3.2 presents the results of a sensitivity analysis in which pneumonia incidence was recalculated based on varying episode lengths (7 days, 15 days and 30 days). Pneumonia incidence (all ages) was 207 per 100,000 person-years (95 % CI 205 to 209) when an episode length of 30 days was assumed. This changed only slightly with the assumption of a 7-day long episode to 219 per 100,000 person years (95 % CI 217 to 221).

Table 3.2: Sensitivity analysis: Overall pneumonia Incidence (1991-2003) using varying assumptions for episode length

Assumptions	Cases (n)	IR/100,000 person-years	LL 95% CI	UL 95% CI
All recorded diagnoses	56332	237	235	239
Episode length 7 days	52121	219	217	221
Episode length 15 days	50250	211	209	213
Episode length 30 days	49259	207	205	209

3.5.2 Incidence by age group and gender

The incidence of pneumonia was strongly related to age and two obvious peaks of incidence were present - the first in children under the age of 5 years where the incidence rate was 191 per 100,000 person years (95% CI 184 to 198) and the second in people over the age of 60 years where the incidence rate was 666 per 100,000 person years (95% CI 659 to 673). The incidence rate was lowest for people aged 20 to 24 (incidence rate 50 per 100,000 person-years, 95% CI 47 to 54).

The incidence of pneumonia was slightly higher in females compared to males (IRR 1.06, 95% CI 1.04 to 1.07). When adjusted for age however, the incidence was lower in females (IRR 0.88, 95% CI 0.86 to 0.89). In general the association between pneumonia and age was similar in men and women, though in people over the age of 65 years the curve for men was shifted to the left by about five years (Figure 3.2(a)). In addition, there was also a slight peak in pneumonia incidence in women aged 30 to 39 years (Figure 3.2(b))

and the incidence rate ratio in comparison to men in the same age group was 1.14 (95% CI 1.07 to 1.21).

Figure 3.2: Pneumonia incidence by gender and age, 1991-2003

Figure 3.2a: Pneumonia incidence by gender and age, 1991-2003

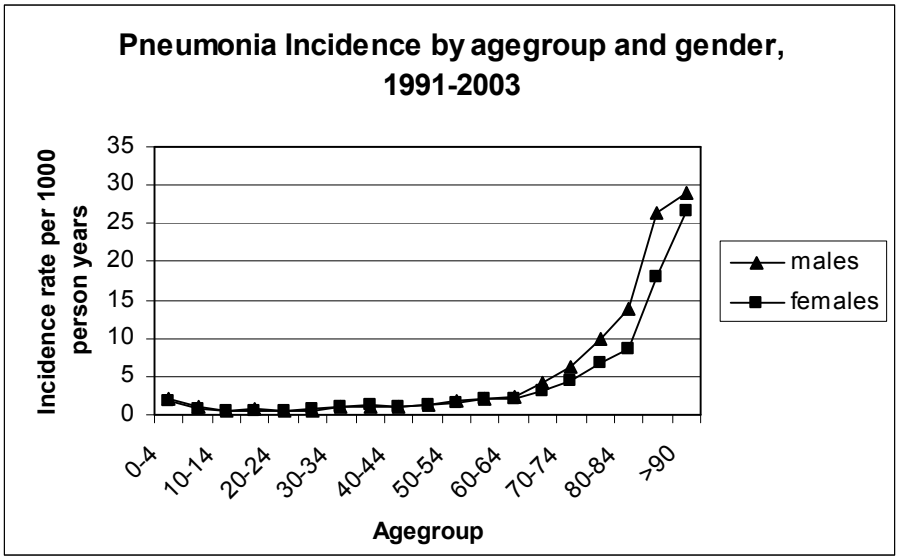


Figure 2b: Pneumonia incidence by gender and age (20-49 year olds), 1991-2003

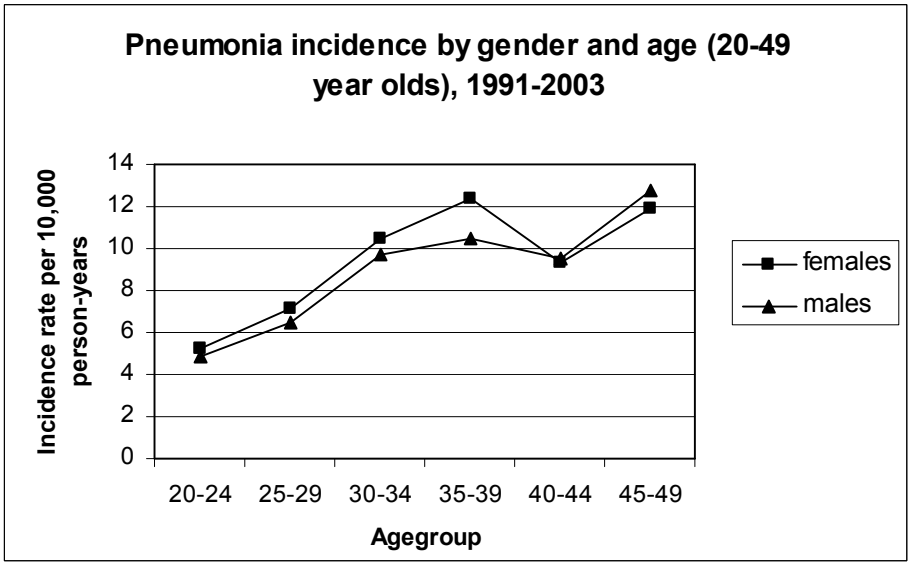


Table 3.3, Table 3.4, and Table 3.5 present the results for the post-hoc sensitivity analysis in which the incidence rates and incidence rate ratios (IRR) were calculated by sex, for varied episode lengths of 7 days, 15 days and 30 days. The post-hoc sensitivity analyses results show that the observed higher rates of pneumonia in women aged 30-39 years persist even on varying assumptions for episode lengths.

Table 3.3: Sensitivity analysis: Pneumonia Incidence in women aged 35-39 years old

Assumptions	Cases (n)	IR/100,000 person-years	LL 95% CI	UL 95% CI
All recorded diagnoses	1084	126	119	134
Episode length 7 days	989	115	108	123
Episode length 15 days	940	110	103	117
Episode length 30 days	917	107	100	114

Table 3.4: Sensitivity analysis: Pneumonia Incidence in men aged 35-39 years old

Assumptions	Cases (n)	IR/100,000 person-years	LL 95% CI	UL 95% CI
All recorded diagnoses	946	106	100	113
Episode length 7 days	863	97	91	104
Episode length 15 days	812	91	85	98
Episode length 30 days	797	90	84	96

Table 3.5: Sensitivity analysis: Pneumonia Incidence rate ratios in the 35-39 years age-group by sex, for varying episode lengths

Assumptions	Unadjusted IRR†	LL 95% CI	UL 95% CI
All recorded diagnoses	1.2	1.1	1.3
Episode length 7 days	1.2	1.1	1.3
Episode length 15 days	1.2	1.1	1.3
Episode length 30 days	1.2	1.1	1.3

†women compared to men

3.5.3 Incidence by deprivation

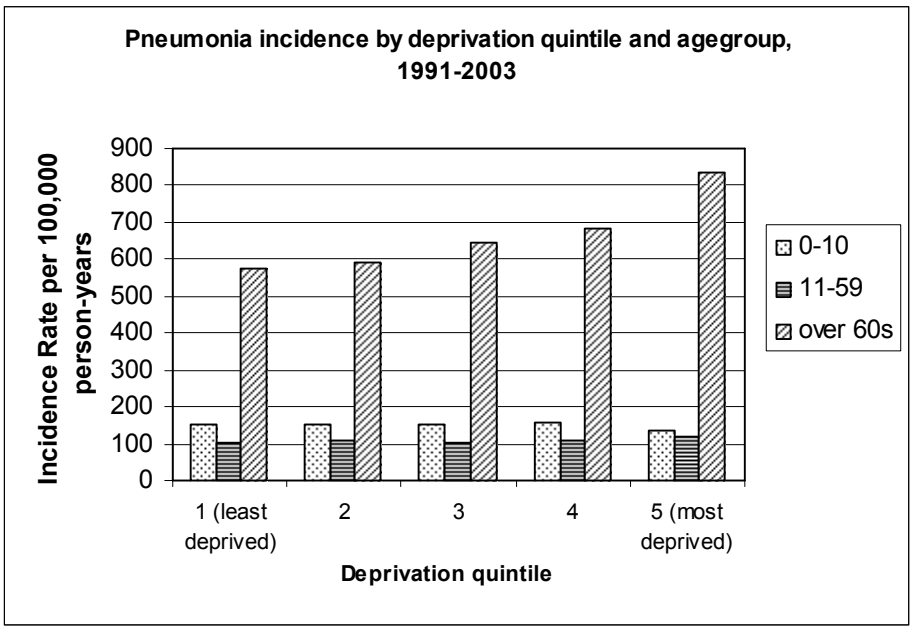
Table 3.6 presents the age and sex adjusted pneumonia incidence rate ratios by deprivation quintile for the period 1991 to 2003. The incidence of pneumonia was associated with socio-economic deprivation. The incidence in people in the most deprived group (Townsend score quintile 5) was 277 per 100,000 person years (95% CI: 271 to 283) and 205 per 100,000 person years (95% CI: 201 to 209) for people in the least deprived quintile. Even after taking into account age and gender effects, those in the most deprived quintile were nearly 30 percent more likely to contract pneumonia as compared to those in the least deprived quintile (IRR 1.28, 95% CI 1.24 to 1.32) (Table 3.6). This study found a significant interaction of deprivation with age group ($p<0.001$) but not with gender ($p=0.535$), when considering pneumonia incidence. In those aged over 60 years, individuals in the most deprived quintile were almost 50 percent more likely to contract pneumonia as compared to those in the least deprived quintile (IRR 1.45, 95% CI 1.40 to 1.46). The statistical effect of the socio-economic gradient became weaker in those aged 11-59 years (IRR 1.20, 95% CI 1.14 to 1.27). In children aged ten

and younger, the results did not show any socio-economic gradient (IRR 0.8, 95 % CI 0.82 to 1.01) (Figure 3.3).

Table 3.6: Age and sex adjusted pneumonia incidence rate ratios by deprivation quintile (1991-2003)

Townsend deprivation quintile	Incidence Rate Ratio (IRR)	Lower 95% CI	Upper 95% CI
Quintile 1 (least deprived)	1.00 (reference category)		
Quintile 2	1.00	0.98	1.03
Quintile 3	1.04	1.01	1.07
Quintile 4	1.09	1.06	1.12
Quintile 5 (most deprived)	1.28	1.24	1.32

Figure 3.3: Pneumonia incidence by deprivation quintile and age group, 1991-2003



Further analysis by splitting the older age-group (60 years and over) into the age-groups (60-79 years) and (80 years and above), showed that the socioeconomic gradient in pneumonia incidence was present primarily in the very elderly (Table 3.7).

Table 3.7: Pneumonia incidence rate ratio by Townsend deprivation quintile in age-groups (60-79) and (80 and above); post-hoc analyses

Townsend deprivation quintile	60-79 yrs IRR (95% CI)	80 yrs and above IRR (95% CI)
1 (least deprived)	1.00	1.00
2	0.80 (0.64-0.99)	1.06 (0.85-1.34)
3	0.87 (0.70-1.08)	1.01 (0.81-1.28)
4	0.83 (0.66-1.03)	0.98 (0.78-1.23)
5 (most deprived)	0.87 (0.69-1.09)	1.31 (1.05-1.65)

3.5.4 Individual read codes

The four most frequent Read codes used by general practitioners for pneumonia were: pneumonia unspecified (H26..00)(36%), bronchopneumonia unspecified (H25..00)(24%), lobar pneumonia (H21..00)(19%) and acute lower respiratory infections (H062.00)(7.6%). Table 3.8 summarises the incidence findings for these pneumonia Read codes individually and Figure 3.4 illustrates the incidence trends for each of these four codes (1991-2003). There was a marked increase in the incidence of acute lower respiratory infections from the mid 1990s [Figure 3.4(c)], and a decrease in the use of the pneumonia unspecified code at the same time [Figure 3.4(a)]. The incidence of the lobar pneumonia code was stable over time [Figure 3.4(d)]. In general,

coding practices for respiratory infections appeared to stabilise from the year 2000 onwards.

Table 3.8: Incidence rates per 100,000 person years for top 4 Read codes (1991-2003), UK general practice population (n=48,960)

Read code	Cases	IR/100,000	95% CI
Pneumonia unspecified (H26..00)	21,210	90	88, 90
Bronchopneumonia unspecified (H25..00)	14,506	61	60, 62
Acute lower respiratory infection (H062.00)	8,860	37	36, 38
Lobar (pneumococcal) pneumonia (H21..00)	4,384	18	17.9, 18.9

Figure 3.4: Trends in pneumonia incidence for individual Read codes, 1991-2003

Fig 3.4a: Pneumonia unspecified

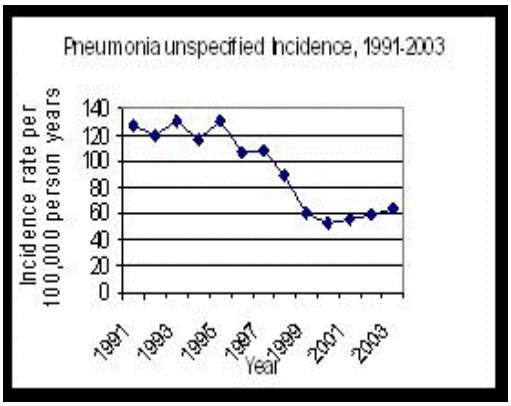


Fig 3.4b: Bronchopneumonia

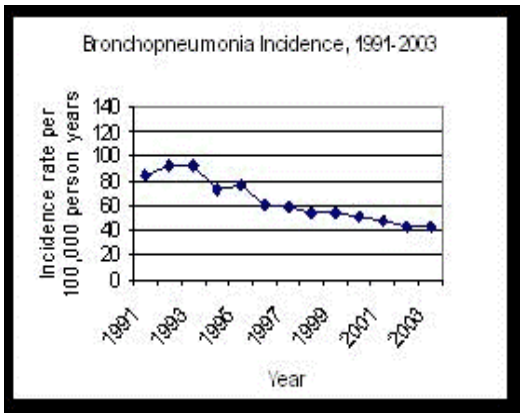


Fig 3.4c: Acute lower respiratory infection

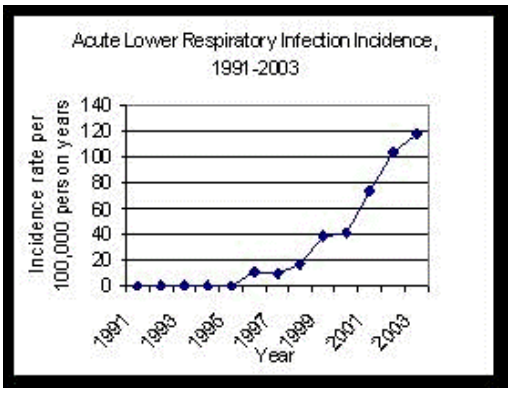
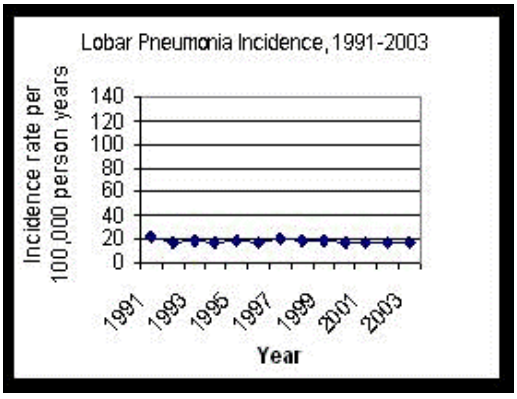


Fig 3.4d: Lobar pneumonia



3.5.5 Incidence by geographical region

Table 3.9 and Figure 3.5 summarise the regional incidence of pneumonia in the UK. The highest overall incidence of pneumonia and acute lower respiratory infections was observed in the south-west region of England (unadjusted IR/100,000 person-years 292, 95% CI: 284 to 300). The lowest overall incidence was observed for Northern Ireland (unadjusted IR/100,000 person-years 129, 95% CI 121 to 138).

Table 3.9: Regional incidence of pneumonia, 1991-2003

Region	Unadjusted IR/100,000 py	LL 95% CI	UL 95% CI
North East England	226	216	237
North West England	241	235	246
Yorkshire and Humber	193	186	200
East Midlands	206	198	213
West Midlands	258	252	264
East England	226	220	232
London	142	138	147
South East England	234	230	239
South West England	292	284	300
Northern Ireland	129	121	138
Wales	149	143	155
Scotland	245	238	253

Figure 3.5: Regional incidence of pneumonia, 1991-2003

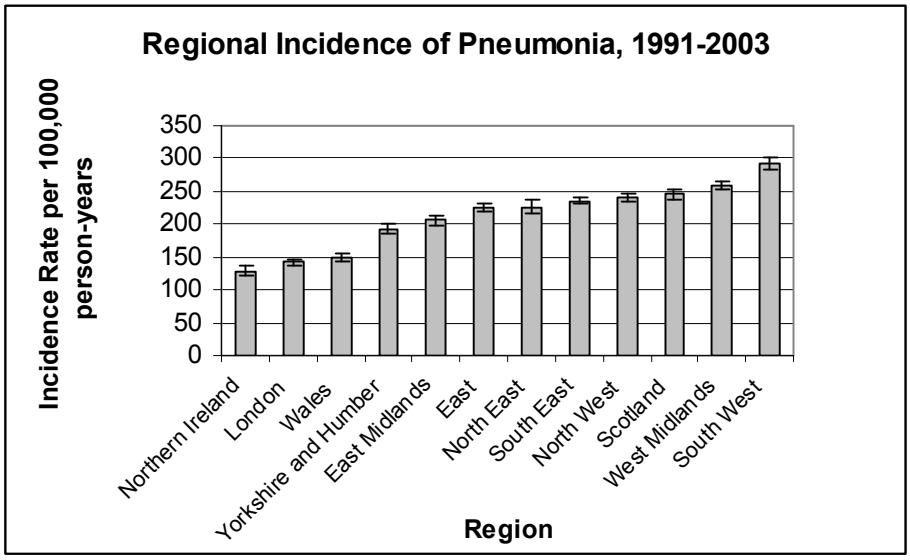


Figure 3.6 on the following page represents variations in pneumonia incidence trends for individual geographical regions. Pneumonia incidence appears to be increasing in South-west England[Figure 3.6(i)], North-west England Figure 3.6(b)], West Midlands [Figure 3.6(e)] and Scotland 2000-01[Figure 3.6(l)] onwards. In the West Midlands rates appear to have stabilised between 2001 and 2003 [Figure 3.6(e)].

Figure 3.6: Pneumonia incidence trends by geographical area, 1991-2003

Fig 3.6a: Pneumonia Incidence, North East England

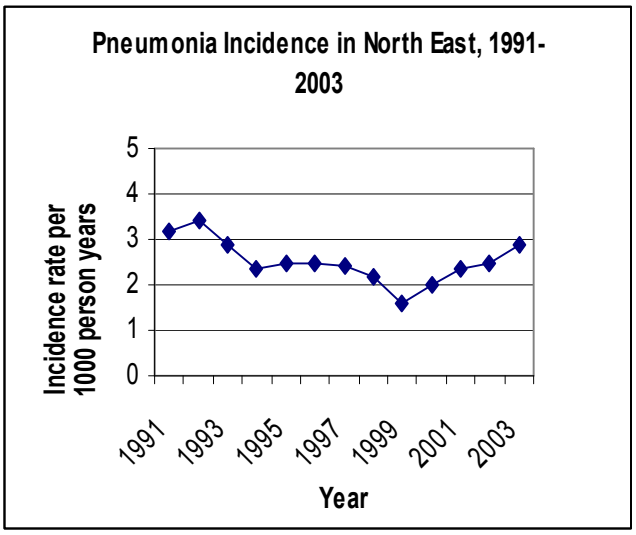


Fig 3.6b: Pneumonia Incidence, North West England

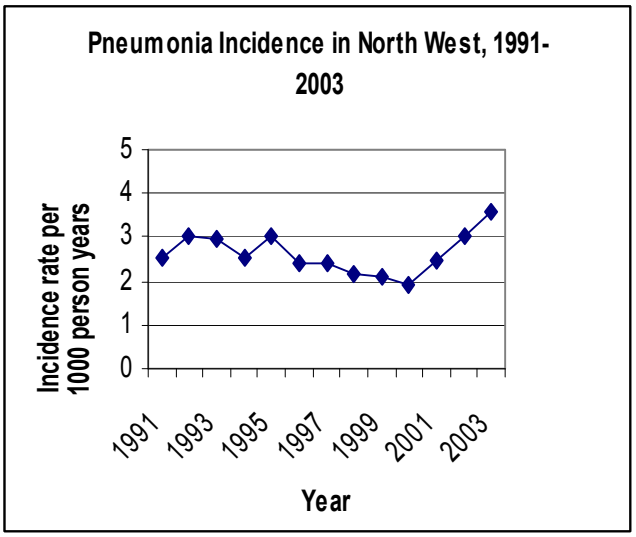


Fig 3.6c: Pneumonia Incidence, Yorkshire & Humber

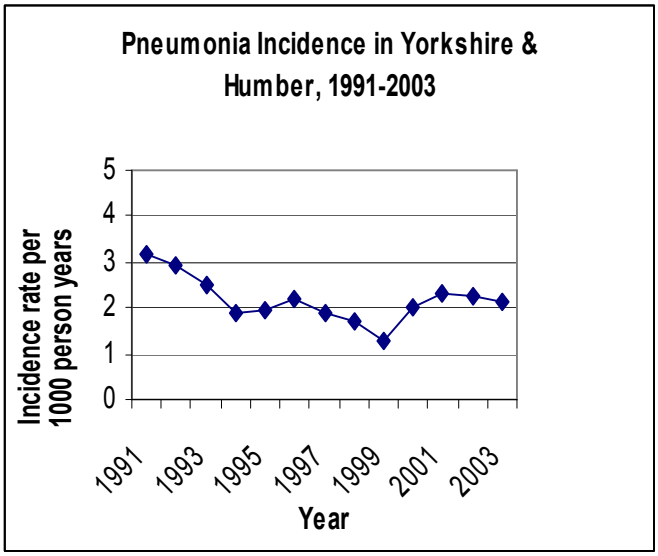


Fig 3.6d: Pneumonia Incidence, East Midlands

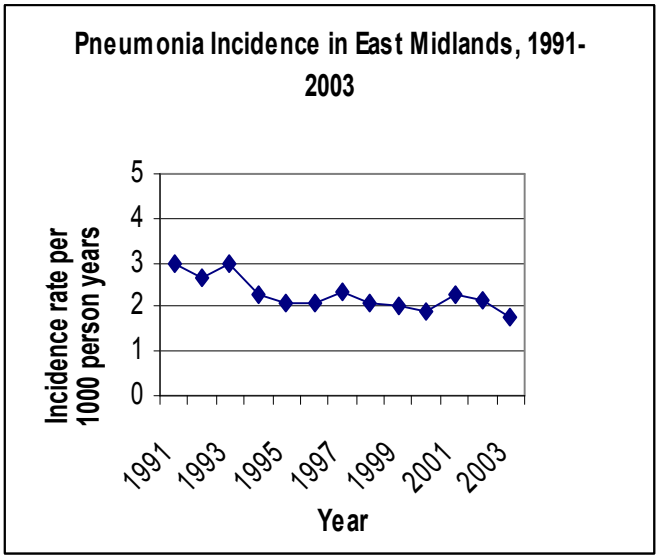


Fig 3.6e: Pneumonia Incidence, West Midlands

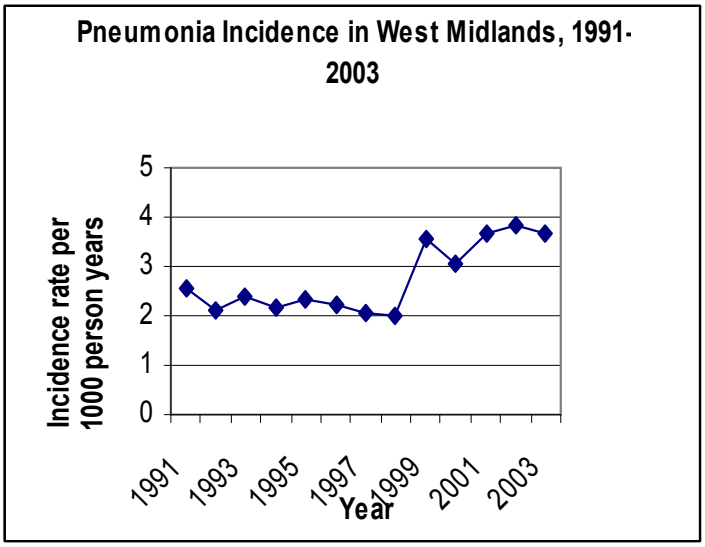


Fig 3.6f: Pneumonia Incidence, East England

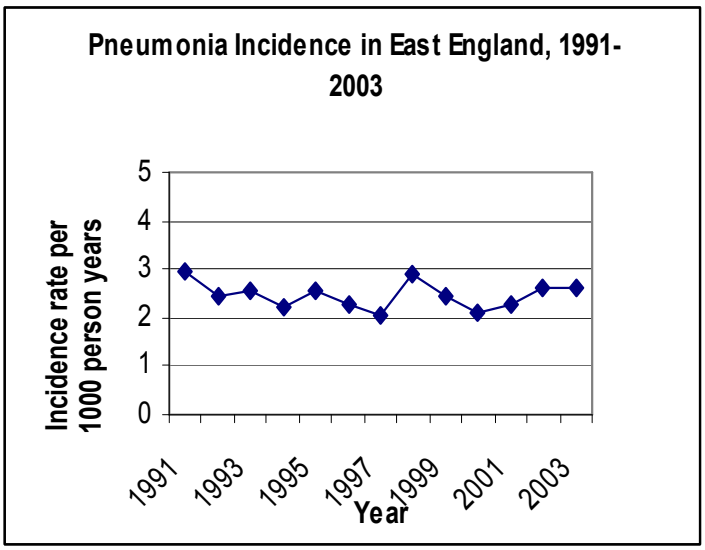


Fig 3.6g: Pneumonia Incidence, London

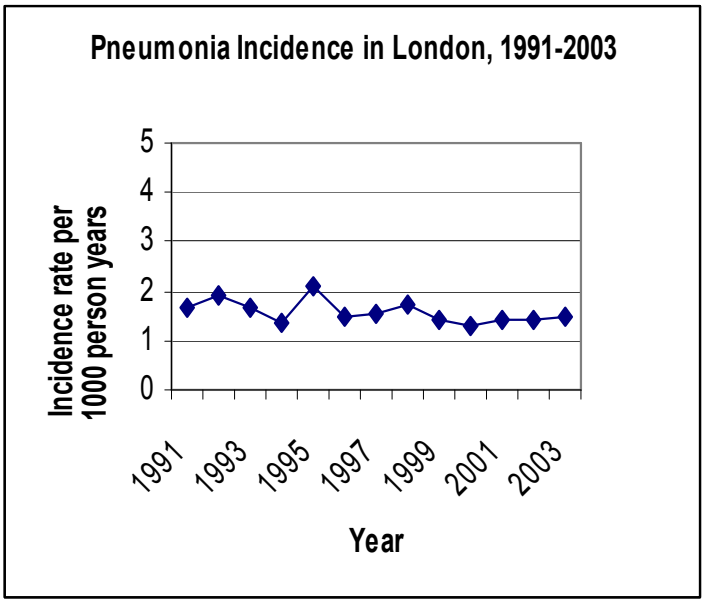


Fig 3.6h: Pneumonia Incidence, East England

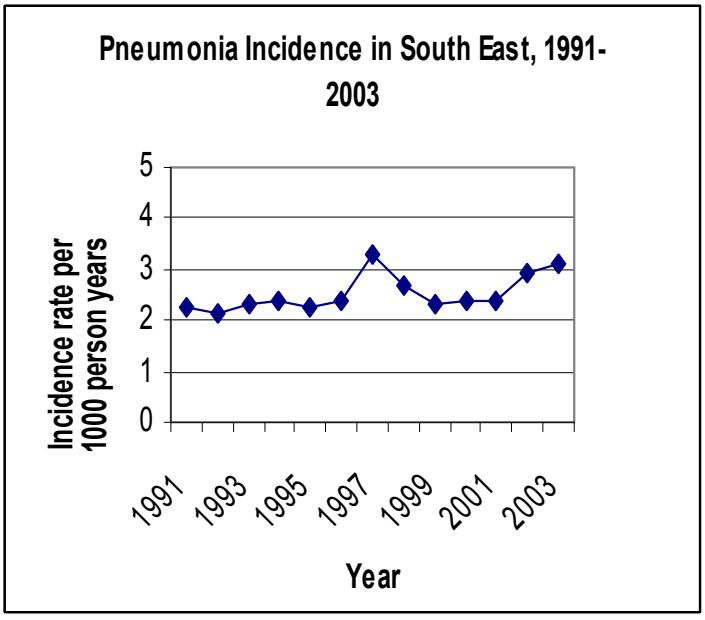


Fig 3.6i: Pneumonia Incidence, South West England

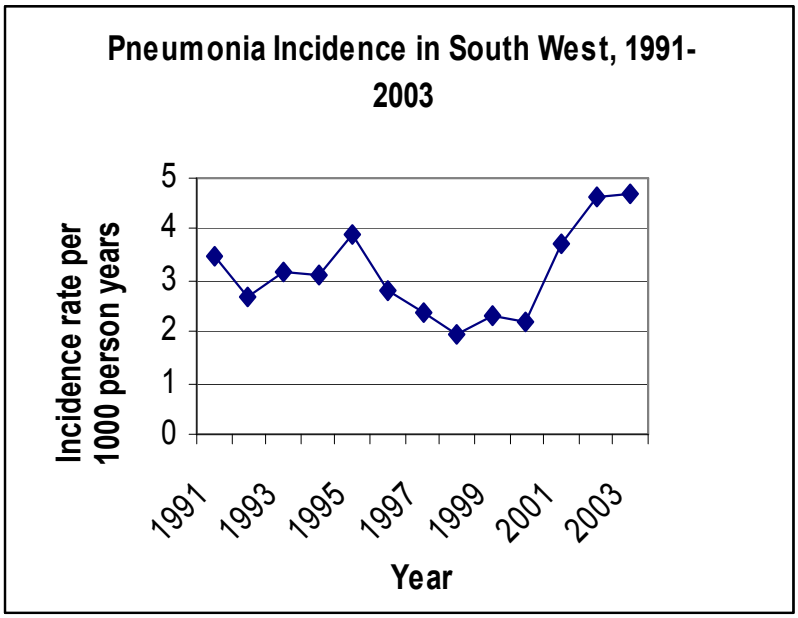


Fig 3.6j: Pneumonia Incidence, Northern Ireland

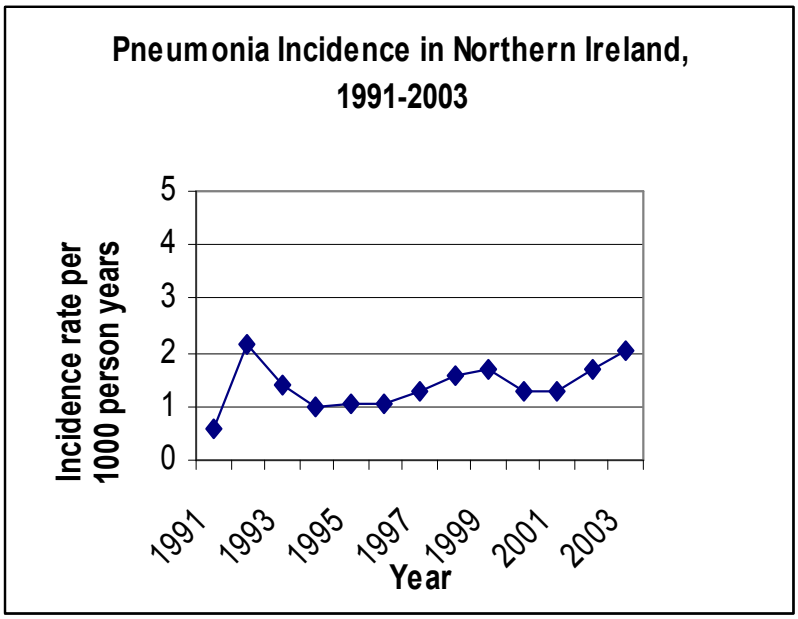


Fig 3.6k: Pneumonia Incidence, Wales

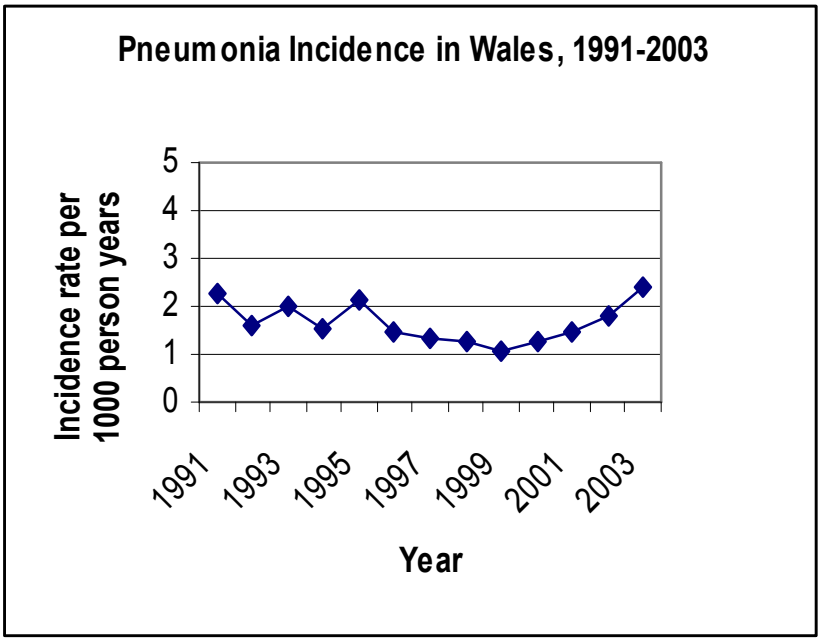


Fig 3.6l: Pneumonia Incidence, Scotland

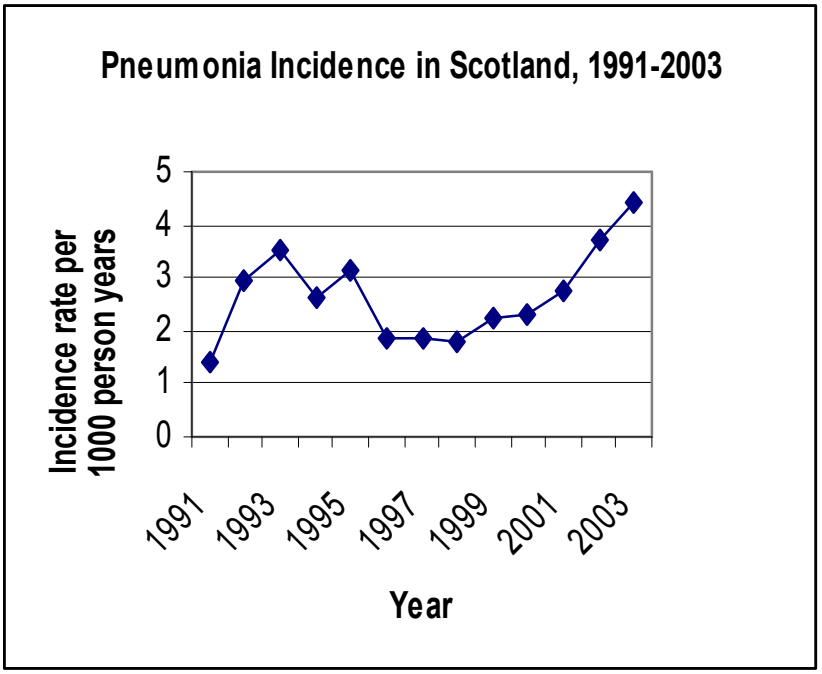


Figure 3.7 presents the geographical variation in the incidence of recorded lobar pneumonia in the UK from 1991 to 2003 and Figure 3.8 presents the same for acute lower respiratory tract infections. The variation is especially marked in the case of acute lower respiratory infections with very low numbers of cases being recorded in Northern Ireland and London. In the case of lobar pneumonia (Figure 3.7), the highest incidence rate is seen in East of England and the lowest rates in Wales and London. No clear geographical divide is obvious in the incidence rates for lobar pneumonia.

Figure 3.7: Regional incidence of lobar pneumonia, 1991-2003

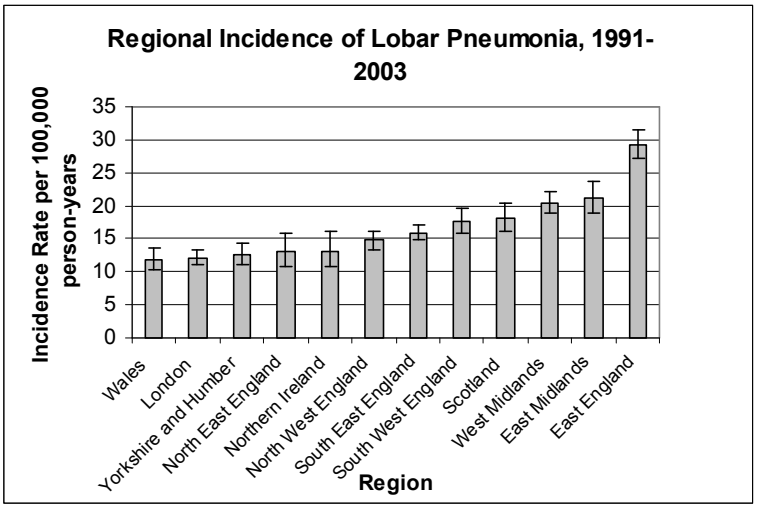
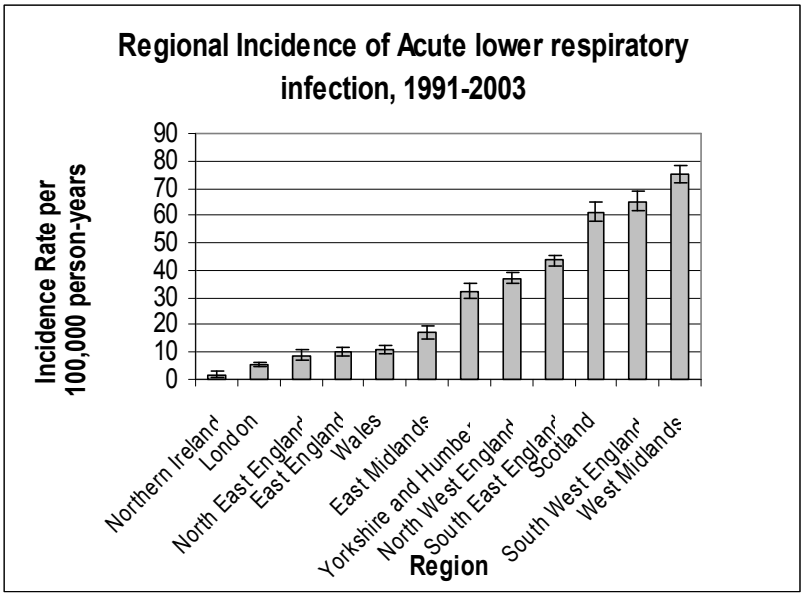


Figure 3.8: Regional incidence of acute lower respiratory infection, 1991-2003



3.6 Discussion

3.6.1 Principal findings

The study findings show that the incidence of pneumonia in the general population is currently 237 per 100,000 person-years and that this remained constant over the last decade. The incidence of pneumonia rises steeply with age in people over the age of 60 years, and the increase in incidence happens approximately 5 years earlier in men compared to women. Pneumonia is also common in children under the age of 5 years. There was evidence of an additional peak in pneumonia incidence in women of childbearing age. The incidence of pneumonia is related to levels of deprivation, particularly in people over the age of 60 years. There was a

regional difference in pneumonia incidence with the lowest incidence in Northern Ireland and the highest incidence in the South-west of London.

3.6.2 Strengths and limitations of this study

This is the largest and most up to date study of pneumonia incidence in a UK general population-based cohort. With 56,332 pneumonia cases this study is almost four times as big as the previous largest incidence study (Table 3.1). The large amount of statistical power in this study provided the opportunity to derive precise estimates of incidence and to stratify results by year, age-group, gender and deprivation. This detailed analysis made it possible to identify the increase in disease incidence present in women of childbearing age not previously identified. Since this study has used general practice data it is also likely that these findings are representative of the true incidence of pneumonia in the general population.

There are some potential limitations with this study which need discussion. It can be difficult to distinguish between incident and prevalent cases from records in routine databases. However, by only including pneumonia records that occur a year after a patient's medical record starts in THIN, we have overcome this issue. There is still potential for overestimation of pneumonia incidence because all recorded pneumonia diagnoses were used. It is possible that a diagnosis may be recorded more than once if the patient re-consults for the same episode of illness. However 79% of cases had a single record of pneumonia over 13 years so this effect cannot be large. A post-hoc sensitivity analysis was conducted using varying assumptions of episode

lengths (counting any recorded diagnoses within specified days of each other as part of a single episode of illness and therefore a “re-consult”). The sensitivity analysis considered varied episode lengths of 7 days, 15 days and 30 days. Incidence patterns and rates did not change significantly under varying assumptions (Table 3.2). There is also the issue of the validity of pneumonia diagnoses, which are based on general practitioner recorded diagnoses. There was no information on x-ray findings in THIN in order to confirm pneumonia diagnoses, but chest infections are commonly seen in general practice and previous evidence suggests that general practitioner diagnoses of pneumonia are reasonably accurate.[5 44 48] In addition, a previous validation study showed that codes from routine primary healthcare databases in the UK are a valid tool for identification of pneumonia.[21 49] Another concern was the consistency of coding practice over time and to investigate this, the study looked at the pattern of use of the four most frequently used pneumonia codes. Collectively these four Read codes accounted for 48,960 of the total 56,332 pneumonia cases in our study (Table 3.8). The results show that coding practices have changed over time with a dramatic increase in the use of acute lower respiratory infection from the mid-1990s (Figure 3.4). The likely explanation for this was a migration in the software coding system from the Oxford Medical Information Systems (OXMIS) codes (which could be mapped onto ICD-8 codes) to Read codes (which map onto ICD-9 codes) which occurred at this time. The OXMIS dictionary was much smaller than the Read dictionary and did not include a code for acute lower respiratory infection. From the mid-1990s when lower respiratory tract infection codes became available, patients presenting with pneumonia-like symptoms seem more

likely to be coded as ‘acute lower respiratory infections’ rather than ‘unspecified pneumonia’. Interestingly, the incidence of ‘lobar pneumonia’ has remained stable over the time period of this study, perhaps because this diagnosis tends to reflect more severe cases and would be more likely to have chest x-rays. On the whole, despite the changes in coding practice, the overall pneumonia incidence has remained relatively stable over the study period.

An area based deprivation index was used as it was not possible to access individual level deprivation data. Area based measures assume that individuals within a geographical unit are homogeneous in character and this may not be true. However, Townsend deprivation scores calculated at enumeration district level (about 200 households) have been shown to be good proxy measures for individual level deprivation measures.[31] For the purpose of this study, Townsend deprivation scores were calculated at output area level (about 150 households). There were also some missing values for Townsend scores: first, because the deprivation score for each patient is obtained by linking to a separate data file of deprivation scores by mapping on postcodes of residence and in the absence of full postcodes for a given patient, this cannot be done. Second, the deprivation scores in THIN are derived using the 2001 Census so only postcodes that existed at the time of the Census can be mapped. Another possible limitation arising from this latter occurrence is that deprivation has been measured at a single point in time (using 2001 Census data) on the assumption that an individual would not be moving between deprivation quintiles over the13-year study period.

3.6.3 Comparison with existing literature

Table 3.10 summarises the pneumonia incidence data from different studies, all of which have used different populations and different methods to obtain cases and so not unexpectedly give differing results. Since each study has considered a slightly different population in terms of age-group, the last column in Table 3.10 gives the IR/1000 calculated using the THIN study population corresponding to the various age-groups to facilitate comparison.

Table 3.10: Studies on pneumonia incidence

Study	Study period	Population	Identification of pneumonia cases	Number of pneumonia cases	Age/age group	Incidence rate/1000 person-years	Incidence rate/1000 person-years (This study)
Foy et al. (1979)[41]	1964-1975	Seattle, US: 64,000-180,000 Group Health Cooperative (prepaid primary care group) registered population	Physician reported diagnosis	15,141	<5 5-9 10-14 15-59 60-69 ≥70 All ages	34 16 8 5-8 10 18 12	2 1 0.6 1 3 10 2.3
Foy et al. (1979)[41]	1965 (non-influenza epidemic period)	Seattle, US: 64,000-180,000 Group Health Cooperative (prepaid primary care group) registered population	Physician reported diagnosis	(not specified)	<5 5-9 10-14 15-19 20-29 30-39 40-49 50-59 >60	12 5.4 1.4 0.7 1.3 1.3 1.8 2.0 3.6	2 1 0.6 0.7 0.6 1.1 1.1 2.0 6.7
Woodhead et al. (1987)[44]	1984-1985	Nottingham, England: 53,137 (15-79 yrs)	General practitioner diagnosed	251	15-79	4.7	2
Jokinen et al. (1993)[42]	1981-1982	Four municipalities in Finland: population 46,979	Patients reported by all physicians working in the area or at referral hospitals, autopsy diagnoses and cause of death on death certificates	546	<5 5-9 10-14 15-59 60-69 70-79 ≥80 All ages	36 17 16 6 15 21 42 12	2 1 0.6 1 3 7 16 2.3
Houston et al. (1995)[45]	1987	Minnesota, US: population 8,100 (≥65 years)	Recorded physician diagnoses in primary care, hospital diagnoses, autopsy diagnoses and cause of death on death certificates	243	≥65	30	8
Almirall et al. (1993)[46]		Barcelona, Spain: population 39,733 (above 13 years)	Diagnosis by primary care physicians and from A&E attendances	105	>13	2.6	2.6 (>15 yrs)
Almirall et al. (2000)[43]	1993-1995	Barcelona, Spain: population 4,368 (≥14 yrs)	Diagnosis by primary care physicians	241	≥14	1.62	2.6 (>15 yrs)
Present study (2008)	1991-2003	England and Wales: General Practice registered population (THIN database):	General practitioner diagnosed	56,332	All ages	2.37	

The present study findings are most similar to the Spanish and Nottingham studies when considering similar age groups[43 44 46] and this is not surprising as the methods used were most similar to the ones used here. However, the present study found lower incidence rates than the American and Finnish studies.[41 42 45] One possible explanation for this is that the Seattle study looked at rates of pneumonia during influenza epidemics and actually during non-epidemic periods their rates were similar to the findings of this study.[41] Interestingly the rates in the above-60 population from the Seattle study were smaller than the present study, and this may be because the Seattle study used data from a prepaid medical care system that is largely composed of employed people and possibly a smaller but healthier population aged over 60 years.

The studies from Finland and Minnesota have two important methodological differences as well when compared to this study. First, both included hospital diagnoses, autopsy diagnoses and diagnoses on death certificates as well as primary care diagnosed pneumonia cases.[42 45] This would result in higher case ascertainment thereby increasing incidence rates. Secondly, when considering hospital based cases it is difficult to determine the catchment area and thereby, the denominator population precisely. Underestimating the catchment area could result in the higher rates found in these studies.

On the whole, all studies show similar incidence patterns in terms of age, with two age related peaks for under fives and over-60s. This study also found that the increase in pneumonia incidence by age occurred about five years earlier

in men than in women. This is in keeping with gender patterns seen in life expectancy statistics.[50] This study showed different gender patterns to other studies which have all found a slightly higher overall incidence rate in males. On adjusting for age however, the incidence was higher in males as expected. Further analysis by gender and age-group showed an almost two-fold rise in diagnoses of acute lower respiratory infections in females aged 30-39 years. A post-hoc sensitivity analysis was conducted by comparing pneumonia incidence in women aged 30-39 years to that in men belonging to the same age-group under varying assumptions of episode lengths. With all assumptions, incidence rates and IRRs showed a significantly higher incidence in women as compared to men in this age-group (Table 3.3, Table 3.4 and Table 3.5). This could be because of higher primary care consultation rates in females resulting in increased ascertainment of milder pneumonia cases.[51-53] Alternatively, it is possible that women in this age group are exposed to a greater risk of chest infections from their children thereby resulting in an actual increase in chest infections among this group.

None of the other incidence studies looked at pneumonia incidence in relation to deprivation. In the present study, pneumonia incidence increased with increasing levels of deprivation. This is consistent with other study findings that socio-economic deprivation measured by Townsend index is a significant predictor of hospital admissions from respiratory diseases.[54] The presence of a socio-economic gradient in the elderly with regards respiratory disease has been debated.[33 55-57] One of the interesting findings of this study was the interaction of deprivation with age, with a marked socio-economic gradient in

those aged over 60 years. Further analysis showed that the gradient was primarily seen in the very elderly in the age-group over 80 years (Table 3.7).

No studies were found that looked at geographical variations in pneumonia incidence in the UK. Though it is accepted that in England a north-south divide is present in England in relation to health, with rates of disease and mortality being higher in the north, this was not observed in the present study.[58] Surprisingly, within England, the lowest overall pneumonia incidence rates over the study period (1991-2003) were observed in London. This is in contrast to the Office of National Statistics report that found the highest mortality rates from respiratory diseases in London.[58] It could be argued that it is possible to have high mortality in the context of low incidence and that this could reflect poor access to healthcare. Alternatively, there could be an issue with coding of respiratory diseases within THIN. To explore this latter issue, a series of post-hoc analyses was conducted:

1) Pneumonia incidence trends were plotted by geographical area in an attempt to identify any differences in coding uptake over time within each region (Figure 3.6)
2) An investigation was carried out into geographical variations in the incidence of lobar pneumonia (previously identified as one of the more stable pneumonia codes (Figure 3.4(d)) and acute lower respiratory infection (previously identified as a code that has been used increasingly since the mid-1990s (Figure 3.4(c)). This was to identify any differences in the usage of codes across regions.

The post-hoc analyses suggest that some of the observed geographical variations could be explained by differences in coding practices across areas. For instance, it is very surprising that practices in Northern Ireland only recorded 8 cases of acute lower respiratory infection over 13 years. However within England, there does appear to be some regional variation in pneumonia incidence as incidence appears to be stable over the years (Figure 3.6) and the unexpected low rates in areas like London could just be a reflection of poor or delayed access to healthcare.

3.7 Summary

This study found that the pneumonia incidence rate in the UK general practice population is currently 237 per 100,000 person-years. Incidence rates remained fairly stable over the study period and no perceptible trends were noted. A slight upward trend was observed in incidence from 2000 to 2003, which may reflect changing in coding practices. Stratified results showed that the incidence of pneumonia is higher in people at the extremes of age, men and people living in socially deprived areas. There is some evidence of geographical variation in pneumonia incidence but this may be a reflection of poor access to healthcare or varying coding practices rather than a true incidence measure.

4 Case-control study: The impact of statins, ACE inhibitors, proton pump inhibitors and histamine 2 receptor antagonists on pneumonia

4.1 Introduction

This chapter introduces the evidence for the potential effect of statins, ACEIs, PPIs and H2RAs on pneumonia risk and then goes on to describe the detailed methods for the case-control study. Unadjusted and adjusted odds ratios and 95 percent confidence intervals showing the association between treatment with the various drugs and pneumonia are presented followed by a discussion of the findings. The findings presented in this chapter have been published in a peer-reviewed journal and the published paper has been included in Appendix 4.[59]

4.2 Background to study

The main aim of this study was to investigate the association between exposures to statins, ACEIs, PPIs and H2RAs, and the risk of acquiring pneumonia using general population-based data from the UK. This section provides an overview of the uses and mechanisms of action of each of these drug classes. Section 4.3 summarises the evidence in relation to these four drug groups and pneumonia risk.

4.2.1 Statins

Statins are a class of lipid regulating drugs used mainly for reducing plasma cholesterol. They act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, which is essential for cholesterol biosynthesis in mammalian cells.[60 61] In addition, statins also appear to have some anti-inflammatory effects and C-reactive protein (a marker of inflammation) levels have been found to be lower in statin users compared to non-users [60-62]. Statins are used both for primary prevention of cardiovascular disease in patients at increased risk, and secondary prevention of cardiovascular disease events in patients with coronary heart disease (including those with a history of angina or acute myocardial infarction).[24] In addition, it has been proposed that statins have pleiotropic effects that include immunomodulatory and anti-inflammatory actions that may decrease sepsis and improve outcomes of respiratory disease.[62 63] Statins could affect the migration of inflammatory cells from blood into the lung and decrease pulmonary inflammation.[64] However concerns have been expressed that this may be at the cost of inhibiting the host immunological defence thereby promoting infection.[64]

4.2.2 Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors are used primarily in heart failure and hypertension as well as prophylaxis of cardiovascular events in patients who have had a myocardial infarction.[24] ACEIs inhibit the conversion of angiotensin-I to its activated form angiotensin-II, which acts as a vasoconstricting agent.[24] A complementary action of ACEIs is to reduce the

degradation of substance P which triggers and upregulates both the cough and swallowing reflex on accumulation.[65] It has been suggested that the increased cough reflex lowers the risk of aspiration pneumonia in the elderly.[65]In addition, ACEIs have been shown to prevent endothelial dysfunction which has a crucial role in the pathophysiology of septic shock, which could influence pneumonia outcomes.[63 66]

4.2.3 Gastric acid suppressants: proton pump inhibitors and histamine 2 receptor antagonists

Gastric acid suppressants are used mainly in the treatment of gastric and duodenal ulcers and gastro-oesophageal reflux disease.[24] They act by inhibiting gastric acid secretion. Histamine 2 receptors are found in the acid-secreting cells in the stomach and on stimulation cause gastric acid secretion. H2 receptor antagonists inhibit histamine actions at all H2 receptors thereby inhibiting gastric acid secretion.[67] Proton pump inhibitors act by irreversibly blocking the hydrogen-potassium adenosine triphosphatase enzyme system (proton pump) terminal step in the gastric acid secretory pathway in the gastric parietal cell.[24 67] The increased susceptibility to respiratory infections is attributed to their property of increasing gastric pH and thus allowing bacterial colonisation.[68 69] Alternatively, gastric acid–suppressive drugs may also have a direct effect on the immune system and proton pump inhibitors appear to inhibit several leukocyte functions.[70]

4.3 Literature review

The main aim of the literature review was to identify studies investigating the impact of statins, ACE inhibitors, PPIs and H2RAs on the risk of acquiring pneumonia in the community. A search was carried out using the terms 'pneumonia' AND 'statins' OR 'ACEI' OR 'ACE inhibitors' OR 'angiotensin converting enzyme inhibitors' OR 'PPI' OR 'proton pump inhibitor' OR 'gastric acid suppressants' OR 'H2 blockers' OR 'H2 receptor antagonists' in the PubMed database. Additional studies were identified from the reference lists of relevant papers. No language, sample size or setting restrictions were applied. Studies dealing specifically with nosocomial pneumonia and prognosis of pneumonia patients were excluded from this review.

The use of statins and ACE inhibitors has been shown to lower the risk of pneumonia and improve outcomes in pneumonia patients (both severity and mortality).[71-76] Statin use has been associated with a 30% reduction in the risk of acquiring pneumonia in the community and a 50% risk reduction in people with diabetes.[71 72] In the case of ACEIs the estimated risk reduction for nosocomial pneumonia and CAP is between 20% and 50%.[73-75]However, other recent studies have not found a significant association with pneumonia risk for either statins or ACEIs.[72 77] It is difficult to draw any conclusions regarding the effect of these drugs on pneumonia incidence in the general population because the methods and study populations have varied between studies. In addition, no study has looked at the effect of all four drugs in a large population-based sample. Table 4.1 and Table 4.2 summarise the key findings of studies looking at the association between these drugs and the risk

of pneumonia. The Okaishi et al. (1999) and Takahashi et al. (2005) studies have not been included in Table 4.1 as they only consider nosocomial pneumonia cases. [74] [75] The Mortensen et al. (2005) study[76] looked at 30-day mortality following a pneumonia diagnosis and will be reviewed in Chapter 7. Similarly, the Majumdar et al. (2006) study has not been presented in Table 4.1 as it used a composite outcome variable of in-hospital mortality or admission to the intensive care unit.[77] One of the studies investigating the association between gastric acid suppressants and pneumonia risk used self-reported clinical manifestations of respiratory infections (fever, common cold, influenza, laryngitis, pneumonia, sinusitis and otitis media) instead of physician diagnosed pneumonia or ALRI and has been excluded from Table 4.2.[78]

Gastric acid suppressants on the other hand, may increase the risk of acquiring pneumonia. Previous studies have shown that treatment with gastric acid suppressants such as proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RAs) may be associated with an increased risk of community-acquired pneumonia (CAP).[68] [78] [79] However, there has been some contradictory evidence with a recent study using hospitalised pneumonia cases finding an increased pneumonia risk with PPIs but not with H2RAs.[69] The study by Sarkar et al[80] found an increased risk of pneumonia with PPIs only within the first month of use, following which the association weakened and became insignificant. These anomalous findings suggest the possibility of other non-causal mechanisms underlying the previously observed

associations between gastric acid suppressants and pneumonia. Residual confounding would be another possible explanation.

Table 4.1: Studies investigating the association between statins, ACE inhibitors and pneumonia risk

Author, year, setting	Study design and study period	Study population	Exposure variable	Outcome variable	Risk estimates
Van de Garde et al. (2006); UK [72]	Case-control study (1987-2001)	Diabetics (≥18 yrs) registered with general practice (GPRD) 4,719 cases and 15,322 matched controls	Current statin use	Recorded diagnosis of pneumonia	Adjusted OR (statin users vs. non-users): 0.49 (95% CI: 0.35-0.69)
Schlienger et al. (2007); UK [71]	Case-control study (1995-2002)	Adults (≥30 yrs) registered with general practice (GPRD) 1,253 cases and 4,838 matched controls	Current statin use	Recorded diagnosis of pneumonia	Adjusted OR (statin users vs. non-users): 0.71 (95% CI: 0.56-0.89)
Ohkubo et al. (2004); 10 country multi-centre study including UK) [73]	Randomised controlled trial (recruitment 1995-1997; median follow-up 3.9 yrs)	6,105 individuals with history of cardiovascular disease in previous 5 years randomised to receive perindopril or a placebo	Current ACEI use	Self-reported pneumonia and pneumonia on death certificate	Relative risk reduction (ACEI vs. placebo): 19% (95% CI: 3 to 37%)
Van de Garde et al. (2006); The Netherlands [81]	Case-control study (1995-2000)	1,108 cases (>18 yrs) and 3,817 matched controls	Current ACEI use	Hospital discharge diagnosis of pneumonia	Adjusted OR (ACEI users vs. non-users): 1.12 (95% CI: 0.88-1.43)
Etminan et al. (2006); Canada [82]	Nested case-control study (1996-2000)	Patients with coronary artery disease with revascularisation procedure 1,666 cases and 33,315 matched controls	Current ACEI use	Hospital diagnosis of pneumonia	Adjusted rate ratio (current ACEI users vs. non-users): 0.98 (95% CI: 0.69-1.40)

Table 4.2: Studies investigating the association between gastric acid suppressants and pneumonia risk

Author, year, setting	Study design and study period	Study population	Exposure variable	Outcome variable	Risk estimates
Laheij et al. (2004); The Netherlands [68]	Nested case-control study (1995-2002)	475 cases and 4960 controls from general practice	Current PPI use Current H2RA use	Recorded diagnoses of probable and confirmed (i.e. chest x-ray) pneumonia	Adjusted OR (current PPI users vs. non-users): 1.73 (95% CI: 1.33-2.25) Adjusted OR (current H2RA users vs. non-users): 1.59 (95% CI: 1.14-2.23)
Canani et al. (2006); Italy [79]	Prospective cohort study (recruitment Dec 2003 to March 2004); 4-month follow-up	Exposed: 91 Children (4-36 months) attending paediatric gastroenterology centres for common GERD-related symptoms and prescribed GA inhibitors for 8 weeks Unexposed group: 95 children attending paediatric centres for routine examination and not treated with GA-inhibitors in previous four months	GA-inhibitor use for 8 weeks (either ranitidine or omeprazole)	Pneumonia confirmed by radiology	Unadjusted OR (GA users vs. non-users): 6.39 (95% CI: 1.38-29.70)
Gulmez et al. (2007); Denmark [69]	Case-control study (2000-2004)	7,642 hospitalised cases and 34,176 frequency-matched controls	Current PPI use Current H2RA use	Hospital discharge diagnosis of pneumonia confirmed by x-ray	Adjusted OR (current PPI users vs. non-users): 1.5 (95% CI: 1.3-1.7) Adjusted OR (current H2RA users vs. non-users): 1.1(95% CI: 0.8-1.3)

Author, year, setting	Study design and study period	Study population	Exposure variable	Outcome variable	Risk estimates
Sarkar et al. (2008); UK [80]	Nested case-control study (1987-2002)	Adults (≥18 yrs) registered with general practice (GPRD) 80,066 cases and 799,881 matched controls	Current PPI use H2RA use in the 2 weeks before pneumonia diagnosis	Recorded diagnosis of pneumonia	Adjusted OR (current PPI users vs. non-users): 1.02 (95% CI: 0.97-1.08) Adjusted OR (H2RA users vs. non-users): 3.90 (95% CI: 3.18-4.78)

4.4 Methods

4.4.1 Study population

This study was a population-based matched case-control study nested within THIN. Data were extracted on patients in the THIN database with at least one year of recorded data after the practice computerisation date. Cases were patients in the database with a diagnosis of pneumonia occurring between 1 July 2001 and 1 July 2002. These years were selected because of the greater consistency of coding practices as evidenced by the trend analyses in Chapter 3 (Figure 3.4 and Section 3.5.4). July was selected as the study start and end month to retain the winter months together in one block so as to take into account seasonal changes in respiratory infection risk. Only the first recorded pneumonia diagnosis within this period was considered for each case so that a person could only be counted as a case once. Analyses were limited to a single year because of the vast number of cases in the database. Identification of cases was done using specific medical Read codes corresponding to a pneumonia diagnosis (Chapter 2, Table 2.2). The date of pneumonia diagnosis was designated the index date. Subjects were restricted to those above 40 years of age as very few people had the drug exposures of interest below this age (Table 4.3). For each case, six controls were matched by practice, sex and age at index date (within three years). Controls were selected from subjects without pneumonia at the time the index case was diagnosed with pneumonia and the study did not exclude controls or cases if they had a recorded pneumonia diagnosis before the selected study period. Previous pneumonia episodes were included as a covariate in the analysis.

This was done to avoid a possible bias by excluding patients who were potentially more susceptible to pneumonia.

Table 4.3: Percentage of people under the age of 40 years exposed to drug of interest

Drug class	Percentage of people aged <40 years exposed
Statins	0.3
ACE inhibitors	0.3
Proton Pump inhibitors	2.6
H2 receptor antagonists	3.5

4.4.2 Exposure definition

Four exposure variables were considered: prescriptions for statins, ACE inhibitors, proton pump inhibitors and H2 receptor antagonists. Data were extracted for all recorded prescriptions of statins, ACE inhibitors, PPIs and H2RAs. A search was conducted within the THIN database for all the drugs in a given drug family that were available as prescription drugs in the NHS as listed in the most recent British National Formulary.[24]Table 4.4 shows the drugs that were prescribed and the prescription frequency within a given drug family.

Table 4.4: Drug exposures considered and frequency of prescription

Drug family	Generic drug name	Percent prescribed within drug family
Statins	Simvastatin	50.0
	Pravastatin	30.7
	Cerivastatin	6.0
	Atorvastatin	4.8
	Fluvastatin	3.6
	Rosuvastatin	3.6
Ace inhibitors	Ramipril	25.0
	Captopril	20.0
	Enalapril	19.0
	Lisinopril	16.0
	Quinapril	7.0
	Trandolapril	2.8
	Fosinopril	2.5
	Cilazapril	2.0
	Perindopril	1.8
	Imidapril	1.2
	Moexipril	0.8
Proton pump inhibitors	Omeprazole	73.1
	Lansoprazole	11.5
	Pantoprazole	4.6
	Esomeprazole	4.6
	Rabeprazole	3.1
Histamine 2 receptor antagonists	Cimetidine	40.0
	Ranitidine	35.8
	Nizatidine	12.6
	Famotidine	11.3
	Ranitidine bismuth citrate	0.8

Exposure to each drug treatment was classified as current when the most recent prescription was within 30 days before the pneumonia index date. For controls this corresponded to the pneumonia index date of the matched case. Prescriptions within 31 to 90 days before the index date were treated as recent exposures and any prescriptions dating more than 90 days before the index date were classified as past exposures. A separate category was defined for 'no-use', where the subject had never been prescribed the particular drug. For each subject, these were mutually exclusive categories.

4.4.3 Covariates

The following comorbidities were evaluated as potential confounders because of their identification as risk factors for pneumonia in previous studies:[32] [33]ischaemic heart disease (IHD), pulmonary disease (including chronic obstructive pulmonary disease (COPD) and asthma), and previous pneumonia episodes.[32] [33]Identification of these conditions was done using search terms that mapped onto the relevant ICD-9 codes (Appendix 2).[34]Covariates included a combined weighted comorbidity score derived using The Charlson Comorbidity Index, as adapted for use with ICD-9 codes.[25] [26] The detailed methods used for deriving the Charlson index score are outlined in Chapter 2 (Section 2.3.4.2) and Appendix 2.

Use of other drugs was also used as a proxy measure of underlying comorbid illness and included prescriptions of oral and inhaled steroids, angiotensin-II receptor antagonists, antacids, beta-blockers, diuretics, calcium channel blockers and nitrates. Other potential confounders considered included current smoking (the most recent record of smoking status was used) and socioeconomic status measured using Townsend deprivation score quintiles (the first quintile being least deprived and the fifth quintile being most deprived). The Townsend index measures multiple deprivation by output area (approximately 150 households) and was derived from Census 2001 data. This has been described more fully in Chapter 2, Section 2.3.4.3.

4.4.4 Statistical analyses

Conditional multiple logistic regression was used to assess the strength of the association between current treatment with the different drugs and the risk of pneumonia. Results have been expressed as odds ratios (OR) with 95% confidence intervals (CI). The multivariate model (model 1) included all variables which were either:

(a) Significant risk factors for both pneumonia and the drug exposure of interest in the univariate analysis; or

(b) Variables modifying the OR for drug associations by at least 10% when included in a bivariate model with the main exposure variable.

In addition, age and sex were *a priori* confounders and included in the multivariate model.

A second model (model 2) was constructed which included all the exposure drugs in one model with potential confounders to take into account co-prescription of these drugs. Tests were carried out to check for interactions with age and gender. A series of sensitivity analyses was conducted using two of the codes included in the definition list of pneumonia: lobar pneumonia and acute lower respiratory tract infection. These two codes were chosen as they were seen to represent two extremes of the coding spectrum: 'lobar pneumonia' being the most stable code over the years and across practices; whereas the 'acute lower respiratory infection' code exhibiting more variation in its use (Chapter 3, Figure 3.4).

4.5 Results

The study sample had 3,709 cases over the age of 40 years and 22,174 age, sex and practice-matched controls. The majority of cases were above 70 years (57%). Table 4.5 summarises characteristics of cases and controls. Cases were more likely to be current smokers, have a diagnosis of ischaemic heart disease, chronic lung disease, history of pneumonia and had a greater burden of comorbid disease as compared to controls (Table 4.5). Cases also had more prescriptions for antacids, oral and inhaled steroids, diuretics, calcium channel blockers, and nitrates than did controls. Finally, cases were more likely to be from deprived areas than controls.

Table 4.5: Characteristics of cases and controls (≥40 years)

Characteristic	Controls (n=22,174) (%)	Cases (n=3,709) (%)	OR (95% CI)
Age (years)			
40-49	2346 (10.6)	392 (10.6)	†
50-59	3553 (16.0)	590 (15.9)	
60-69	3677 (16.6)	612 (16.5)	
70-79	5396 (24.3)	900 (24.3)	
80 and above	7202 (32.5)	1215 (32.8)	
Sex			
Male	10200 (46.0)	1710 (46.1)	†
Female	11974 (54.0)	1999 (53.9)	
Ischaemic heart disease	2937 (13.3)	629 (17.0)	1.4 (1.2-1.5)
Current smokers	4158 (18.8)	995 (26.8)	1.7 (1.6-1.8)
Chronic lung disease	2304 (10.4)	916 (24.7)	2.9 (2.7-3.2)
Charlson Comorbidity Index score			
0	11280 (50.9)	1079 (29.1)	1.0 (reference)
1-2	7801 (35.2)	1621 (43.7)	2.5 (2.3-2.7)
3-5	2874 (13.0)	880 (23.7)	4.0 (3.6-4.4)
>5	219 (1.0)	129 (3.5)	7.9 (6.3-10.0)
Steroids	4460 (20.1)	1482 (40.0)	2.8 (2.6-3.0)
ACE-II Inhibitors	700 (3.2)	144 (3.9)	1.3 (1.0-1.5)
Antacids	382 (1.7)	88 (2.4)	1.4 (1.1-1.8)
Beta-blockers	5119 (23.1)	852 (23.0)	1.0 (0.9-1.1)
Fibrates	209 (0.9)	45 (1.2)	1.3 (0.9-1.8)
Diuretics	8193 (37.0)	1829 (49.0)	1.9 (1.7-2.0)
Calcium channel blockers	4154 (18.7)	845 (22.8)	1.3 (1.2-1.4)
Nitrates	3223 (14.5)	698 (18.8)	1.4 (1.3-1.5)
Previous pneumonia episodes	637 (2.9)	377 (10.2)	4.1 (3.6-4.8)
Townsend deprivation score quintile			
1 (least deprived)	4869 (22.0)	702 (18.9)	1.0 (reference)
2	4893 (22.1)	739 (19.9)	1.1 (1.0-1.2)
3	4222 (19.0)	735 (19.8)	1.3 (1.1-1.4)
4	3832 (17.3)	672 (18.1)	1.3 (1.2-1.5)
5 (most deprived)	2854 (12.9)	588 (15.9)	1.6 (1.4-1.8)
Missing	1504 (6.8)	273 (7.4)	1.7 (1.3-2.2)

† Matching variable
OR: odds ratio

4.5.1 Identification of potential confounders for inclusion in final multivariate regression model

Table 4.6, Table 4.7, Table 4.8 and Table 4.9 present the results of the confounder analysis to identify which of the potential confounders are significantly related to exposure variables (i.e. prescriptions of statins, ACEIs, PPIs and H2RAs). The confounder analysis involved the identification of significant risk factors for both pneumonia (Table 4.5) and a given drug exposure (Tables 4.6 to 4.9) in the univariate analysis. Based on these analyses, the following variables emerged as important confounders for the various drug exposures:

- Current smoking, Charlson Comorbidity Index score, ischaemic heart disease, chronic lung disease, previous pneumonia episodes, deprivation and prescriptions for calcium channel blockers, nitrates, steroids and diuretics were significantly associated with both pneumonia and statins.
- Prescriptions for diuretics, antacids, nitrates, ischaemic heart disease, chronic lung disease, and previous pneumonia episodes were significantly associated with both pneumonia and ACE inhibitors.
- Current smoking, ischaemic heart disease, previous pneumonia episodes, chronic lung disease, Charlson Comorbidity Index score, and prescriptions for diuretics, nitrates, calcium channel blockers and antacids were significantly associated with both pneumonia and PPIs

Current smoking, ischaemic heart disease, previous pneumonia episodes, chronic lung disease, Charlson Comorbidity Index score, and prescriptions for diuretics, nitrates, antacids, calcium channel blockers and steroids were significantly associated with both pneumonia and H2RAs.

Table 4.6: Association between potential confounder variables and exposure to statins (subjects aged 40 years and above) (n=25883)

Confounder	Statin no (n=23679) (%)	Statin yes (n=2204) (%)	OR	95% CI	P value
Ischaemic heart disease					
No	21336 (90.0)	981 (44.5)	1.00		
Yes	2343 (10.0)	1223 (55.5)	11.40	10.3-12.5	**<0.001**
Smoking					
No	19113 (80.7)	1617 (73.4)	1.0		
Yes	4566 (19.3)	587 (26.6)	1.5	1.4-1.7	**<0.001**
Chronic lung disease					
No	20772 (87.7)	1891 (85.8)	1.0		
Yes	2907 (12.3)	313 (14.2)	1.2	1.0-1.3	**0.009**
Charlson Comorbidity Index score					
0	12005 (50.7)	354 (16.1)	1.0		
1-2	8246 (34.8)	1176 (53.4)	4.8	4.3-5.5	***P trend***
3-5	3149 (13.3)	605 (27.5)	6.5	5.7-7.5	**<0.001**
>5	279 (1.2)	69 (3.1)	8.4	6.3-11.1	
Steroids					
No	18361 (77.5)	1580 (71.7)	1.0		
Yes	5318 (22.5)	624 (28.3)	1.4	1.2-1.5	**<0.001**
ACE-II Inhibitors					
No	23035 (97.3)	2004 (90.9)	1.0		
Yes	644 (2.7)	200 (9.1)	3.6	3.0-4.2	**<0.001**
Antacids					
No	23251 (98.2)	2162 (98.1)	1.0		
Yes	428 (1.8)	42 (1.9)	1.1	0.8-1.5	0.741
Beta-blockers					
No	18943 (80.0)	964 (44.0)	1.0		
Yes	4736 (20.0)	1235 (56.0)	5.1	4.7-5.6	**<0.001**
Fibrates					
No	23520 (99.0)	2192 (99.5)	1.0		
Yes	159 (0.7)	12 (0.5)	0.8	0.4-1.5	0.482
Diuretics					
No	14935 (63.1)	926 (42.0)	1.0		
Yes	8744 (36.9)	1278 (58.0)	2.4	2.2-2.6	**<0.001**
Calcium channel blockers					
No	19771 (83.5)	1113 (50.5)	1.0		
Yes	3908 (16.5)	1091 (49.5)	5.0	4.5-5.4	**<0.001**
Nitrates					
No	20928 (88.4)	1034 (46.9)	1.0		
Yes	2751 (11.6)	1170 (53.1)	8.6	7.8-9.4	**<0.001**
Previous pneumonia episodes					
No	22765 (96.1)	2104 (95.5)	1.0		
Yes	914 (3.9)	100 (4.5)	1.2	1.0-1.5	0.117
Townsend deprivation score quintile					
1 (least deprived)	5155 (21.8)	416 (18.9)	1.0		
2	5174 (21.9)	458 (20.8)	1.1	0.9-1.3	
3	4534 (19.2)	423 (19.2)	1.2	1.0-1.3	***P trend***
4	4078 (17.2)	426 (19.3)	1.3	1.1-1.5	**0.019**
5 (most deprived)	3103 (13.1)	339 (15.4)	1.4	1.2-1.6	
Missing	1635 (6.9)	142 (6.4)	1.1	0.9-1.3	

OR: odds ratio; CI: confidence interval

Table 4.7: Association between potential confounder variables and exposure to ACEIs (ages 40 years and above) (n=25883)

Confounder	ACEI no (n=21502) (%)	% ACEI yes (n=4381) (%)	OR	95% CI	P value
Ischaemic heart disease					
No	19343 (90.0)	2974 (68.0)	1.0		
Yes	2159 (10.0)	1407 (32.0)	4.2	3.9-4.6	**<0.001**
Smoking					
No	17205 (80.0)	3525 (80.5)	1.0		
Yes	4297 (20.0)	856 (19.5)	1.0	0.9-1.1	0.501
Chronic lung disease					
No	19052 (88.6)	3611 (82.4)	1.0		
Yes	2450 (11.4)	770 (17.6)	1.7	1.5-1.8	**<0.001**
Charlson Comorbidity Index score					
0	11474 (53.4)	885 (20.2)	1.0		
1-2	7423 (34.5)	1999 (45.6)	3.5	3.2-3.8	***P trend***
3-5	2416 (11.2)	1338 (30.5)	7.2	6.5-7.9	**<0.001**
>5	189 (0.9)	159 (3.6)	10.9	8.7-13.6	
Steroids					
No	17026 (79.2)	2915 (66.5)	1.0		
Yes	4476 (20.8)	1466 (33.5)	1.9	1.8-2.1	**<0.001**
ACE-II Inhibitors					
No	2239 (98.8)	3800 (86.7)	1.0		
Yes	263 (1.2)	581 (13.3)	12.3	10.6-14.3	**<0.001**
Antacids					
No	21135 (98.3)	4278 (97.7)	1.0		
Yes	367 (1.7)	103 (2.4)	1.4	1.1-1.7	**0.004**
Beta-blockers					
No	17639 (82.0)	2273 (51.9)	1.0		
Yes	3863 (18.0)	2108 (48.1)	4.2	4.0-4.5	**<0.001**
Fibrates					
No	21347 (99.3)	4365 (99.6)	1.0		
Yes	155 (0.7)	16 (0.4)	0.5	0.3-0.8	**0.009**
Diuretics					
No	15117 (70.3)	744 (17.0)	1.0		
Yes	6385 (29.7)	3637 (83.0)	11.6	10.6-12.6	**<0.001**
Calcium channel blockers					
No	18650 (86.7)	2234 (51.0)	1.0		
Yes	2852 (13.3)	2147 (49.0)	6.3	5.9-6.7	**<0.001**
Nitrates					
No	19081 (88.7)	2881 (65.8)	1.0		
Yes	2421 (11.3)	1500 (34.2)	4.1	3.8-4.4	**<0.001**
Previous pneumonia episodes					
No	20721 (96.4)	4148 (94.7)	1.0		
Yes	781 (3.6)	233 (5.3)	1.5	1.3-1.7	**<0.001**
Townsend deprivation score quintile					
1 (least deprived)	4769 (22.2)	802 (18.3)	1.0		
2	4721 (22.0)	911 (20.8)	1.2	1.0-1.3	
3	4084 (19.0)	873 (20.0)	1.3	1.1-1.4	***P trend***
4	3665 (17.0)	839 (19.2)	1.4	1.2-1.5	**<0.001**
5 (most deprived)	2781 (13.0)	661 (15.1)	1.4	1.3-1.6	
Missing	1482 (7.0)	295 (6.7)	1.2	1.0-1.4	

OR: odds ratio; CI: confidence interval

Table 4.8: Association between potential confounder variables and exposure to PPIs (ages 40 years and above) (n=25883)

Confounder	PPI no (n=20799) (%)	PPI yes (n=5084) (%)	OR	95% CI	P value
Ischaemic heart disease					
No	18390 (88.4)	3927 (77.2)	1.0		
Yes	2409 (11.6)	1157 (22.8)	2.2	2.1-2.4	**<0.001**
Smoking					
No	16793 (81.0)	3937 (77.0)	1.0		
Yes	4006 (19.0)	1147 (23.0)	1.2	1.1-1.3	**<0.001**
Chronic lung disease					
No	18496 (88.9)	4167 (82.0)	1.0		
Yes	2303 (11.1)	917 (18.0)	1.8	1.6-1.9	**<0.001**
Charlson Comorbidity Index score					
0	10904 (52.4)	1455 (28.6)	1.0		
1-2	7254 (34.9)	2168 (42.6)	2.2	2.1-2.4	***P trend***
3-5	2455 (11.8)	1299 (25.6)	4.0	3.6-4.3	**<0.001**
>5	186 (1.0)	162 (3.2)	6.5	5.3-8.1	
Steroids					
No	16692 (80.3)	3249 (64.0)	1.0		
Yes	4107 (19.8)	1835 (36.0)	2.3	2.1-2.5	**<0.001**
ACE-II Inhibitors					
No	20250 (97.4)	4789 (95.7)	1.0		
Yes	549 (2.6)	295 (5.8)	2.3	2.0-2.6	**<0.001**
Antacids					
No	20546 (98.8)	4867 (95.7)	1.0		
Yes	253 (1.2)	217 (4.3)	3.6	3.0-4.4	**<0.001**
Beta-blockers					
No	16456 (79.1)	3456 (68.0)	1.0		
Yes	4343 (21.0)	1628 (32.0)	1.8	1.7-1.9	**<0.001**
Fibrates					
No	29653 (99.0)	5059 (99.5)	1.0		
Yes	146 (0.7)	25 (0.5)	0.7	0.5-1.1	0.099
Diuretics					
No	13411 (64.5)	2450 (48.2)	1.0		
Yes	7388 (35.5)	2634 (57.8)	2.0	1.8-2.1	**<0.001**
Calcium channel blockers					
No	17324 (83.3)	3560 (70.0)	1.0		
Yes	3475 (16.7)	1524 (30.0)	2.1	2.0-2.3	**<0.001**
Nitrates					
No	18305 (88.0)	3657 (72.0)	1.0		
Yes	2494 (12.0)	1427 (28.0)	2.9	2.7-3.1	**<0.001**
Previous pneumonia episodes					
No	20098 (96.7)	4771 (94.0)	1.0		
Yes	701 (3.4)	313 (6.2)	1.9	1.6-2.2	**<0.001**
Townsend deprivation score quintile					
1 (least deprived)	4592 (22.1)	979 (19.3)	1.0		
2	4585 (22.1)	1047 (20.6)	1.1	0.9-1.2	
3	3989 (19.2)	968 (19.0)	1.1	1.0-1.3	***P Trend***
4	3512 (16.9)	992 (19.5)	1.3	1.2-1.5	**<0.001**
5 (most deprived)	2682 (12.9)	760 (15.0)	1.3	1.2-1.5	
Missing	1439 (6.9)	338 (6.7)	1.1	0.9-1.3	

OR: odds ratio; CI: confidence interval

Table 4.9: Association between potential confounder variables and exposure to H2RAs (ages 40 years and above) (n=25883)

Confounder	H2RA no (n=20736) (%)	H2RA yes (n=5147) (%)	OR	95% CI	P value
Ischaemic heart disease					
No	18336 (88.0)	3981 (77.4)	1.0		
Yes	2400 (11.6)	1166 (22.6)	2.2	2.1-2.4	**<0.001**
Smoking					
No	16798 (81.0)	3932 (76.4)	1.0		
Yes	3938 (19.0)	1215 (23.6)	1.3	1.2-1.4	**<0.001**
Chronic lung disease					
No	18452 (89.0)	4211 (81.8)	1.0		
Yes	2284 (11.0)	936 (18.2)	1.8	1.7-2.0	**<0.001**
Charlson Comorbidity Index score					
0	10967 (53.0)	1392 (27.0)	1.0		***P Trend***
1-2	7163 (34.5)	2259 (44.0)	2.5	2.3-2.7	**<0.001**
3-5	2426 (11.7)	1328 (25.8)	4.3	4.0-4.7	
>5	180 (0.9)	168 (3.2)	7.4	5.9-9.1	
Steroids					
No	16700 (80.5)	3241 (63.0)	1.0		
Yes	4036 (19.5)	1906 (37.0)	2.4	2.3-2.6	**<0.001**
ACE-II Inhibitors					
No	20142 (97.0)	4897 (95.0)	1.0		
Yes	594 (3.0)	250 (5.0)	1.7	1.5-2.0	**<0.001**
Antacids					
No	20518 (99.0)	4895 (95.0)	1.0		
Yes	218 (1.0)	252 (5.0)	4.8	4.0-5.8	**<0.001**
Beta-blockers					
No	16446 (79.0)	3466 (67.0)	1.0		
Yes	4290 (21.0)	1681 (33.0)	1.9	1.7-2.0	**<0.001**
Fibrates					
No	20592 (99.0)	5120 (99.5)	1.0		
Yes	144 (0.7)	27 (0.5)	0.8	0.5-1.1	0.180
Diuretics					
No	13416 (64.7)	2445 (47.5)	1.0		
Yes	7320 (35.0)	2702 (52.5)	2.0	1.9-2.2	**<0.001**
Calcium channel blockers					
No	17262 (83.0)	3622 (70.0)	1.0		
Yes	3474 (17.0)	1525 (30.0)	2.1	2.0-2.2	**<0.001**
Nitrates					
No	18215 (87.8)	3747 (72.8)	1.0		
Yes	2521 (12.2)	1400 (27.2)	2.7	2.5-2.9	**<0.001**
Previous pneumonia episodes					
No	20003 (96.5)	4866 (94.5)	1.0		**<0.001**
Yes	733 (3.5)	281 (5.5)	1.6	1.4-1.8	
Townsend deprivation score quintile					
1 (least deprived)	4598 (22.2)	973 (19.0)	1.0		
2	4592 (22.2)	1040 (20.2)	1.1	1.0-1.2	
3	3933 (19.0)	1024 (20.0)	1.2	1.1-1.4	***P Trend***
4	3545 (17.0)	959 (18.6)	1.3	1.2-1.4	**<0.001**
5 (most deprived)	2656 (12.8)	786 (15.3)	1.4	1.3-1.6	
Missing	1412 (6.8)	365 (7.0)	1.2	1.1-1.4	

OR: odds ratio; CI: confidence interval

Table 4.10, Table 4.11, Table 4.12 and Table 4.13 present the results of the bivariate analysis, whereby potential confounder variables were included in a bivariate model with the exposure and outcome variables. For the various exposures, the covariates which modified the crude odds ratio by at least 10% are listed below:

- For the association between statins and pneumonia: Charlson Comorbidity Index score, ischaemic heart disease, prescriptions of nitrates and diuretics
- For the association between ACE inhibitors and pneumonia: Charlson Comorbidity Index score, prescriptions of steroids and diuretics
- For the association between PPIs and pneumonia: Charlson Comorbidity Index score and prescriptions of steroids
- For the association between H2RAs and pneumonia: Charlson Comorbidity Index score and prescriptions of steroids

Table 4.10: Bivariate analysis: Association between statins and pneumonia, adjusted for individual confounders

Confounder adjusted for	OR	95% CI	P value (LR test)
Unadjusted	**1.20**	1.05-1.35	**0.005**
Ischaemic heart disease	**1.03**	0.90-1.18	**<0.001**
Smoking	1.16	1.03-1.31	**<0.001**
Chronic lung disease	1.19	1.05-1.34	**<0.001**
Charlson Comorbidity Index score	**0.85**	0.74-0.96	**<0.001**
Steroids	1.13	1.00-1.28	**<0.001**
ACE-II Inhibitors	1.18	1.04-1.33	**0.031**
Antacids	1.19	1.05-1.35	**0.0015**
Beta-blockers	1.19	1.05-1.35	0.9311
Fibrates	1.18	1.04-1.33	0.3599
Diuretics	**1.04**	0.91-1.17	**<0.001**
Calcium channel blockers	1.10	0.97-1.25	**<0.001**
Nitrates	**1.04**	0.91-1.18	**<0.001**
Previous pneumonia episodes	1.17	1.03-1.32	**<0.001**
Townsend deprivation score quintile	1.18	1.05-1.34	**<0.001**

Note: ±10% change in unadjusted OR = 1.08, 1.32
OR: odds ratio; CI: confidence interval
LR: likelihood ratio

Table 4.11: Bivariate analysis: Association between ACE inhibitors and pneumonia, adjusted for individual confounders

Confounder adjusted for	OR	95% CI	P value (LR test)
Unadjusted	1.50	1.37-1.64	**<0.001**
Ischaemic heart disease	1.44	1.31-1.57	**<0.001**
Smoking	1.49	1.36-1.63	**<0.001**
Chronic lung disease	1.41	1.29-1.55	**<0.001**
Charlson Comorbidity Index score	**1.09**	0.99-1.20	**<0.001**
Steroids	**1.35**	1.23-1.48	**<0.001**
ACE-II Inhibitors	1.50	1.36-1.64	0.7693
Antacids	1.50	1.37-1.64	**0.0024**
Beta-blockers	1.53	1.39-1.68	0.1282
Fibrates	1.50	1.37-1.64	0.3568
Diuretics	**1.15**	1.05-1.27	**<0.001**
Calcium channel blockers	1.42	1.3-1.56	**0.0006**
Nitrates	1.43	1.3-1.56	**<0.001**
Previous pneumonia episodes	1.47	1.34-1.60	**<0.001**
Townsend deprivation score quintile	1.50	1.36-1.63	**<0.001**

Note: ±10% change in unadjusted OR = 1.35, 1.65
OR: odds ratio; CI: confidence interval
LR: likelihood ratio

Table 4.12: Bivariate analysis: Association between proton pump inhibitors and pneumonia, adjusted for individual confounders

Confounder adjusted for	OR	95% CI	P value (LR test)
Unadjusted	1.90	1.75-2.05	**<0.001**
Ischaemic heart disease	1.86	1.72-2.01	**<0.001**
Smoking	1.87	1.73-2.02	**<0.001**
Chronic lung disease	1.77	1.63-1.91	**<0.001**
Charlson Comorbidity Index score	**1.52**	1.4-1.64	**<0.001**
Steroids	**1.63**	1.51-1.77	**<0.001**
ACE-II Inhibitors	1.89	1.75-2.04	0.1307
Antacids	1.88	1.74-2.04	**<0.001**
Beta-blockers	1.90	1.76-2.06	0.4486
Fibrates	1.89	1.75-2.05	0.192
Diuretics	1.79	1.65-1.93	**<0.001**
Calcium channel blockers	1.86	1.72-2.01	**<0.001**
Nitrates	1.84	1.70-1.99	**<0.001**
Previous pneumonia episodes	1.82	1.68-1.97	**<0.001**
Townsend deprivation score quintile	1.89	1.75-2.04	**<0.001**

Note: ±10% change in unadjusted OR = 1.71, 2.09
OR: odds ratio; CI: confidence interval
LR: likelihood ratio

Table 4.13: Bivariate analysis: Association between histamine 2 receptor antagonists and pneumonia, adjusted for individual confounders

Confounder adjusted for	OR	95% CI	P value (LR test)
Unadjusted	1.64	1.51-1.77	**<0.001**
Ischaemic heart disease	1.60	1.48-1.74	**<0.001**
Smoking	1.60	1.48-1.73	**<0.001**
Chronic lung disease	1.53	1.41-1.66	**<0.001**
Charlson Comorbidity Index score	**1.30**	1.20-1.41	**<0.001**
Steroids	**1.39**	1.28-1.51	**<0.001**
ACE-II Inhibitors	1.63	1.51-1.77	0.0489
Antacids	1.62	1.5-1.76	**0.047**
Beta-blockers	1.64	1.52-1.78	0.6558
Fibrates	1.64	1.51-1.77	0.1913
Diuretics	1.54	1.42-1.66	**<0.001**
Calcium channel blockers	1.61	1.48-1.74	**<0.001**
Nitrates	1.59	1.47-1.72	**<0.001**
Previous pneumonia episodes	1.59	1.47-1.72	**<0.001**
Townsend deprivation score quintile	1.63	1.51-1.77	**<0.001**

Note: ±10% change in unadjusted OR = 1.48, 1.80
OR: odds ratio; CI: confidence interval
LR: likelihood ratio

4.5.2 Association between various drug exposures and pneumonia

Table 4.14 shows the crude and adjusted odds ratios for the different drug exposures. Model 1 includes all significant confounders (based on confounder analysis) in the analysis. After adjustment for age, sex, ischaemic heart disease, current smoking, underlying comorbidity, derivation and concurrent prescriptions of diuretics and nitrates, a significant association was seen between current statin use and decreased pneumonia risk (adjusted OR 0.78, 95% CI 0.65-0.94). After adjustment for confounders, a current prescription of ACEI was associated with a significantly reduced risk of pneumonia (adjusted OR 0.75, 95% CI 0.65-0.86). In contrast, current PPI use was significantly associated with an increased risk of pneumonia (adjusted OR 1.55, 95% CI 1.36-1.77). However, no association was found between current use of histamine 2 receptor antagonists and pneumonia risk after adjustment for confounders (adjusted OR 1.14, 95% CI 0.92-1.40). No interactions were found with age or gender for any of the drug exposures. In addition the analysis was repeated by including all the four exposure drugs in the final model with other confounding factors. This was to adjust for co-prescription of the exposure drugs under investigation. As is evident from Table 4.14 (Model 2), the odds ratios obtained from Model 1 and Model 2 remained largely unchanged. Table 4.15 and Table 4.16 present the sensitivity analysis carried out using different Read codes to define pneumonia: lobar pneumonia and acute lower respiratory tract infection. The protective effect of statins persisted when considering lobar pneumonia, with a 60% decrease risk of lobar pneumonia in current statin users (Table 4.15). Current ACE inhibitor use was still protective for lobar pneumonia but the results were no longer statistically

significant probably because of the loss of statistical power. Gastric acid suppressants were associated with an increased risk of lobar pneumonia but this was not statistically significant. When considering acute lower respiratory infection (Table 4.16), a statistically significant result was obtained only in the case of current PPI use which was associated with an almost 50% increase in ALRI risk. Statins on the other hand, did not show any protective effect in the case of ALRI.

Table 4.14: Association between current treatment with different drugs and pneumonia (n=25,883)

Exposure	Number exposed (%)		Crude OR (95% CI)	Model 1: Adjusted OR (95% CI)	Model 2: Adjusted OR (95% CI)
	Cases (3,709)	Controls (22,174)			
Statin use					
No use	3,350 (90.3)	20,329 (91.7)	1.00	1.00	1.00
Current (within 30 days)	178 (4.8)	1,050 (4.7)	1.04 (0.88-1.23)	0.78† (0.65-0.94)	0.78 (0.65-0.94)
Recent (31-90 days)	116 (3.1)	501 (2.3)	1.43 (1.16-1.76)	1.06 (0.86-1.33)	1.07 (0.85-1.34)
Past (>90 days)	65 (1.8)	294 (1.3)	1.36 (1.03-1.78)	1.04 (0.78-1.39)	1.04 (0.78-1.38)
ACE Inhibitor use					
No use	2,904 (78.3)	18,598 (83.9)	1.00	1.00	1.00
Current (within 30 days)	294 (7.9)	1,692 (7.6)	1.14 (1.00-1.30)	0.76‡ (0.66-0.88)	0.76 (0.65-0.87)
Recent (31-90 days)	181 (4.9)	703 (3.2)	1.70 (1.43-2.01)	1.18 (0.98-1.42)	1.18 (0.98-1.42)
Past (>90 days)	330 (8.9)	1,181(5.3)	1.85 (1.62-2.11)	1.19 (1.03-1.38)	1.15 (1.00-1.34)
PPI use					
No use	2,638 (71.1)	18,161 (81.9)	1.00	1.00	1.00
Current (within 30 days)	387 (10.4)	1,257 (5.7)	2.18 (1.92-2.46)	1.55‡ (1.36-1.77)	1.54 (1.35-1.77)
Recent (31-90 days)	195 (5.3)	558 (2.5)	2.43 (2.05-2.87)	1.69 (1.42-2.03)	1.69 (1.41-2.03)
Past (>90 days)	489 (13.2)	2,198 (9.9)	1.56 (1.40-1.74)	1.17 (1.04-1.31)	1.16 (1.03-1.31)
H2RA use					
No use	2,736 (73.8)	18,000 (81.2)	1.00	1.00	1.00
Current (within 30 days)	122 (3.3)	518 (2.3)	1.59 (1.30-1.94)	1.14‡‡ (0.92-1.40)	1.08 (0.88-1.34)
Recent (31-90 days)	67 (1.8)	317 (1.4)	1.43 (1.09-1.87)	1.12 (0.84-1.49)	1.04 (0.79-1.39)
Past (>90 days)	784 (21.1)	3,339 (15.1)	1.58 (1.44-1.73)	1.18 (1.07-1.30)	1.03 (0.93-1.15)

OR: odds ratio; CI: confidence interval

Model 1: This contained the following variables:

† Adjusted for age, sex, ischaemic heart disease, smoking, comorbidity, chronic lung disease, previous pneumonia, deprivation and prescriptions of diuretics, steroids, calcium channel blockers & nitrates

‡ Adjusted for age, sex, ischaemic heart disease, smoking, chronic lung disease, comorbidity, previous pneumonia, deprivation and prescriptions of diuretics, calcium channel blockers, antacids, steroids & nitrates

‡‡ Adjusted for age, sex, ischaemic heart disease, smoking, chronic lung disease, comorbidity, previous pneumonia, deprivation and prescriptions of diuretics, antacids & nitrates

Model 2: In addition to all the variables in Model 1, this also included all the main exposure drugs i.e. statins, ACEIs, PPIs and H2RAs

Table 4.15: Sensitivity analysis: Association between current treatment with different drugs and lobar pneumonia (n= 1558)

Exposure	Number exposed (%)		Crude OR (95% CI)	Adjusted OR (95% CI)
	Cases (223)	Controls (1335)		
Statin use				
No use	206 (92.4)	1214 (90.9)	1.00	1.00
Current (within 30 days)	8 (3.6)	73 (5.5)	0.65 (0.31-1.36)	**0.40[†](0.18-0.91)**
Recent (31-90 days)	8 (3.6)	29 (2.2)	1.59 (0.72-3.52)	1.24 (0.52-2.95)
Past (>90 days)	1 (0.5)	19 (1.4)	0.31 (0.04-2.32)	0.19 (0.02-1.50)
ACE Inhibitor use				
No use	178 (79.8)	1107 (82.9)	1.00	1.00
Current (within 30 days)	15 (6.7)	110 (8.2)	0.85 (0.48-1.52)	0.56[‡] (0.30-1.05)
Recent (31-90 days)	10 (4.5)	49 (4.0)	1.30 (0.65-2.61)	0.74 (0.34-1.62)
Past (>90 days)	20 (9.0)	69 (5.2)	**1.82 (1.07-3.08)**	0.90 (0.49-1.66)
PPI use				
No use	158 (70.9)	1117 (83.7)	1.00	1.00
Current (within 30 days)	19 (8.5)	76 (5.7)	**1.84 (1.08-3.13)**	1.33[‡] (0.75-2.36)
Recent (31-90 days)	13 (5.8)	36 (2.7)	**2.62 (1.34-5.10)**	1.95 (0.97-3.92)
Past (>90 days)	33 (14.8)	106 (7.9)	**2.22 (1.45-3.40)**	1.49 (0.93-2.41)
H2RA use				
No use	162 (72.7)	1098 (82.3)	1.00	1.00
Current (within 30 days)	7 (3.1)	18 (1.4)	**2.74 (1.11-6.74)**	1.44[‡‡] (0.55-3.74)
Recent (31-90 days)	6 (2.7)	20 (1.5)	2.17 (0.84-5.66)	1.34 (0.48-3.74)
Past (>90 days)	48 (21.5)	199 (14.9)	**1.67 (1.16-2.39)**	1.18 (0.80-1.74)

OR: odds ratio; CI: confidence interval

† Adjusted for age, sex, ischaemic heart disease, smoking, comorbidity, chronic lung disease, previous pneumonia, deprivation and prescriptions of diuretics, steroids, calcium channel blockers & nitrates

‡ Adjusted for age, sex, ischaemic heart disease, smoking, chronic lung disease, comorbidity, previous pneumonia, deprivation and prescriptions of diuretics, calcium channel blockers, antacids, steroids & nitrates

‡‡ Adjusted for age, sex, ischaemic heart disease, smoking, chronic lung disease, comorbidity, previous pneumonia, deprivation and prescriptions of diuretics, antacids & nitrates

Table 4.16: Sensitivity analysis: Association between current treatment with different drugs and acute lower respiratory infection (n=8400)

Exposure	Number exposed (%)		Crude OR (95% CI)	Adjusted OR (95% CI)
	Cases (1,203)	Controls (7,197)		
Statin use				
No use	1063 (88.4)	6634 (92.2)	1.00	1.00
Current (within 30 days)	83 (6.9)	319 (4.4)	**1.68 (1.30-2.17)**	1.13 † (0.84-1.51)
Recent (31-90 days)	39 (3.2)	167 (2.3)	**1.49 (1.04-2.14)**	0.91 (0.62-1.35)
Past (>90 days)	18 (1.5)	77 (1.1)	1.49 (0.89-2.49)	1.04 (0.60-1.80)
ACE Inhibitor use				
No use	987 (82.0)	6272 (87.2)	1.00	1.00
Current (within 30 days)	101 (8.4)	442 (6.1)	**1.49 (1.18-1.88)**	0.97‡ (0.75-1.26)
Recent (31-90 days)	36 (3.0)	190 (2.6)	1.24 (0.86-1.78)	0.83 (0.55-1.23)
Past (>90 days)	79 (6.6)	293 (4.1)	**1.77 (1.36-2.30)**	1.15 (0.85-1.54)
PPI use				
No use	882 (73.3)	6006 (83.5)	1.00	1.00
Current (within 30 days)	108 (9.0)	335 (4.7)	**2.24 (1.78-2.82)**	**1.45‡ (1.13-1.87)**
Recent (31-90 days)	50 (4.2)	170 (2.4)	**1.99 (1.44-2.75)**	1.39 (0.98-1.96)
Past (>90 days)	163 (13.6)	686 (9.5)	**1.65 (1.37-2.00)**	1.18 (0.96-1.45)
H2RA use				
No use	911 (75.7)	6024 (83.7)	1.00	1.00
Current (within 30 days)	27 (2.2)	121 (1.7)	1.50 (0.99-2.29)	1.03‡‡ (0.66-1.60)
Recent (31-90 days)	22 (1.8)	81 (1.1)	**1.85 (1.14-2.99)**	1.48 (0.89-2.48)
Past (>90 days)	243 (20.2)	971 (13.5)	**1.70 (1.44-2.00)**	**1.26 (1.06-1.51)**

OR: odds ratio; CI: confidence interval

† Adjusted for age, sex, ischaemic heart disease, smoking, comorbidity, chronic lung disease, previous pneumonia, deprivation and prescriptions of diuretics, steroids, CCBs & nitrates

‡ Adjusted for age, sex, ischaemic heart disease, smoking, chronic lung disease, comorbidity, previous pneumonia, deprivation and prescriptions of diuretics, calcium channel blockers, antacids, steroids & nitrates

‡‡ Adjusted for age, sex, ischaemic heart disease, smoking, chronic lung disease, comorbidity, previous pneumonia, deprivation and prescriptions of diuretics, antacids & nitrates

4.6 Discussion

4.6.1 Summary of main findings

Our findings suggest that current statin users have a reduction in the risk of pneumonia of nearly 22%. Similarly, a current prescription for ACE inhibitors was associated with a reduction in the risk of pneumonia by 25%. No protective effects were found with historical use of these drugs. The study did not find a significant association between current prescription for H2RAs and pneumonia risk. Current prescriptions for PPIs were associated with a significantly increased risk of pneumonia of nearly 55%.

4.6.2 Strengths and limitations of this study

This is one of the largest population-based case-control studies of pneumonia with 3,709 cases and 22,174 controls. The THIN database holds longitudinal data on over 5 million people registered at 300 general practices throughout the UK. This makes these study findings applicable to the UK general population and ensures no recall bias as exposures were recorded prospectively before the diagnosis of pneumonia. Moreover, because this case-control study is nested within a longitudinal cohort, the present study has avoided temporal biases relating to timing of exposure. Cases have been matched to control subjects individually, therefore minimising confounding by age, sex and local clinical and community factors such as prescribing policies. Findings have been adjusted for socio-economic status, presence of comorbid illnesses and smoking.

One potential limitation is the possibility for misclassification of pneumonia due to variable coding practices. If this is the case, it would be independent of exposure status and bias our results towards unity. There is also the issue of the validity of the pneumonia diagnoses, which are based on general practitioner recorded diagnoses. As mentioned previously in Chapter 3, there was no information on x-ray findings in THIN to confirm pneumonia diagnoses. However, chest infections are commonly seen in general practice and previous evidence suggests that general practitioner diagnoses of pneumonia are reasonably accurate.[5 44 48] Another limitation is that the drug exposure data relates to prescriptions so there is no certainty that the drugs were actually used. This means there could be some overestimation of exposure to the various drugs in the analysis. However, such a misclassification would be non-differential and only bias results towards unity. In spite of these limitations the pattern of results for each of the exposures is generally consistent with that in other comparable studies.[68 69 71 72]There may also be some misclassification of some of the confounding variables such as chronic lung disease, ischaemic heart disease and the Charlson's Comorbidity Index score due to variable coding practices. Once again, even if present, these misclassifications should be independent of exposure and outcome status. An adapted form of the Charlson's Comorbidity Index was used to measure and adjust for comorbid conditions in a comprehensive manner.[25 34] One possible criticism of this choice of index is that the Charlson's index was developed to predict mortality and therefore the weighting used in calculating a comorbidity score may not be appropriate when morbidity is the outcome. However, this index is well validated and has been accepted for use with

morbid outcomes.[83] 'Confounding by indication' is another concern expressed by reviewers of previous studies, and occurs when the disease which has prompted the use of specific medication may itself increase the risk of the outcome. It is not possible to directly link prescriptions to indication in THIN but it is possible to cross-tabulate with medical conditions which are a common indication for the given drug. In the UK statins are commonly prescribed for hypercholesterolemia and primary or secondary prophylaxis of cardiovascular diseases. 56% patients on statins had a history of myocardial infarction and 27% patients had a history of diabetes. Approximately 15% of patients prescribed PPIs and histamine 2 receptor antagonists had a recorded diagnosis of either peptic or duodenal ulcers. This study has attempted to overcome any possible confounding by indication by adjusting for total comorbidity burden (using the Charlson's Comorbity Index) and also adjusted for conditions like ischaemic heart disease. Other drug prescriptions were included as covariates in the multivariate model (nitrates, calcium channel blockers, diuretics, antacids, oral steroids) as proxy measures of comorbidity. In addition, tests were conducted to check for interactions with common indications for the drug groups. For statins no interaction was found with either ischaemic heart disease (p=0.6711) or diabetes (p=0.7777). No interactions were seen with peptic/duodenal ulcers for either PPIs (p=0.7292) or H2RAs (p=0.2044).

4.6.3 Comparison with existing literature

The present study findings for statins are similar to a previous study by Schleinger et al (2007) that looked at the association between current statin

use (prescription within 30 days before pneumonia index date) and uncomplicated pneumonia, showing a 30% reduction in pneumonia risk (adjusted OR 0.71, 95% CI 0.56-0.89).[71] This is not surprising as they used data from the UK General Practice Research Database (GPRD), which is very similar to the THIN database and employed similar methods. However, the present study has used a more comprehensive weighted index of comorbidity, the CCI, with less chances of residual confounding. This could explain the smaller protective effect observed with statin use in this study. Another study by van de Gard et al (2006) using GPRD data found a greater pneumonia risk reduction with statins of about 50% (adjusted OR 0.49, 95% CI 0.35-0.69), but they limited their analysis to pneumonia risk in diabetes patients.[72] This could imply that statins are of greater benefits in diabetes patients.

The literature review did not find any truly comparable studies looking at the impact of ACE inhibitors on pneumonia risk. Previous studies have reported a reduced risk of between 50-60% for nosocomial pneumonia in hospitalised patients.[74] [75] The PROGRESS trial (a trial of the use of ACE inhibitors in stroke patients) showed a 19% risk in pneumonia compared to people receiving placebo, though this finding was only on the borderline of statistical significance.[73] However a case-control study by van de Gard et al (2005) found no significant association between ACE inhibitors and community-acquired pneumonia.[72] The present study found a 25% reduction in pneumonia risk with the use of ACE inhibitors after adjustment for confounders. These contradictory findings could be because the study by van de Gard et al. only considered hospitalised cases of CAP which would

potentially be the more serious cases of pneumonia. Missing out uncomplicated pneumonia cases would result in an underestimation of the pneumonia incidence thereby driving the results towards unity.

Three comparable studies have looked at the association between gastric acid suppressants and pneumonia risk.[68 69] The study by Laheij et al (2004) used general practice data from the Netherlands. They found an association between current use of gastric acid suppressants and an increased pneumonia risk. Current PPI use was associated with an almost 90% increase in pneumonia risk (adjusted OR 1.89, 95% CI 1.36-2.62) and current H2RA use was associated with a 60% increased pneumonia risk (adjusted OR 1.63, 95% CI 1.07-2.48).[68] Their study sample was derived from a cohort of patients on acid-suppressant drugs and comparisons were between different acid-suppressant drugs i.e. PPIs and H2RAs. There was no control group that was unexposed to acid-suppressants. Using data from Denmark, Gulmez et al (2007) showed a 50% increase in pneumonia risk with current PPI use (adjusted OR 1.5, 95% CI 1.3-1.7) but as in the present study, did not find a significant association between current H2RA use and pneumonia.[69] This study results showed a 55% increase in pneumonia risk with current PPI use which is similar to the findings in the Denmark study (Gulmez et al 2007) even though they used only hospitalised cases of CAP. It is surprising that both the Denmark study[69]and this study did not find an association between H2RA use and pneumonia as the proposed mechanism of action by which this group of drugs increases pneumonia risk is similar to that for PPIs i.e. their ability to raise the gastric pH.[68 69] This could be explained by two factors: first, it is well

established that PPIs cause greater gastric acid suppression than H2RAs [67] and second, both these drugs are commonly available as over the counter drugs not requiring medical prescriptions making accurate ascertainment of exposure to these drugs difficult. A recent study by Sarkar et al (2008) used data from the GPRD to investigate the association between current PPI use and pneumonia risk and did not find any evidence for an increased risk.[80] This is surprising given the similar population and methods used to the present study. They did however find an increased risk of pneumonia in the first few days of starting PPI therapy and acknowledge that their findings do not appear to have a biological explanation based on the known mechanism of action for these drugs. They attribute previous study findings of an increased pneumonia risk with PPI use, to residual confounding. However, the present study has used a very comprehensive comorbidity index which includes all the conditions that they have adjusted for. One possible explanation for the difference in results could be the actual choice of codes used to define pneumonia. The sensitivity analyses (Table 4.15 and Table 4.16) using different codes yielded different results. For example, while the association between lobar pneumonia and current PPI use was not significant (Adj. OR: 1.33; 95% CI: 0.75-2.36), there was a significantly increased risk of Acute lower respiratory tract infection (ALRI) with current PPI use (Adjusted OR: 1.45; 95% CI: 1.13-1.87). Chapters 2 and 3 have explored the issue of pneumonia coding in THIN and rationale to include the Read code for ALRI in the code list used to define pneumonia.[37] Both the study by Sarkar et al. (2008) and the present study share the limitation of not having radiographic evidence to corroborate the pneumonia diagnosis; but by omitting ALRI codes

there is a risk of underestimating the actual pneumonia burden in UK general practice. This is because current British Thoracic Society guidelines[4] do not stipulate the necessity of chest radiographs for pneumonia diagnosed and managed in the community and conservative coding in the absence of radiographic confirmation could lead to missing potential pneumonia cases.

4.7 Summary

The study results showed that current statin and ACE inhibitor use was associated with a decreased risk of pneumonia while there was an increased risk with PPI use. No protective effects were observed with the historical use of either statins or ACEIs but there was evidence that recent historical use of PPIs was associated with an increased pneumonia risk. No significant association was found between current prescriptions for H2RAs and the occurrence of pneumonia.

5 The impact of statins, ACE inhibitors, proton pump inhibitors and histamine 2 receptor antagonists on pneumonia: The self-controlled case-series method

5.1 Introduction

This chapter explores an alternative methodological approach to overcoming potential bias in the case-control study design: the self-controlled case-series analysis.

5.2 Background to study

One of the inherent limitations of a case-control study design is in the selection of controls, thereby introducing the possibility of residual confounding (due to unknown confounders). Selection bias may occur when the disease which has prompted the use of specific medication may itself increase the risk of the outcome (confounding by indication or channelling bias).[84] For example, pneumonia is often a terminal event of other comorbid conditions which may have prompted prescriptions of statins or ACEIs.[11] This would mean that subjects exposed to a particular drug are systematically different from those who are unexposed. An alternative study design which eliminates confounding because of selection bias is the case-series. This is a modified cohort method which only uses data on cases and combines the statistical power of the cohort method with the economy of the case-control method.[85] The case-series method involves dividing individual patient follow-up time into exposed and unexposed periods (which may vary in duration),

and comparison of event rates in these different periods (i.e. a self-controlled study design). Cases not exposed at any time are excluded from the analysis. The case series method has been used successfully for estimating the relative incidence of rare adverse reactions after vaccination[85] and the association between prescription medications and the risk of motor vehicle crashes.[86] In the present study, the case series analysis involved a comparison of pneumonia incidence rates within exposed periods (period covered by prescription as well as periods following end of medication when there is a likely residual influence of the drug) compared to pneumonia incidence rates occurring within unexposed periods (periods not covered by prescription which are out of the influence of the drug).

5.3 Methods

The study population comprised all individuals (aged 40 years and above) with a recorded diagnosis of pneumonia during the period 1st July 2001 and 1st July 2002. Records relating to prescriptions for any statins, ACEIs, PPIs and H2RAs listed in the BNF were extracted for each individual. Prescription records were grouped into courses of treatment. The prescription intervals for each of these drugs were examined graphically and the modal interval between prescriptions was found to be four weeks. For the purpose of the analyses an assumption was therefore made that all prescriptions lasted 30 days. The graphical representation of prescription intervals also showed a maximum interval of 16 weeks for a few patients and so a post-exposure 'washout' period of 60 days was considered in the analyses to decrease the likelihood of misclassification of exposure periods. For the same reason, any

prescriptions separated by more than 90 days were considered separate courses of treatment. Exposure status at the start of the study period was assessed for each case: any person with a prescription date recorded within 90 days prior to the 1st of July 2001 was considered exposed at the start of the study.

The available follow-up time for each individual was classified into the following categories based on their exposure to the medications of interest:

1. Unexposed or control period: Time when unexposed to the medication of interest (baseline)
2. Pre-exposure washout period: 30 days up to the date of first prescription in each course of treatment. This was done because while the case-series approach overcomes confounding due to differences between people being studied, time-dependent risk factors for pneumonia that could increase the likelihood of a person being exposed to the drug of interest, could produce within-person confounding. For example, a diagnosis of ischaemic heart disease is recognised as a risk factor for pneumonia and may also trigger a prescription for statins. Excluding the time before the first recorded prescription of the exposure drugs in each treatment course would minimise confounding due to indication.
3. Exposed or risk period: 30 days following the prescription date (the underlying assumption being that all prescriptions were for 30 days worth of medication).
4. Post-exposure washout period: 60 days following the last prescription in a given course of treatment

Poisson regression models were used to calculate incidence rate ratios (IRRs) comparing the incidence rates of pneumonia in the exposure period with the incidence rate during the baseline period. The outcome event of interest was the first recorded diagnosis of pneumonia in the study period. One of the assumptions of a case-series analysis is that the cumulative incidence of events in the population over the observation period is low.[85] Subsequent events were not included in the analysis as given the one year study period it was difficult to rule out that subsequent pneumonia episodes were independent occurrences. The pneumonia incidence rate in the exposure periods as well the periods immediately prior to and post the exposure has been compared to the incidence rate in the unexposed period.

5.4 Results

Table 5.1 summarises the results of the case-series analysis, comparing pneumonia incidence rates in exposed periods to unexposed periods.

Table 5.1: Incidence rate ratios (IRRs) for pneumonia, by drug use, calculated using the self-controlled case series analytical method (2001-2002)

Drug exposure	Number of exposed cases	Period 2: pre-exposure washout period[1]		Period 3: Active exposure period[2]		Period 4: Post-exposure washout period[3]	
		IRR	95% CI	IRR	95% CI	IRR	95% CI
Statins	233	1.61	0.97-2.67	0.87	0.57-1.31	2.14	1.36-3.37
ACE inhibitors	480	1.72	1.20-2.46	0.79	0.59-1.05	1.91	1.42-2.58
Proton pump inhibitors	667	1.76	1.31-2.37	1.24	0.98-1.58	1.69	1.30-2.19
H2 receptor antagonists	284	1.60	1.01-2.54	1.15	0.79-1.68	1.16	0.80-1.68

Note: All comparisons to baseline pneumonia incidence rate in unexposed periods
[1]Pre-exposure washout period: 30 days before first prescription
[2]Active exposure period: period of medication use
[3]Post-exposure washout period: 60 days following end of exposure to demarcate period of potential residual effects from medication before return to baseline

Interestingly, except in the case of statins there is a significantly increased incidence of pneumonia in the pre-exposure washout period i.e. the month immediately prior to being prescribed either ACE inhibitors or the gastric acid suppressants. Exposure to statins and ACE inhibitors appeared to be associated with lower pneumonia incidence whereas gastric acid suppressant use appeared to be linked to increased pneumonia incidence. In the period

immediately following cessation of statin, ACE inhibitor or PPI use (post-exposure washout period), there was a significantly marked increase in pneumonia incidence.

5.5 Discussion

5.5.1 Principal findings

Statins and ACE inhibitors were associated with lower pneumonia incidence whereas gastric acid suppressant use was linked to increased pneumonia incidence. However, none of these findings were statistically significant.

5.5.2 Strengths and limitations of this study

The main strength of the case-series study design is the ability to control for all fixed confounders (i.e. those that don't vary with time over the observation period) such as socio-economic status, gender and possibly even severity of underlying disease. On the other hand, the case-series method controls for confounding by factors which are constant within each individual, it does not reduce confounding due to risk factors which vary over time. Age is a time-varying confounder but as this analysis only considered a one-year follow-up period, there was no necessity to adjust for age. Another limitation that has been discussed in the case-control study as well is that of exposure ascertainment using prescription data which is not synonymous with actual use because of either patient compliance issues, or availability of drugs like gastric acid suppressants over-the-counter. A further issue specific to the case-series analysis is the assumption that exposure is temporary, and should

be of a short-duration compared to the overall study period.[85] Statins are normally prescribed for prevention or treatment of chronic cardiovascular conditions and cannot be reasonably expected to meet this assumption. In this study sample, the mean duration of statin treatment was 199 days (S.D. ± 135) and Figure 5.1 shows that there were cases who were unexposed to statins in the study period (1st July 2001 to 1st July 2002). Similarly, in many cases ACE inhibitors would be long-term prescriptions for hypertensive and post-myocardial infarction patients, thus violating the assumption of short-term exposures in the case series method. In this study sample, the mean duration of ACEI treatment was 182 days (S.D. ±128) and Figure 5.2 shows the distribution of length of ACEI exposures within the one year study period.

Figure 5.1: Duration of statin treatment in days in case series sample within the study period (1st July 2001 to 1st July 2002)

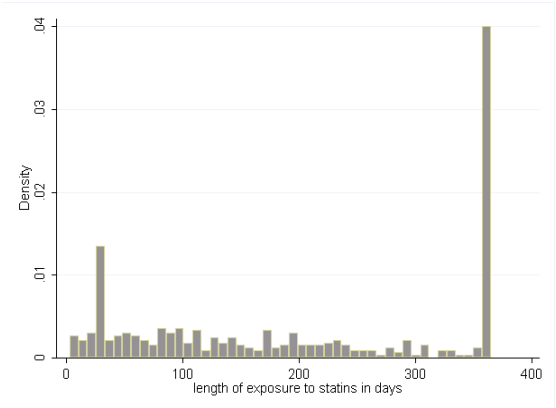
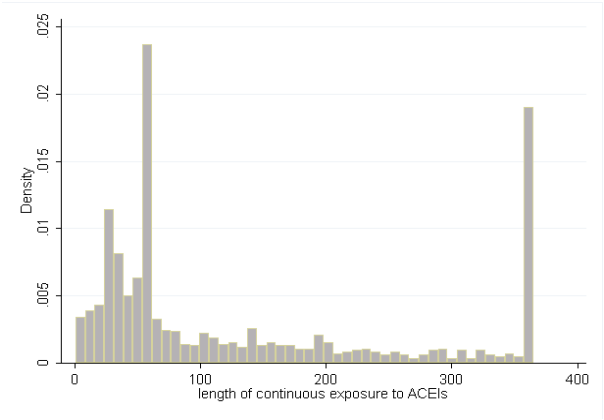


Figure 5.2: Duration of ACEI treatment in days in case series sample within the study period (1st July 2001 to 1st July 2002)



The fact that there were cases with variable exposures to statins could be due to an erroneous assumption that all prescriptions were a month long given the lack of data on prescription duration. One way around this would be to only consider unexposed periods before the first ever prescription and assume that a patient would have a life-long prescription to statins and ACE inhibitors once these were initiated.

5.5.3 Comparison with existing literature

The literature review did not identify any other study looking at the same research question using a case-series approach. Most other studies investigating the impact of statins, ACE inhibitors and gastric acid suppressants on pneumonia risk have adopted a case-control study approach.[68 69 71 72 80-82] Direct comparisons are not possible as previous

studies have reported results using odds ratios and the case-series results are reported as incidence rate ratios. Nevertheless, it is important to note that while none of the case-series analysis findings were statistically significant, they are similar to the case-control analysis results (Chapter 4) in directionality.

For each of the drug exposures except for statins there was a significantly increased incidence of pneumonia in the month immediately prior to being prescribed either ACE inhibitors or the gastric acid suppressants. This may reflect the contribution of underlying comorbidity to increasing the pneumonia risk or drug prescriptions prompted by a pneumonia diagnosis. Another interesting observation was that in the period immediately following cessation of statin, ACE inhibitor or PPI use, there was a significantly marked increase in pneumonia incidence. The intuitive expectation would have been that incidence rate ratios in the post-exposure periods would show the same directionality as those in the exposed periods, assuming that there was some residual impact of the drug exposures. The contrary finding could be explained in two ways. First, that the drugs were stopped in response to signs of pneumonitis, lung inflammation as may be the case of statins. Second, the underlying assumption that none of the confounders changed with time, could be wrong and while age was not an issue in this study because of the one-year time period, it is possible that factors like underlying comorbidity or disease severity could vary with time.

5.6 Summary

To summarise, exposure to statins and ACE inhibitors appeared to be associated with lower pneumonia incidence whereas gastric acid suppressant use appeared to be linked to increased pneumonia incidence. While none of these findings were statistically significant, they showed the same direction as that observed in the case-control study- some protective effects with statins and ACE inhibitors while some increase in risk with gastric acid suppressants. The self-controlled case-series analysis is a potentially useful method to overcome fixed confounding effects (per individual) and further work should be carried out to refine this method for pharmacoepidemiological applications.

6 Mortality from pneumonia in general practice compared to general population: Cohort study

6.1 Introduction

This chapter summarises the literature on pneumonia mortality and then describes the detailed methods employed for the study. Results are presented for mortality in people with pneumonia in UK general practice as compared to the general population at discrete time-periods following pneumonia diagnosis. This is followed by a discussion of the results. The work presented in this chapter has been written-up as a paper and been accepted for publication in a peer-reviewed journal and a copy of the accepted draft is included in Appendix 4 for reference.[87]

6.2 Background to the study

Pneumonia is an important cause of death in the United Kingdom.[4]Previous evidence suggests that less than a third of people with a diagnosis of pneumonia in the UK are admitted to hospital,[38]and therefore the majority of cases of pneumonia in the UK are diagnosed and managed by general practitioners. In general, studies of pneumonia prognosis have used hospital-based cohorts which do not consider the full spectrum of disease or longer-term outcomes.[6 11 88-95] Therefore, the main objective of this study was to calculate all-cause mortality in people with pneumonia in UK general practice as compared to the general population at discrete time-periods following

pneumonia diagnosis: short-term mortality within 30 days of a pneumonia diagnosis, medium-term mortality between 31-90 days post-pneumonia and long-term mortality that occurs more than 90 days.

6.3 Literature review: Pneumonia mortality

A literature review was carried out to identify studies investigating either short or long term mortality in pneumonia patients. A search was carried out in PubMed using the search terms 'pneumonia' AND 'mortality' OR 'cohort' OR 'longitudinal'. In addition, the reference lists of relevant papers were searched for further articles. Nineteen studies were identified initially, of which eight studies were based in the UK. A decision was taken to restrict the review to studies in the UK in keeping with the objective of this study. Table 6.1 summarises the results of the literature review. All these studies were hospital based and their findings on pneumonia mortality ranged from 8 to 58%. Follow-up periods ranged from 30 days following a pneumonia diagnosis to six weeks post-diagnosis. Some studies did not specify the time of follow-up, merely stating 'follow-up till clinical recovery'. None of the UK based studies considered long-term mortality outcomes in pneumonia cases.[6 89-93 95 96]

6.4 Methods

6.4.1 Study design, exposure definition and population

This study used a cohort design for the analysis. The main exposure variable was diagnosis of pneumonia (yes/no). Data were extracted on patients in the THIN database with at least one year of recorded data after the practice

computerisation date, who had a diagnosis of pneumonia occurring between 1st July 2001 and 1st July 2002. Identification of cases was done by using specific medical Read codes corresponding to a pneumonia diagnosis (Chapter 2, Table 2.2).[97] For each case, the first recorded pneumonia diagnosis within this period was used. The date of pneumonia diagnosis was designated the index date. For every case, a general population sample of similar characteristics was determined by matching six controls by practice, sex and age at index date (within three years). Follow-up data on these patients was available till 5th July 2005. For controls the pneumonia diagnosis date corresponded to the index date of the matched case. Initially 4964 pneumonia cases and 29,697 controls of all ages were identified for the study period 1st July 2001 to 1st July 2002. 29 (0.6%) cases had a recorded date of death before the day of pneumonia diagnosis and were excluded. The most likely explanation for this is either an error in recording or delayed entry of post-mortem diagnoses. 118 (0.4%) controls had death dates before the index date (pneumonia diagnosis date of matched case) and were also excluded. 677 (13.6%) cases and 9 (0.03%) controls died on the day of pneumonia diagnosis (or index date of matched case) and were automatically excluded by Stata during the Cox regression analysis as they did not contribute any person-time. However, this process could have excluded potentially severe pneumonia cases and biased our results by underestimating case mortality. To overcome this issue, the death date was artificially extended by 1 day for these cases and controls. The final analysis was based on 4,935 cases and 29,579 controls.

6.4.2 Outcome definition

The outcome of interest was all-cause mortality in pneumonia cases and controls over the entire study follow-up period from 1st July 2001 to 5th July 2005. Deaths within 30 days of a pneumonia diagnosis are more likely to be pneumonia-related deaths and are now conventionally classified as such.[11]Other studies have considered mortality at 90 days and beyond.[11 56 98] For this reason mortality was investigated over three discrete time periods following a diagnosis of pneumonia: short-term mortality within 30 days of a pneumonia diagnosis, medium-term mortality between 31-90 days post-pneumonia and long-term mortality that occurs more than 90 days following a pneumonia diagnosis.

Table 6.1: Studies on pneumonia mortality in the UK

Study	Study period and study design	Population	Identification of pneumonia cases	Number of deaths (%)
White et al. (1981)[95]; UK	1974-1980 Hospital-based prospective study; Follow-up till end of hospital stay	210 adult patients (mean age 54 yrs; range 12-100 yrs) admitted to hospital	Clinical diagnosis of acute pneumonia and radiological evidence of consolidation	17 (8%) in-hospital deaths
Macfarlane et al. (1982)[91]; UK	1980-1981; Hospital-based prospective study; Follow-up after discharge till recovery	127 pneumonia patients (<80 yrs) admitted to hospital; 72.4% male; mean age 51 yrs (range 13-79 yrs)	History and clinical signs of acute lower respiratory tract infection with fresh pulmonary shadowing on x-rays	19 (15%) in-hospital deaths
McNabb et al. (1984)[90]; UK	1979-1982; Hospital-based prospective study; Follow-up till clinical recovery	80 adults admitted to hospital with community-acquired pneumonia Mean age 64 yrs (range 21-91 yrs); 61% male	Clinical features of acute lower respiratory tract infection and evidence of fresh pulmonary shadowing on chest radiograph	9 (11%) in-hospital deaths
BTS (1987)[96]; UK	1982-1983; Hospital-based prospective study; Follow-up for 6 weeks (± 9 days) after admission	511 adults aged15-74 yrs Recruited from hospital; 453 in final analysis mean age ± S.D: 48.4 yrs ± 17.8 60.5 % male	Acute illness with radiological pulmonary shadowing; either at least segmental or in more than one lobe which was neither pre-existing nor of other known cause	26 (5.7%) at 6 weeks
Venkatesan et al. (1990)[93]; UK	1987-1988; Hospital-based prospective study; Follow-up till clinical recovery and resolution of radiographic	73 Patients 65 yrs and above admitted to hospital with pneumonia; median age 79 yrs (range 65-97 yrs).	Acute lower respiratory tract infection with new, previously unrecorded shadowing on chest radiograph	24 (33%) at 6 weeks

Study	Study period and study design	Population	Identification of pneumonia cases	Number of deaths (%)
	shadowing			
Hirani and Macfarlane (1997)[89]; UK	1984-1993; Hospital-based prospective study; Follow-up till hospital discharge	57 patients admitted to ICU with severe CAP; 66.7% male, mean age 57 yrs (range 15-83 yrs)	Physician diagnosis of Pneumonia	33 (57.9%) in-hospital deaths
Lim et al. (2001)[92]; UK	1997; Nested case-control study using hospital-based cohort; Follow-up till end of hospital stay	519 patients (≥75yrs) with a primary discharge diagnosis of pneumonia recorded at 5 study hospitals; mean age ± S.D: 83.8 yrs ± 5.4 yrs	Shadowing on an admission chest radiograph with infection, inpatient treatment for pneumonia and discharge/death diagnosis of pneumonia	114 (22%) in-hospital deaths
Lim et al. (2001)[6]; UK	1998; Hospital-based prospective study; Follow-up till 30 days after diagnosis	267 patients (≥16 yrs) admitted to hospital with CAP; 50.6% men; mean age ± S.D: 65.4 ± 19.6 yrs; 41%> 75 yrs Follow-up: 30 days after pneumonia diagnosis	Presence of an acute illness of 21 days or less duration with features of lower respiratory tract infection, new radiographic shadowing with no other cause, treatment with antibiotics for pneumonia by physician	30-day mortality: 40 (15%)

6.4.3 Covariates

Factors that could impact mortality were included as covariates: sex, age, coexisting comorbidity burden, current smoking (the most recent record of smoking status was used) previous pneumonia episodes (before 1st July 2001) and deprivation on pneumonia mortality.[94 99 100] Other covariates included the Charlson Comorbidity Index score (as a marker of underlying disease burden) and Townsend deprivation score quintiles to measure deprivation (the first quintile being least deprived and the fifth quintile being most deprived). These have been discussed in detail in Chapter 2 Sections 2.3.4.2 and 2.3.4.3.

6.4.4 Statistical analyses

The overall mortality was determined in pneumonia cases as compared to controls in a univariate analysis. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. Adjustment was carried out for sex, age-group, comorbidity using Charlson's Comorbidity Index scores (CCI), smoking, deprivation (measured using Townsend's deprivation index score) and previous pneumonia. Kaplan Meier survival curves were plotted for all-cause mortality in pneumonia cases versus controls. Proportional hazards assumptions were checked using a likelihood ratio test, which compared the hazards ratios in two discrete time periods, on either side of the median follow-up time. Cox regression analysis was used to calculate short, medium and long-term mortality in pneumonia cases as compared to controls. The likelihood ratio test was carried out to assess any interactions with age, sex, deprivation and comorbidity.

6.5 Results

The study sample had 53.7% females and the mean age at the index date was 57.6 years (S.D. 26.93). The median follow-up time was 3.3 person-years (interquartile range: 0.99). Among cases there were 913 deaths within 30 days (18.5%), 97 deaths (2.5%) within 31-90 days and 508 deaths (13.2%) in the period >91 days following pneumonia diagnosis till the end of the study period. Deaths in controls were 107 (0.4%) within 30 days, 189 (0.7%) in 31-90 days and 2743 (9.5%) in the period >91 days. In total 1518 (30.8%) pneumonia cases and 3039 (10.3%) controls died during the study follow-up period. This was equivalent to overall mortality rate of 135.4 per 1000 person-years (95% CI: 128.7-142.4) in cases and 35.2 per 1000 person-years (95% CI: 33.9-36.4) in controls.

Figure 6.1 compares Kaplan Meier survival curves for pneumonia cases and controls for all cause mortality over the same follow-up period (2001-2005) and suggests the proportional hazards assumption is not met due to a dramatic increase in deaths in the early part of the follow-up period in people with pneumonia. The log-log plot for case status in Figure 6.2 shows that the two curves are not parallel i.e. the risk of death in pneumonia cases relative to general population controls does not remain constant over time (global test for case status: p value <0.001).

Figure 6.1: Kaplan Meier survival plots: all-cause mortality in pneumonia cases as compared to the controls, 2001-2005

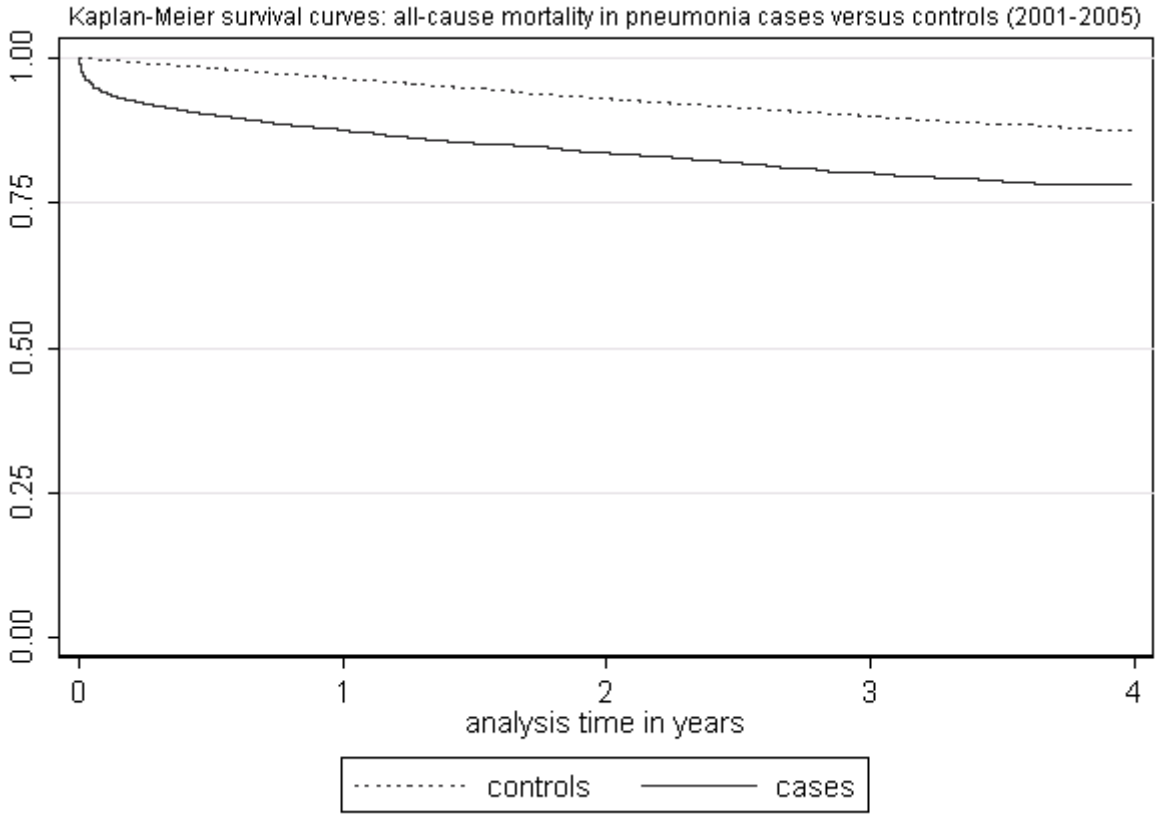


Figure 6.2: Log-log plot to check for proportional hazards assumption by case status

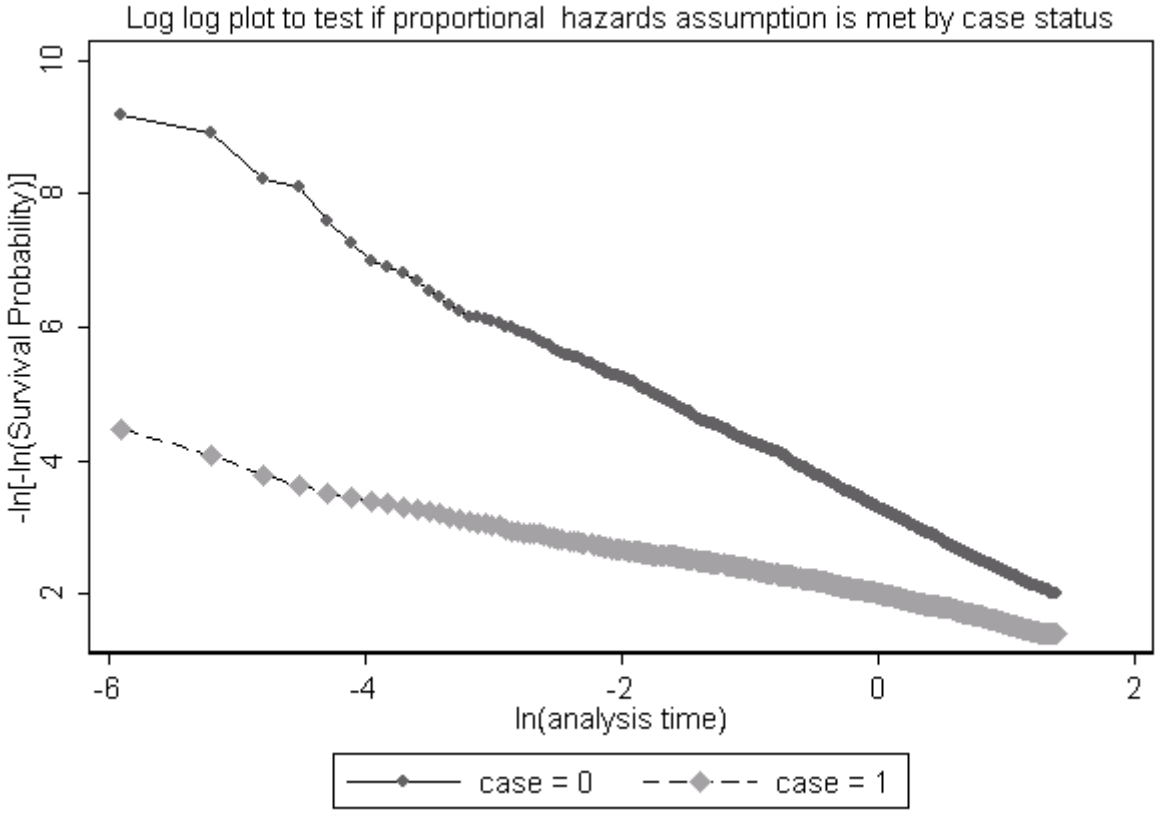


Table 6.2 shows unadjusted and adjusted hazard ratios for all-cause mortality over the entire study follow-up period (2001-2005). Age (p trend <0.001), male sex (p=0.047), deprivation (p trend <0.001) and comorbidity burden (p trend <0.001) were significantly associated with increased all-cause mortality in the combined cohort population. Current smoking was associated with decreased mortality in the entire cohort (p<0.001). The adjusted HR for all-cause

mortality in pneumonia cases versus controls was 4.37 (95% CI: 4.09-4.66; p<0.001).

Since the proportional hazards assumption was not met (p<0.001) the adjusted HRs for cases compared to controls have been calculated over three discrete time-periods during the study in Table 6.3. Cases were almost 46 times more likely to die in the 30 days immediately following a pneumonia diagnosis (adj. HR 45.90, 95% CI: 36.8-55.2). In the medium term the adjusted HR was 3.20 (95% CI: 2.48-4.10). Even in the long term (more than 90 days following a diagnosis of pneumonia), cases were almost 20 percent more likely to die compared to controls (adj. HR 1.19, 95% CI: 1.08-1.31).

Statistically significant interactions were found for mortality with age (p=0.001) and deprivation (p=0.03) but not with sex (p=0.67) or comorbidity (p=0.06). In other words, mortality in pneumonia cases and controls differed by age group and deprivation. Therefore, Table 6.4 shows the adjusted HR for short and long-term mortality in cases as compared to general population controls stratified by age group and deprivation quintile. Only the adult age groups (>19 years) are shown as there were very few deaths in the younger age groups. When examining the age-stratified hazard ratios for long-term mortality in cases compared to general population there was a smaller increase in risk for the elderly age group (75 years and older) than in the two younger age groups (60-74 years) and (19-59 years). Although a statistically significant interaction was observed with Townsend score, there was no obvious trend or dose response in these data.

Table 6.2: Factors affecting all-cause mortality in pneumonia cases and controls over study period (2001-2005), median follow-up 3.3 years (n=34514)

Risk factor	Deaths in cases (%)	Deaths in controls (%)	Unadjusted HR (95% CI)	Adjusted HR[†] (95% CI)
Controls		3039 (10.3)	1.00	1.00
Cases	1518 (30.8)		3.68 (3.46-3.92)	4.37 (4.09-4.66)
Sex				
Females	819 (31.0)	1627 (10.5)	1.00	1.00
Males	699 (30.5)	1412 (10.3)	0.99 (0.94-1.05)	1.06 (1.00-1.13)
Agegroup				
<5 yrs	2 (0.6)	1 (0.1)	0.08 (0.03-0.25)	0.08 (0.03-0.26)
5-18	2 (0.6)	1 (0.1)	0.07 (0.02-0.23)	0.07 (0.02-0.21)
19-59	100 (6.4)	87 (0.9)	1.00 (reference)	1.00 (reference)
60-74	316 (31.3)	388 (6.3)	5.90 (5.02-6.93)	5.25 (4.46-6.17)
≥75 yrs	1098 (65.0)	2562 (25.5)	22.57 (19.49-26.14)	19.50 (16.78-22.66)
			P trend <0.001	*P trend <0.001*
Charlson Comorbidity Index score				
0	242 (12.5)	869 (5.0)	1.00	1.00
1-2	681 (34.9)	1278 (14.0)	3.26 (3.03-3.51)	1.60 (1.48-1.72)
3-5	502 (54.7)	785 (26.4)	6.81 (6.29-7.38)	2.27 (2.09-2.46)
>5	93 (72.1)	107 (49.1)	16.03 (13.78-18.63)	3.93 (3.37-4.59)
			P trend <0.001	*P trend <0.001*
Current smokers				
No	1180 (34.0)	2478 (10.9)	1.00	1.00
Yes	338 (23.1)	561 (8.2)	0.73 (0.68-0.79)	0.87 (0.75-0.87)
Townsend deprivation score quintile				
1 (least deprived)	268 (27.3)	530 (8.1)	1.00	1.00
2	284 (29.4)	664 (10.4)	1.23 (1.12-1.35)	1.08 (0.98-1.19)
3	303 (32.3)	603 (10.9)	1.36 (1.24-1.50)	1.10 (1.00-1.21)
4	266 (29.6)	586 (11.5)	1.38 (1.25-1.51)	1.09 (0.99-1.21)
5 (most deprived)	263 (34.0)	458 (11.6)	1.51 (1.34-1.73)	1.20 (1.09-1.33)
Missing	134 (35.7)	198 (9.5)	-	-
			P trend <0.001	*P trend 0.001*
Previous pneumonia				
No	1367 (30.5)	2902 (10.1)	1.00	1.00
Yes	151 (33.9)	137 (18.3)	2.00 (1.76-2.23)	1.01 (0.90-1.14)

[†] Variables adjusted for each other
HR: hazard ratio; CI: confidence interval

Table 6.3: Mortality in pneumonia cases compared to controls, by time period following pneumonia diagnosis (n=34,514)

Time following pneumonia diagnosis	Deaths in cases (%)	Deaths in controls (%)	Unadjusted HR (95% CI)	P value	Adjusted †HR (95% CI)	P value
Within 30-days	913 (18.5)	107 (0.4)	54.36 (44.50-66.42)	<0.001	45.90 (36.8-55.2)	<0.001
Within 31-90 days	97 (2.5)	189 (0.7)	3.82 (2.99-4.88)	<0.001	3.20 (2.48-4.10)	<0.001
>90 days	508 (13.2)	2743 (9.5)	1.43 (1.30-1.57)	<0.001	1.19 (1.08-1.31)	<0.001
Total deaths	**1518 (30.8)**	**3039 (10.3)**				

† Adjusted for sex, age, comorbidity, smoking status, deprivation and previous pneumonia
HR: hazard ratio; CI: confidence interval

Table 6.4: Mortality in pneumonia cases compared to controls: Interactions with age and deprivation, by time period following pneumonia diagnosis

Interaction term	30-day mortality Adjusted HR (95% CI)	Medium term mortality (31-90 days following pneumonia) Adjusted HR (95% CI)	Long-term mortality (>90 days following pneumonia) Adjusted HR (95% CI)
Age group†			
19-59 yrs	89.77 (21.46-375.58)	9.0 (2.45-33.0)	2.81 (1.95-4.06)
60-74 yrs	58.71 (33.74-102.18)	4.0 (1.86-8.60)	2.50 (2.05-3.06)
75 yrs and above	52.04 (41.70-64.90)	4.5 (3.40-5.90)	1.52 (1.35-1.71)
Townsend deprivation quintile‡			
1 (least deprived)	73.57 (43.75-123.71)	4.40 (2.29-8.61)	2.08 (1.66-2.62)
2	43.68 (29.18-65.38)	2.60 (1.32-5.08)	1.58 (1.26-1.98)
3	56.93 (35.66-90.88)	4.25 (2.35-7.69)	1.96 (1.58-2.43)
4	45.83 (28.88-72.74)	5.11 (2.89-9.06)	5.11 (2.89-9.06)
5 (most deprived)	61.37 (33.82-111.36)	5.29 (2.99-9.38)	1.90 (1.51-2.40)
Missing	45.90 (23.60-89.10)	9.25 (4.19-20.41)	2.41 (1.70-3.42)

† Adjusted for sex, comorbidity, smoking status, deprivation and previous pneumonia
‡Adjusted for sex, age, comorbidity, smoking status and previous pneumonia

6.6 Discussion

6.6.1 Summary of main findings

A diagnosis of pneumonia in general practice is an important predictor of death even after allowing for age, sex, comorbidity and deprivation. The prognosis is very poor in the first 30 days with cases being almost 46 times more likely to die than controls. However, the risk of mortality remains high even in the long-term with pneumonia cases almost 20% more likely to die as the general population.

6.6.2 Strengths and limitations of this study

The main strengths of this study are the large number of pneumonia cases (n=4,935) and controls (n=29,579) available for follow-up. The study population included the full-spectrum of pneumonia cases from those managed in the community to more severe cases requiring hospitalisation. There was 4 years of follow-up data which made it possible to study pneumonia outcomes in the long-term as well as the short-term.

One possible weakness is the misclassification of pneumonia diagnosis due to variable coding practices and absence of confirmatory chest radiography. Chest infections are commonly seen in general practice and previous evidence suggests that general practitioner diagnoses of pneumonia are reasonably accurate.[5] [44] [48] [97]Furthermore it seems likely that if misclassification is present, the main one will be lower respiratory tract infections being miscoded as pneumonia and this misclassification would lead

to an underestimate of the mortality associated with pneumonia diagnoses. As discussed in Chapter 2, Section 2.3.1 and Chapter 3, Section 3.6.2, this study included diagnoses of acute lower respiratory tract infections in the definition of pneumonia to ensure that the full spectrum of the disease was covered, from mild to more severe cases. This is because it is not the norm to request a chest radiograph when diagnosing and managing pneumonia in the community.[4]There is the possibility that pneumonia deaths in some vulnerable groups could have been missed, such as new immigrants and other groups not registered with general practice and if so this will lead to an underestimation of the overall mortality rates. If this is the case, it is unlikely to have a large impact in absolute terms as 99% of the UK population is reported to be registered with NHS general practices.[15] Moreover, at the time of data extraction THIN covered 4% of the UK population and has been shown to be representative of the UK population and all subgroups.[15]

6.6.3 Comparison with existing literature

A review of the literature found that most past studies of pneumonia prognosis in the UK or countries with similar health-care systems have been hospital based.[6 88-96 101-103] Some studies have also looked at out-patients but hospitals are their main population source.[11 98 102] Only one other study investigated pneumonia patients diagnosed in primary care in the Netherlands but this only considered patients aged 60 years and above.[104] Despite these differences, the present study findings support previous evidence that there is significantly higher long-term mortality in patients with pneumonia as compared to the general population and the risk of mortality is about 20% more in cases.[98 101]

[103] This study looked at deaths from all-causes and the increased mortality could be a reflection of underlying illnesses, but the observed increase persisted after adjustment for underlying comorbidity. The results showed an 18.5% 30-day mortality from pneumonia in general practice which is higher than the 30-day mortality of 8-15% in hospital-based studies.[6 102] This implies that using hospital-based rates would underestimate mortality in pneumonia by missing deaths in the community. The Netherlands study observed 5.3% 30-day mortality from pneumonia and non-pneumonia lower respiratory tract infections in primary care which is much lower than this study's findings. They only considered older patients (≥60 years) but excluded people with hospitalisations in the 2 weeks prior to a general practitioner diagnosis.[104] The present study however considered both hospitalised and community-managed cases of lower respiratory infections and by excluding the 677 cases that had deaths recorded on the day of diagnosis (i.e. probably hospital-discharge diagnoses), a 30-day mortality rate of 5.6% was obtained which is closer to the findings of the Netherlands study.

As in other studies[56 98] the mortality risk increased with age in both pneumonia cases and in the general population. In pneumonia cases there was a statistically significant interaction between mortality and age. Surprisingly, an age-stratified analysis did not show an increasing trend in mortality by age group (Table 6.4). The lower relative mortality in older pneumonia cases (aged 60 years and above) may be because this age group is already at a higher risk of dying in the general population. It has been suggested that age loses its weight as a prognostic factor for pneumonia when only including

older patients and other factors such as underlying comorbidity have more prognostic value.[105] Alternatively, younger people have such a low baseline risk that a few extra deaths could have a large relative impact. Another possible explanation for the observed lower relative mortality in older pneumonia cases is the presence of a healthy survivor effect.[92] This has been described by Janssen et al. (2005) as mortality selection whereby frail people tend to die at younger ages, leaving a more selected and robust population that survives well into the older age groups.[106]

The present study also found a significant interaction of mortality in both cases and general population controls with deprivation using the likelihood ratio test. However, the 95 % CIs for the stratified results were overlapping and there was no clear trend in the association between deprivation and mortality. A recent study in Canada by Vrbova et al[56] did not find any significant association between socio-economic status (measured by median neighbourhood income) and pneumonia mortality at either 30 days or 1 year. The present study on the other hand, has used a more comprehensive deprivation measure, the Townsend index score. Nevertheless, it is still an area-based measure and it would be worthwhile to see if an individual level deprivation measure would yield similar results.

Comorbidity was a significant predictor of mortality in this study cohort and other studies have shown it is an important determinant of mortality in pneumonia.[11 56 99 103] It is generally accepted that pneumonia is often a terminal event after prolonged serious illness and has been labelled 'the old

man's friend'.[11] Interestingly, in this study the mortality in pneumonia cases remained high both in the short and long term even after adjusting for comorbidity.

Surprisingly, in this study cohort of pneumonia cases and controls, current smokers were less likely to die as compared to never smokers. This is probably a reflection of incomplete recording of smoking status, rather than a true finding. Previous studies have found discrepancies in primary care records for former smokers [107] with 46 percent ex-smokers being wrongly coded as non-smokers.[108] Moreover, it is likely that ex-smokers are people who quit smoking in response to a diagnosis of a smoking-related illness, which anyway places them at a higher mortality risk than the general population.

6.7 Summary

The 30-day prognosis in pneumonia cases was very poor with a nearly fifty-fold increased mortality risk as compared to general population controls. Even in the long-term pneumonia appeared to be an independent predictor of mortality irrespective of age, sex or coexisting comorbidity. Younger people were at a relatively higher risk of pneumonia mortality.

7 Cohort study: The impact of statins, ACE inhibitors, proton pump inhibitors and histamine 2 receptor antagonists on pneumonia mortality

7.1 Introduction

This chapter reviews the evidence to date regarding the effect of statins, ACEIs, PPIs and H2RAs on pneumonia mortality and then goes on to describe the detailed methods for the survival study. Unadjusted and adjusted hazard ratios (HR) and 95% CI showing the association between treatment with the various drugs and pneumonia mortality are presented followed by a discussion of the findings. The findings presented in this chapter have been accepted for publication in a peer-reviewed journal (Appendix 4) [109].

7.2 Background

Pneumonia is an important cause of morbidity and mortality in the United Kingdom.[4] A search was carried out using the terms 'pneumonia' AND 'mortality' OR 'cohort' OR 'longitudinal' in the PubMed database. Additional studies were identified from the reference lists of relevant papers. No language or setting restrictions were applied. Table 7.1 summarises the findings of previous studies investigating the impact of statins and ACEIs on pneumonia mortality.[71 76 77 110 111] With the exception of the study by Schleinger et al (2007), these studies used hospitalised pneumonia patients as their study population and have provided conflicting evidence on whether

statins and ACEIs decrease mortality from pneumonia or not. In addition, previous studies have also suggested that PPIs and H2RAs are associated with pneumonia morbidity[68 69 78-80] but have not looked at the impact of these drugs on pneumonia mortality. The aim of this study was to investigate the effect of statins, ACEIs, PPIs and H2RAs on short and long-term mortality in pneumonia cases in a general practice population.

Table 7.1: Summary of studies investigating the association between statins, ACEIs and pneumonia mortality

Author, year, setting	Study design and study period	Study population	Exposure variable	Outcome variable	Results
Majumdar et al (2006)[77] Canada	Population-based prospective cohort study 2000-2002	3,415 adults (>17 yrs) admitted to hospital with pneumonia	Use of statins for at least 1 week before admission and during hospital stay.	Composite outcome variable: in-hospital mortality or admission to ICU	Adjusted OR for mortality/admission to ICU (statin users compared to non-users)= 0.78 (95% CI 0.6-1.05)
Schlienger et al (2007)[71] UK	Population-based retrospective nested case-control study (GPRD) Jan 1, 1995- April 30, 2002	1,253 cases and 4,838 controls matched on age, sex, practice and index date (4 controls to a case)	Current, recent and past statin use	-Uncomplicated pneumonia -Hospitalisation for pneumonia with survival -Fatal pneumonia	Adjusted OR (current statin use versus non-use) 0.71 (95% CI 0.56-0.89)
Mortensen et al (2005) [110] Texas, USA	Retrospective cohort 1 Jan 1999 to 1 Dec 2002	787 patients >18 years admitted with a diagnosis of pneumonia (confirmed by chest x-ray)	Use of statins at time of presentation with pneumonia	30-day mortality	Adjusted OR (statin users versus non-users): 0.36 (95% CI 0.14-0.92)
Mortensen et al (2005)[76] Texas, USA	Retrospective cohort 1 Jan 1999 to 1 Dec 2002	787 patients >18 years admitted with a diagnosis of pneumonia (confirmed by chest x-ray)	Use of ACEIs at presentation	30-day mortality	Adjusted OR (ACEI users versus non-users): 0.44 (95% CI 0.22-0.89)
Chalmers et al (2008)[111] UK	Prospective cohort Jan 2005 to Nov 2007	1007 patients admitted with radiologically confirmed community-acquired pneumonia	Use of statins on admission	30-day mortality	Adjusted OR (statin users versus non-users): 0.46 (95% CI 0.25-0.85)

7.3 Methods

7.3.1 Study design and population

Cases were patients in the THIN database with a diagnosis of pneumonia occurring between 1st July 2001 and 1st July 2002. Only those patients were considered who had at least one year of recorded data following the practice computerisation date. The analysis was restricted to those aged 40 years and above as very few people had the drug exposures of interest below this age (Chapter 4, Table 4.3). Identification of cases was done by using specific medical Read codes corresponding to a pneumonia diagnosis (Chapter 2, Table 2.2). Follow-up data for these patients was available till 5th July 2005. 3710 pneumonia cases aged 40 years and above were identified for the study period 1st July 2001 to 1st July 2002. As described earlier in Chapter 6, Section 6.4.1, 29 (0.8%) cases had dates of death recorded before the pneumonia diagnosis date. These could be attributed either to errors in recording or post-mortem diagnoses and were excluded. Of the remaining 3681 cases, 671 (18%) died on the day of diagnosis. These were excluded automatically when the Cox regression analysis was carried out in Stata, as they did not contribute any person-time. This could have excluded potentially serious pneumonia cases or delayed presenters and biased the results. The same approach was followed as for the mortality study described in Chapter 6 and the death date was artificially extended by 1 day for these cases and the final analysis included 3681 cases.

7.3.2 Exposure definition

Data was extracted for all recorded prescriptions of statins, ACE inhibitors, PPIs and H2RAs. Exposure to each drug treatment was classified as current when the most recent prescription was within 30 days before the pneumonia index date. For controls this corresponded to the pneumonia index date of the matched case. Prescriptions within 31 to 90 days before the index date were treated as recent exposures and any prescriptions dating more than 90 days before the index date were classified as past exposures. An additional category was created for 'no-use' where the subject had never been prescribed the particular drug. For each subject, these were mutually exclusive categories.

7.3.3 Outcome definition

The study separately considered 30-day post-pneumonia all-cause mortality and all-cause mortality following pneumonia over the total follow-up time as outcome measures. Conventionally, deaths within 30 days of a pneumonia diagnosis are classified as pneumonia-related deaths.[11] However there is evidence that some patients treated for pneumonia remain at high risk of subsequent mortality for several years which is why the study also considered all-cause mortality during the course of the entire follow-up period.[98 101 103] This would allow an estimation of whether any drug effects were short-term or long-term. Unlike the approach adopted in Chapter 6, this study did not consider medium term mortality (deaths within 31-90 days of pneumonia diagnosis) or long term mortality (deaths in the period >91 days after pneumonia diagnosis) separately and only looked at the overall impact of the

drug exposures on pneumonia mortality over the entire study follow-up period (median follow-up 2.8 years). One of the reasons influencing this decision was the loss of statistical power because of few deaths occurring in these discrete time-periods.

7.3.4 Potential confounders

As described in previous chapters (Chapter 2, Section 2.3.4.2), a combined weighted comorbidity index, the Charlson Index adapted for use with ICD-9 codes.[25 34] Other potential confounders considered included age, sex, current smoking (the most recent record of smoking status was used) and socioeconomic status measured using Townsend deprivation score quintiles (the first quintile being least deprived and the fifth quintile being most deprived) (Chapter 2, Section 2.3.4.3).

7.3.5 Statistical analyses

The effect of statins, ACEIs, PPIs and H 2RAs on pneumonia mortality was investigated using Cox regression. Proportional hazards assumptions were checked for each of the drug exposures using log-log plots and the global test for proportional hazards. Kaplan-Meier survival curves were plotted for all-cause mortality over the entire study period for each of the drug exposures by status of use. The outcome measures used were adjusted hazard ratios (HR) and 95% confidence intervals (CI). A series of post-hoc sensitivity analyses were carried out using other cardiovascular drugs like diuretics, calcium channel blockers and nitrates to test the possibility of a healthy user effect.

7.4 Results

The median follow-up time was 2.8 years (inter-quartile range (IQR): 3.33). 905 (24.6%) cases died within 30 days of a pneumonia diagnosis and 1501 (40.8%) died over the entire follow-up period.

7.4.1 Proportional hazards assumption

Proportional hazards assumptions were not satisfied for any of the drug exposures over the study follow-up period (Table 7.2 and Figure 7.1). This merely indicates that the exposure variable has different effects at different time-points and was not an issue when considering short-term mortality occurring within 30 days of a pneumonia diagnosis (Figure 7.1). However, this could be a problem when assessing the combined long-term mortality and the hazard ratios were therefore examined on either side of the median person-year time (2.8 years) for each drug exposure but no significant difference was observed in the hazard ratios for the different time periods for any of the exposure drugs as the 95% confidence intervals were overlapping (Table 7.3). As a result, only a single estimate has been presented for long-term mortality in subsequent tables.

Table 7.2: Global test for proportional hazards assumption

Variable	P value (Global test)
Statins	0.0476
ACE inhibitors	<0.0010
Proton pump inhibitors	0.0026
H2 receptor antagonists	0.0381

Figure 7.1: Log-log plot to examine the proportional hazards assumption

Fig 13a: Statins

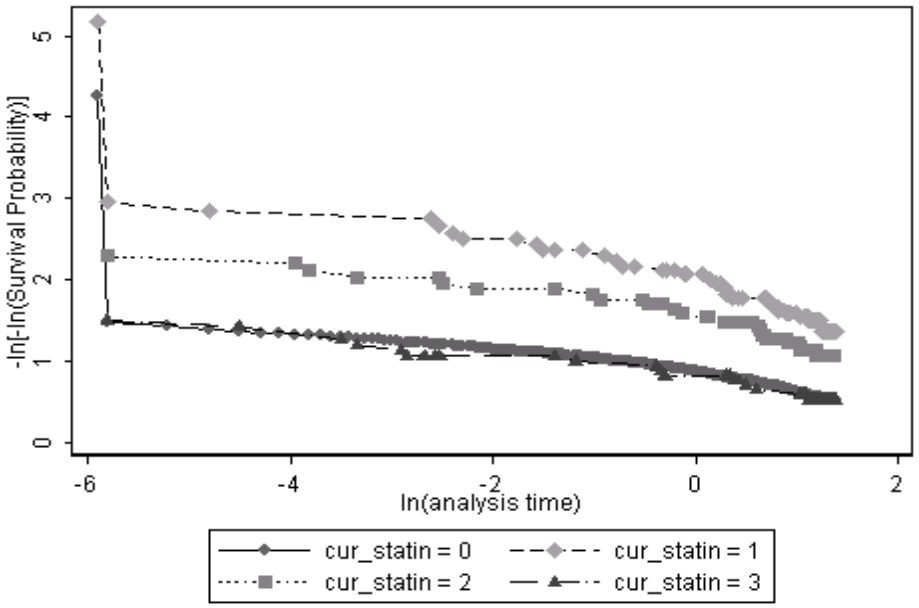


Fig 7.1b: ACE inhibitors

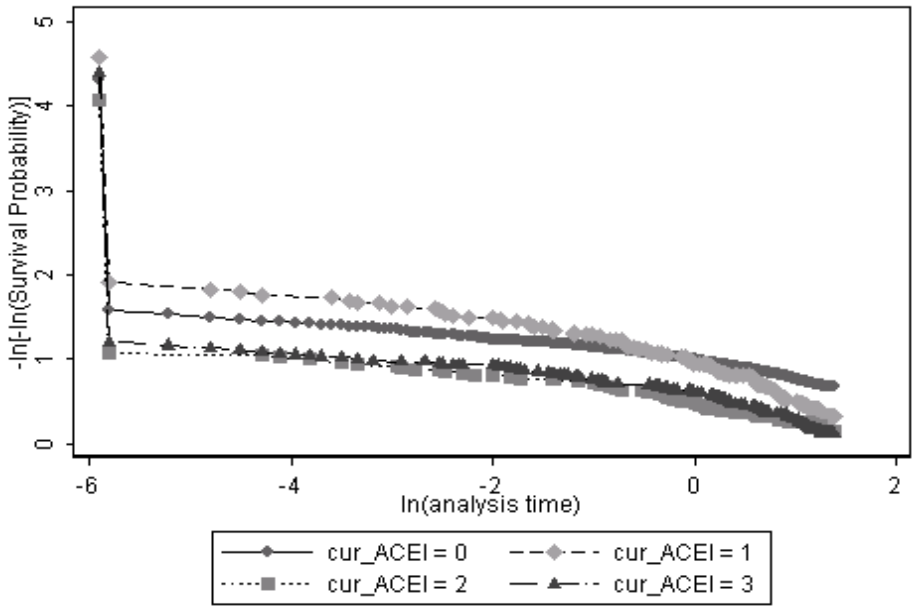


Fig 7.1c: Proton pump inhibitors

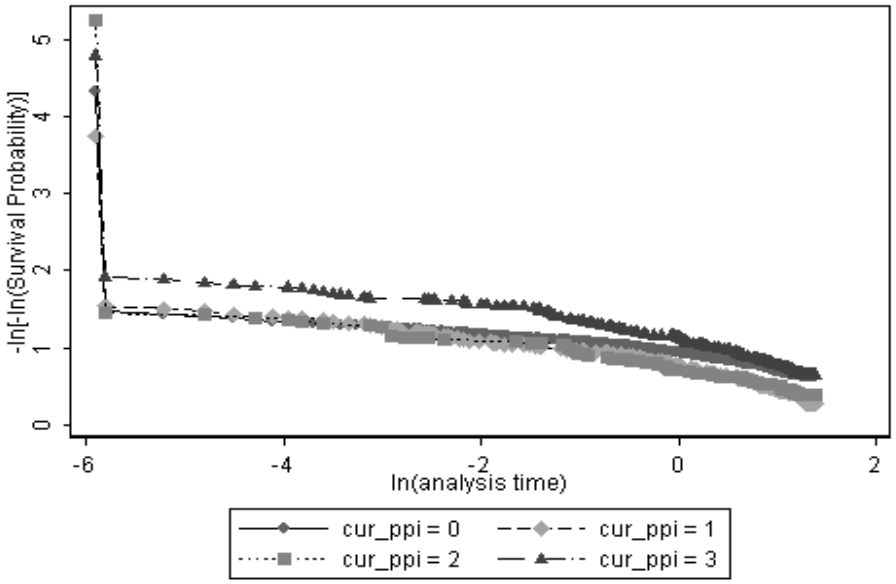


Fig 7.1d: H2 receptor antagonists

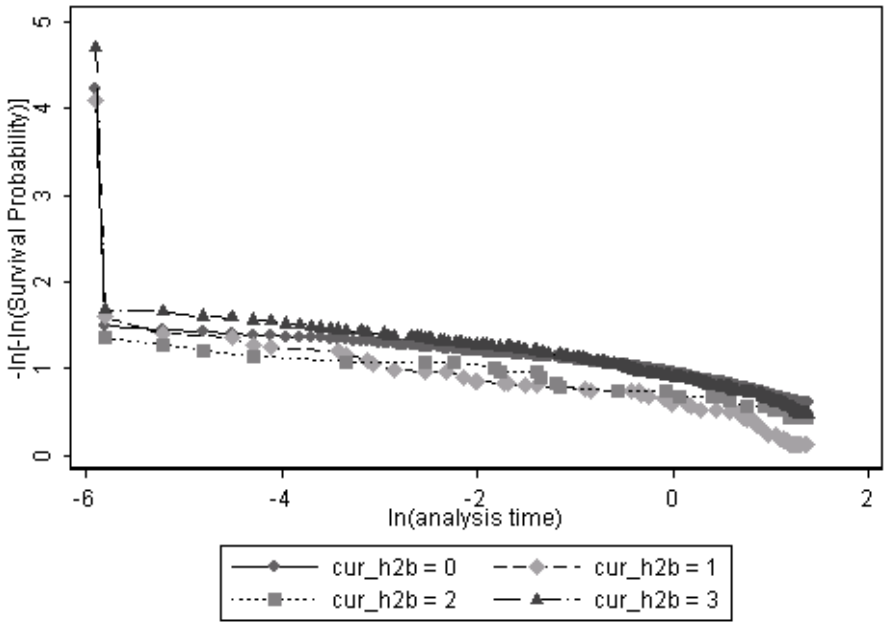


Table 7.3: All-cause mortality: hazard ratios (exposed/unexposed), examined on either side of the midpoint of person-time (median value 2.8 years)

Drug	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio[1] (95% CI)	Adjusted Hazard Ratio[2] (95% CI)
Statins (ever/never)			
Time<2.8 years	0.53 (0.42-0.66)	0.68 (0.55-0.85)	0.60 (0.48-0.76)
Time ≥2.8 years	1.14 (0.56-2.30)	1.17 (0.57-2.37)	0.92 (0.45-1.89)
ACEIs (ever/never)			
Time<2.8 years	1.40 (1.25-1.57)	1.14 (1.01-1.28)	0.99 (0.88-1.12)
Time ≥2.8 years	3.22 (1.96-5.29)	2.24 (1.36-3.68)	1.85 (1.10-3.09)
PPIs (ever/never)			
Time<2.8 years	1.06 (0.95-1.19)	1.03 (0.92-1.16)	0.95 (0.85-1.07)
Time ≥2.8 years	1.92 (1.17-3.13)	1.72 (1.05-2.81)	1.44 (0.87-2.37)
H2RAs (ever/never)			
Time<2.8 years	1.09 (0.97-1.22)	1.04 (0.92-1.17)	0.92 (0.82-1.03)
Time ≥2.8 years	1.99 (1.21-3.27)	1.71 (1.04-2.81)	1.49 (0.90-2.48)

[1] Adjusted for age and sex
[2] Adjusted for age, sex, townsend's deprivation score, current smoking and Charlson Comorbidity Index score

7.4.2 Kaplan Meier Survival curves

Figure 7.2 presents the Kaplan Meier survival curves plotted for the entire study period, for each of the drug exposures. Cases on statins at the time of pneumonia diagnosis were least likely to die and some protective effects were observed with recent statin use as well which persisted into the long term. There was no difference in mortality between historical users of statins and non-users [Figure 7.2(a)]. ACEI use at the time of a pneumonia diagnosis seemed to be associated with decreased mortality only in the early follow-up period up to nine months, but from this point onwards this subgroup of patients is at a greater risk of dying compared to non-users. Past and present users of ACEIs appear to be associated with a worse outcome than non-users. This could be a reflection of underlying comorbidity which cannot be controlled for in the Kaplan Meier survival plots [Figure 7.2(b)]. Current users of PPIs are at a decreased mortality risk compared to non-users but historical use of these drugs appears to be associated with a worse mortality outcome [Figure 7.2(c)]. Use of H2RAs appears to be associated with an increased mortality risk [Figure 7.2(d)].

Figure 7.2: Kaplan Meier survival curves for various drug exposures (2001-2005)

Fig 7.2a: Statins

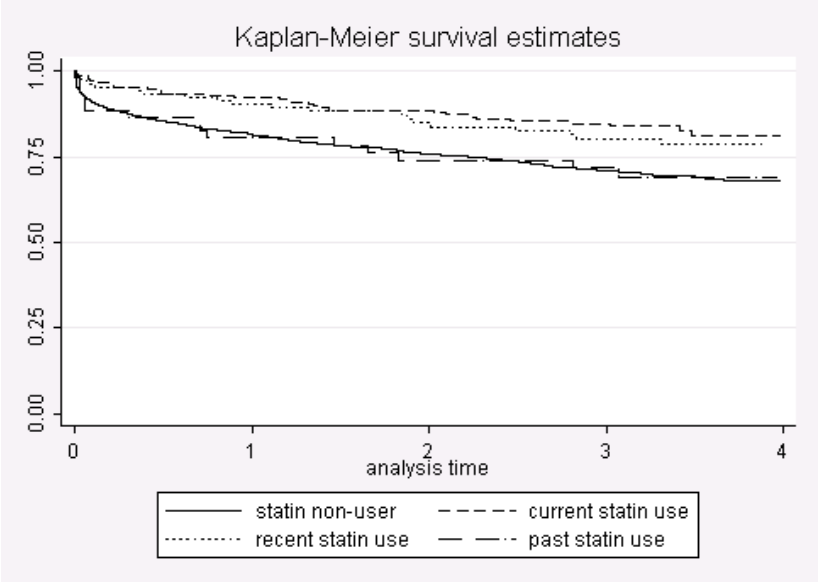


Fig 7.2b: ACE inhibitors

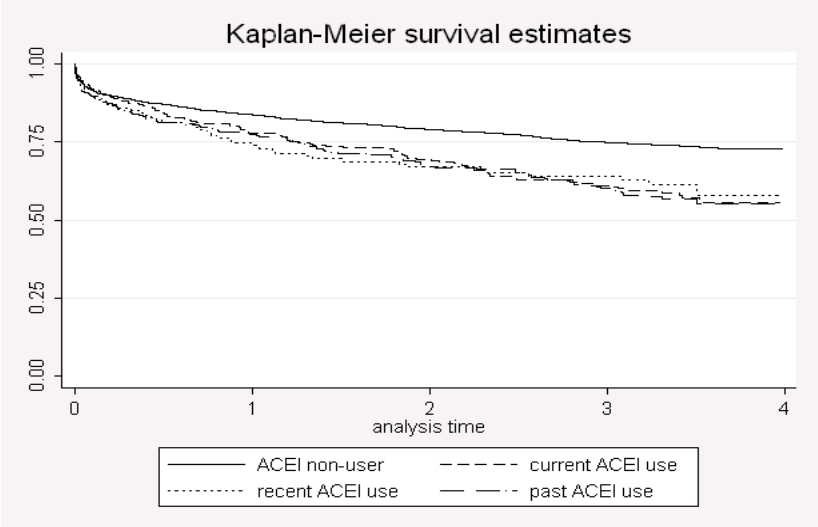


Fig 7.2c: Proton pump inhibitors

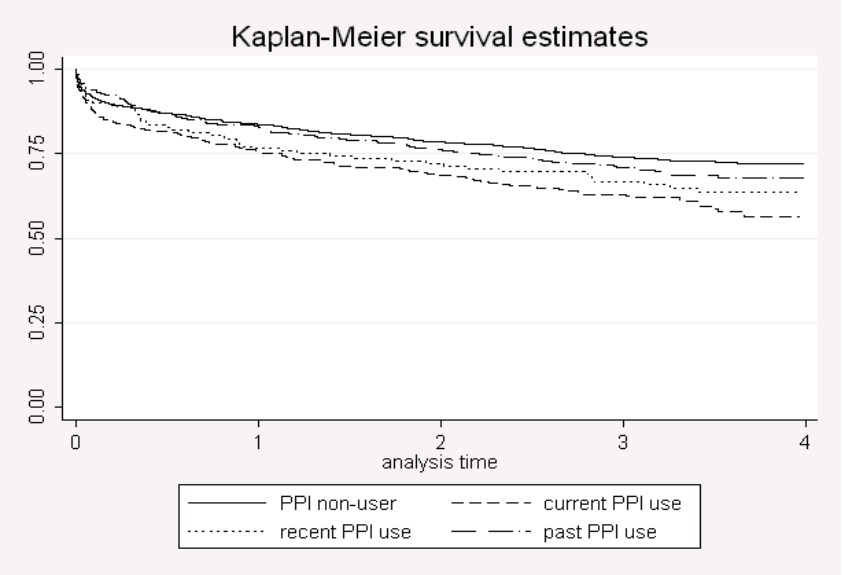
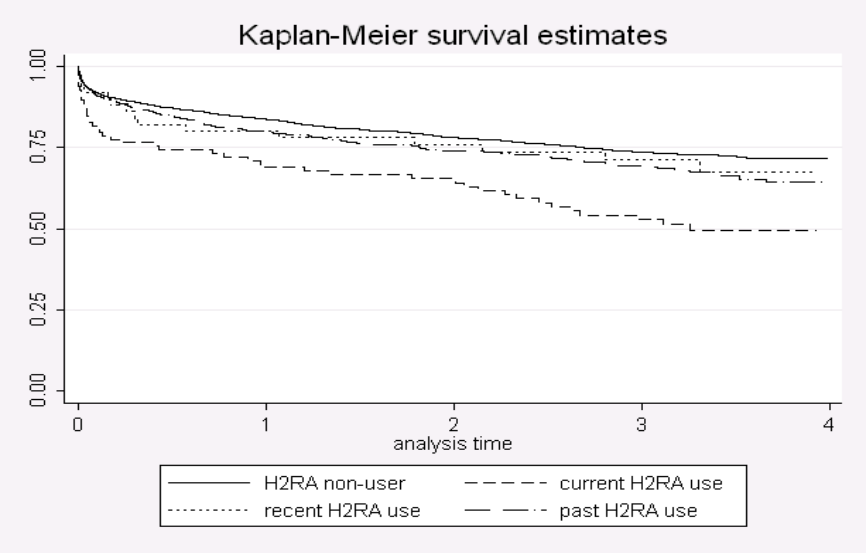


Fig 7.2d: Histamine 2 receptor antagonists



7.4.3 30-day mortality

Table 7.4 presents the adjusted hazard ratios showing the association between various drug exposures and mortality within 30 days of pneumonia diagnosis. Statin use in the 30 days prior to pneumonia diagnosis was associated with a 67% decrease in 30-day mortality as compared to not using statins (adjusted HR: 0.33, 95% CI: 0.19-0.58). Recent use of statins (ceased a month prior to diagnosis) was associated with a 42% decrease in mortality (adjusted HR 0.58, 95% CI: 0.34-0.99). ACEI use in the 30 days prior to pneumonia diagnosis decreased the 30-day mortality risk by 38% as compared to no-use (adjusted HR: 0.62, 95% CI: 0.47-0.82). No significant impact on mortality was observed for current users of H2RAs or PPIs and 30-day mortality. However, there appeared to be a protective effect with past use (prescriptions ceased more than three months prior to pneumonia diagnosis) for both gastric acid suppressants.

Table 7.4: between 30-day mortality following pneumonia and various drug exposures (n=3681)

Drug	Numbers dead (% deaths within each category) (n=905)	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio[1] (95% CI)	Adjusted Hazard Ratio[2](95% CI)	Adjusted Hazard Ratio[3](95% CI)
Statin use					
No use	860 (25.9)	1.00	1.00	1.00	1.00
Current (within 30 days)	12 (6.8)	0.25 (0.14-0.44)	0.37 (0.21-0.65)	0.33 (0.19-0.59)	0.33 (0.19-0.58)
Recent (31-90 days)	14 (12.2)	0.45 (0.27-0.77)	0.67 (0.39-1.14)	0.58 (0.34-0.99)	0.58 (0.34-0.99)
Past (>90 days)	19 (29.3)	1.11 (0.71-1.76)	1.49 (0.95-2.36)	1.35 (0.85-2.13)	1.36 (0.86-2.16)
ACEI use					
No use	687 (23.8)	1.00	1.00	1.00	1.00
Current (within 30 days)	54 (18.6)	0.77 (0.58-1.01)	0.67 (0.51-0.89)	0.61 (0.46-0.80)	0.62 (0.47-0.82)
Recent (31-90 days)	61 (34.1)	1.47 (1.13-1.91)	1.27 (0.98-1.65)	1.10 (0.84-1.43)	1.13 (0.87-1.48)
Past (>90 days)	103 (31.7)	1.36 (1.11-1.67)	1.14 (0.93-1.40)	0.98 (0.79-1.20)	1.03 (0.83-1.27)
PPI use					
No use	665 (25.4)	1.00	1.00	1.00	1.00
Current (within 30 days)	100 (26.1)	1.03 (0.84-1.28)	0.92 (0.75-1.14)	0.85 (0.69-1.06)	0.90 (0.72-1.12)
Recent (31-90 days)	53 (27.6)	1.09 (0.82-1.44)	1.07 (0.81-1.41)	0.93 (0.70-1.23)	0.98 (0.74-1.31)
Past (>90 days)	87 (17.9)	0.69 (0.55-0.86)	0.79 (0.63-0.98)	0.74 (0.59-0.92)	0.77 (0.61-0.97)
H2B use					
No use	672 (24.7)	1.00	1.00	1.00	1.00
Current (within 30 days)	38 (31.7)	1.29 (0.93-1.79)	1.05 (0.75-1.45)	0.92 (0.66-1.28)	0.92 (0.66-1.28)
Recent (31-90 days)	19 (28.8)	1.16 (0.74-1.84)	1.26 (0.80-1.98)	1.11 (0.70-1.76)	1.11 (0.70-1.76)
Past (>90 days)	176 (23.0)	0.91 (0.77-1.07)	0.92 (0.78-1.08)	0.81 (0.68-0.96)	0.81 (0.68-0.96)

[1] Adjusted for age and sex
[2] Adjusted for age, sex, Townsend's deprivation score, current smoking and Charlson Comorbidity Index score
[3] Adjusted for age, sex, Townsend's deprivation score, current smoking and Charlson Comorbidity Index score and co-prescription of other exposure drugs

7.4.4 All-cause mortality

Table 7.5 presents the adjusted hazard ratios showing the association between various drug exposures and all-cause mortality in pneumonia cases over the entire study period. Both current and recent use of statins was associated with a decrease in long-term mortality (adjusted HR: 0.45, 95% CI: 0.32-0.62) and (adjusted HR: 0.62, 95% CI: 0.43-0.89) respectively. There was no significant association between long-term mortality and the use of ACEIs, PPIs or H_2RAs.

Table 7.5: Association between all-cause mortality in pneumonia cases over median follow-up period of 2.8 yrs and various drug exposures (n=3681)

Drug	Numbers dead (% deaths within each category) (n=1501)	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio[1] (95% CI)	Adjusted Hazard Ratio[2] (95% CI)	Adjusted Hazard Ratio[3] (95% CI)
Statin use					
No use	1406 (42.3)	1.00	1.00	1.00	1.00
Current (within 30 days)	36 (20.3)	0.40 (0.29-0.56)	0.51 (0.37-0.72)	0.46 (0.33-0.64)	0.45 (0.32-0.62)
Recent (31-90 days)	31 (30.0)	0.57 (0.40-0.81)	0.74 (0.52-1.06)	0.64 (0.45-0.91)	0.62 (0.43-0.89)
Past (>90 days)	28 (43.1)	1.01 (0.70-1.50)	1.25 (0.86-1.83)	1.16 (0.80-1.69)	1.13 (0.77-1.65)
ACEI use					
No use	1090 (37.8)	1.00	1.00	1.00	1.00
Current (within 30 days)	136 (46.7)	1.24 (1.04-1.48)	1.02 (0.86-1.22)	0.91 (0.76-1.09)	0.92 (0.77-1.11)
Recent (31-90 days)	96 (53.6)	1.60 (1.30-1.97)	1.32 (1.07-1.62)	1.14 (0.92-1.40)	1.18 (0.95-1.46)
Past (>90 days)	179 (55.1)	1.59 (1.36-1.86)	1.24 (1.06-1.46)	1.06 (0.90-1.25)	1.11 (0.94-1.30)
PPI use					
No use	1041 (16.3)	1.00	1.00	1.00	1.00
Current (within 30 days)	185 (20.2)	1.26 (1.08-1.47)	1.08 (0.93-1.27)	1.00 (0.85-1.17)	1.03 (0.88-1.21)
Recent (31-90 days)	90 (19.5)	1.21 (0.98-1.51)	1.14 (0.92-1.41)	0.99 (0.79-1.23)	1.03 (0.82-1.28)
Past (>90 days)	185 (14.8)	0.92 (0.79-1.08)	1.00 (0.86-1.17)	0.94 (0.80-1.10)	0.95 (0.81-1.12)
H2B use					
No use	1077 (39.6)	1.00	1.00	1.00	1.00
Current (within 30 days)	65 (54.2)	1.49 (1.16-1.92)	1.18 (0.92-1.52)	1.04 (0.81-1.34)	1.05 (0.81-1.35)
Recent (31-90 days)	30 (45.5)	1.18 (0.82-1.70)	1.20 (0.84-1.73)	1.04 (0.72-1.50)	1.06 (0.73-1.52)
Past (>90 days)	329 (42.5)	1.06 (0.94-1.20)	1.03 (0.91-1.17)	0.91 (0.81-1.04)	0.91 (0.80-1.04)

[1] Adjusted for age and sex
[2] Adjusted for age, sex, Townsend's deprivation score, current smoking and Charlson Comorbidity Index score
[3] Adjusted for age, sex, Townsend's deprivation score, current smoking and Charlson Comorbidity Index score and co-prescription of other exposure drugs

7.4.5 Sensitivity analyses: Testing for 'healthy user effect'

Table 7.6 presents the results of sensitivity analyses to assess the likelihood of an underlying 'healthy user effect', in the association between statins and pneumonia mortality. Separate analyses were conducted with other cardiovascular drugs (diuretics, calcium channel blockers and nitrates) as exposure variables and no significant decrease was observed in all-cause mortality over the study period. In fact, current, recent and historical use of diuretics was associated with an increased mortality risk.

Table 7.6: Association between all-cause mortality in pneumonia cases over median follow-up period of 2.8yrs and selected cardiovascular drug exposures (n=3681)

Drug	Numbers dead (%) (n= 1501)	Adjusted Hazard Ratio[1] (95% CI)
Calcium channel blockers		
No use	1113 (39.1)	1.00
Current (within 30 days)	94 (37.5)	0.77 (0.59-1.00)
Recent (31-90 days)	79 (43.9)	0.85 (0.62-1.15)
Past (>90 days)	215 (53.5)	1.06 (0.86-1.29)
Nitrates		
No use	1167 (39.0)	1.00
Current (within 30 days)	94 (50.0)	0.84 (0.64-1.09)
Recent (31-90 days)	81 (54.7)	0.94 (0.69-1.29)
Past (>90 days)	159 (44.7)	0.79 (0.63-1.00)
Diuretics		
No use	503 (26.9)	1.00
Current (within 30 days)	404 (54.1)	1.36 (1.14-1.64)
Recent (31-90 days)	251 (60.9)	1.40 (1.12-1.75)
Past (>90 days)	393 (52.9)	1.44 (1.18-1.75)

[1] Adjusted for age, sex, Townsend's deprivation score, current smoking and Charlson Comorbidity Index score

7.5 Discussion

7.5.1 Summary of main findings

Current statin use was associated with a lower risk of short and long-term all-cause mortality in pneumonia cases. Current ACEI use was associated with a nearly 40% decrease in 30-day mortality but had no impact on long-term mortality. No significant impact on either short or long-term pneumonia mortality was observed for H2RAs or PPIs following adjustment for potential confounders though there appeared to be a slight decrease in 30-day mortality in historical users of gastric acid suppressants.

7.5.2 Strengths and limitations of this study

The main strengths of this study are the large number of pneumonia cases available for follow-up (n=3681). The study looked at prognosis in the full spectrum of pneumonia cases: those managed in the community as well as severe cases requiring hospitalisation. The THIN database has records on all prescriptions so we had comprehensive data on drug exposure. The study investigated both all-cause mortality and 30 day-mortality in pneumonia cases to investigate short-term and long-term effects of the considered drug exposures. An adapted form of the Charlson's Comorbidity Index was used to measure and adjust for comorbid conditions.[25 34] The Charlson's Index was developed specifically to predict mortality and we have been able to adjust for any confounding by comorbidity using a robust measure.[25]

One possible weakness is that no formal assessment was done for the severity of pneumonia but the scope of this present study was merely to investigate the association between these drug exposures and mortality in pneumonia cases as a first step. Another limitation which was also discussed in Chapter 4 is that the exposure data relates to prescriptions so there is no certainty that the drugs were actually used. This means there could be some overestimation of exposure to the various drugs in the analysis. However, such a misclassification would be non-differential and only bias results towards unity. Lastly, exposure status was determined at the time of diagnosis and it is inevitable that as follow-up time increases, some random error would creep in because of a change in exposure status. Such a random error would only push the results towards unity. However, ascertaining exposures at a point after diagnosis would result in a systematic error because of the 'immortal time bias'.[112]

7.5.3 Comparison with existing literature

Other studies have found a 30-64% decrease in 30 day-mortality associated with statin use compared to the present study finding of a 67% decrease.[71 110 111] Some of these have been smaller studies (with between 800 to 1250 pneumonia cases) [71 110 111] while the studies by Chalmers et al. (2008) and Thomsen et al. (2008) only considered hospitalised cases of pneumonia.[111 113] The study by Schlienger et al (2007) used data from the UK General Practice Research Database (GPRD) which is similar to the THIN database so it is not surprising that results are similar.[71] However, unlike other studies the present study also looked at long-term mortality in pneumonia cases and found a 55%

decrease in statin users. These effects are independent of comorbidity, age, sex, smoking and deprivation and may be explained by immunomodulatory effects of statins. In observational studies, bias cannot be ruled out and the observed effect could be explained by the 'healthy user effect' as pointed out by Majumdar et al [77] i.e. that statin users are likely to be more proactive in seeking healthcare and follow healthier lifestyles resulting in a lower mortality risk. If this is true, then a similar decrease in mortality would be observed with other prescription drugs. Separate analyses were therefore conducted with diuretics, calcium channel blockers and nitrates as exposure variables and did not find a significant decrease in all-cause mortality over the study period (Table 7.4 and Table 7.6). This suggests that the results for statins cannot be explained by the 'healthy user effect'. In addition, there is the possibility that statin users are simultaneously on other prescription drugs, making it difficult to assess if the observed results reflect the independent effect of statins. This study has attempted to overcome this by including all the four drugs: ACEIs, statins, PPIs and H2RAs in the final regression model (Table 7.4 and Table 7.5). Lastly, some authors have attributed the protective effects of statins to 'confounding by indication' which arises when the indication for prescribing the drug is also associated with the outcome.[111] This study has adjusted for confounding by indication using a very comprehensive comorbidity index, CCI which includes the indications for the drug exposures of interest, such as ischaemic heart disease, diabetes, gastroeosophageal ulcers.[25]

This study showed a nearly 40% decrease in 30-day mortality with the current use of ACE inhibitors. Initially some authors suggested that the mechanism of

action by which these drugs lower the risk of acquiring pneumonia (especially aspiration pneumonia) is the induction of the cough reflex.[114] However, once pneumonia is acquired this would not explain how ACEIs could alter the clinical course of the disease i.e. the severity or survival. Recently, these effects have been attributed to the pleiotropic effects of ACEIs, possibly by action on the vascular endothelium.[63 66] The study by Mortensen et al (2005) showed a 56% decrease in 30-day mortality after adjusting for variables relating to clinical management such as initial antibiotics within 4 hours, oxygenation assessment within 24 hours and use of guideline concordant antimicrobial therapy.[76] Chalmers et al. (2008) suggest that the observed beneficial effects of ACE inhibitors in previous studies reflected co-prescription with statins.[111] However, the protective effect of ACEIs with regards 30-day mortality persisted even after accounting for co-prescription of other drugs in our study. Interestingly unlike statins, ACEI use at the time of pneumonia diagnosis did not influence mortality in the long-term.

The literature review did not find any study investigating the effect of gastric acid suppressants on mortality in pneumonia. These drugs may cause increased susceptibility to pneumonia due to their property of increasing gastric pH, thus allowing bacterial colonisation.[68 69] Among the gastric acid suppressants, current use of both H2RAs and PPIs was not associated with either short-term or long-term mortality in pneumonia cases. Surprisingly, this study did find a decrease in 30-day mortality associated with historical use of these drugs. It is likely that this observation is a statistical artefact as it does not appear to satisfy the criteria of biological plausibility. Unlike statins and

ACEIs, both H2RAs and PPIs are also available as non-prescription drugs and drug exposures are more difficult to ascertain with accuracy using prescriptions data. There could also be some residual confounding that we have been unable to control for.

7.6 Summary

In people diagnosed with pneumonia current statin use was associated with a 67% decrease in 30-day mortality and a 55% decrease in long-term mortality over a median follow-up period of 2.8 years. ACE inhibitor use was associated with a 38% decrease in 30-day mortality but no association was found with long-term all-cause mortality following a pneumonia diagnosis. No significant impact on either short or long-term pneumonia mortality was observed for histamine-2 receptor antagonists or proton pump inhibitors.

8 Conclusions and Recommendations

8.1 Conclusions

To reiterate, the aims of this thesis were as follows:

(1) To determine the overall incidence and mortality for pneumonia in general practice

(2) To determine how incidence and mortality for pneumonia vary by socio-demographic characteristics like age, sex and deprivation

(3) To investigate whether statins, angiotensin converting enzyme inhibitors and gastric acid suppressants like proton pump inhibitors and histamine 2 receptor antagonists modify the risk of acquiring pneumonia and its prognosis

The key findings in response to the thesis aims are summarised in section 8.2. Section 8.3 outlines the clinical and public health implications of these findings and Section 8.4 discusses recommendations on the basis of this work for further studies.

8.2 Summary of main findings

8.2.1 Pneumonia incidence in primary care

The overall incidence of pneumonia was 237 per 100,000 person-years (95% CI: 235 to 239) and this rate was stable between 1991 and 2003. The incidence of pneumonia was slightly lower in females as compared to males (age-adjusted incidence rate ratio (IRR) 0.88, 95% CI: 0.86, 0.89). Pneumonia

was most common in children under the age of four years and adults over the age of 65 years. In addition, a peak in incidence was observed in women aged 30-39 years. Possible explanations included higher primary care consultation rates in women with younger children resulting in increased ascertainment of milder pneumonia cases; or an actual increase in pneumonia because of increased risk of exposure to chest infections from their children. In people over the age of sixty years, the increase in incidence happened approximately 5 years earlier in men compared to women.

There was an increased incidence of pneumonia with higher levels of socioeconomic disadvantage such that people living in the most deprived areas of the UK were 28% more likely to get pneumonia than those in the least deprived areas (age and gender-adjusted IRR 1.28, 95% CI 1.24 to 1.32). The link with deprivation was particularly strong in the very elderly, aged 80 years and above.

8.2.2 Mortality in pneumonia cases compared to the general population

The mortality study showed that people with a diagnosis of pneumonia had a markedly increased mortality in the short-term, with cases 46 times more likely to die in the first 30 days after diagnosis. Some increase in mortality persisted during longer-term follow-up (median follow-up time of 2.8 years) which could not be accounted for by other underlying comorbid conditions. Younger people were at a relatively higher risk of pneumonia mortality. Therefore, a diagnosis of pneumonia emerged as an important predictor of mortality in younger patients (19-59 years) who are not typically classified as ‘high risk’.

8.2.3 The impact of statins, ACE inhibitors, PPIs and histamine 2 receptor antagonists on the risk of acquiring pneumonia

Statin and ACE inhibitor (ACEI) use was associated with a lower risk of pneumonia but these effects were smaller than those observed in previous studies. However, no protective effects were observed with historical use of statins or ACEIs. Possible mechanisms of action by which these two drugs exert their effects were the action of ACE inhibitors on the cough reflex; and the immunomodulatory effect of statins. More recent literature has suggested that both ACE inhibitors and statins have pleiotropic effects that may decrease sepsis and improve outcomes of respiratory disease. These could explain why only current use of the drugs had a protective effect. The possibility of 'residual confounding', 'confounding by indication' and the presence of a 'healthy user effect' were also investigated in sensitivity analyses and while they cannot be completely ruled out, it appears that the observed protective effects are not merely a statistical artefact.

The current use of proton pump inhibitors (PPI) was associated with an increased risk of acquiring pneumonia. Recent historical use of PPIs also increased pneumonia risk. However, no significant association was found between prescriptions for H2 receptor antagonists and pneumonia. Both these drugs are gastric acid suppressants and it is widely suggested that the resulting increased gastric pH facilitates bacterial colonisation of the respiratory tract. The observed increase in pneumonia risk with PPIs but not H2RAs could be explained by the greater acid suppressive action of PPIs.

8.2.4 The impact of statins, ACE inhibitors, PPIs and histamine 2 receptor antagonists on pneumonia mortality

In people diagnosed with pneumonia current statin use was associated with a 67% decrease in 30-day mortality and a 55% decrease in long-term mortality over a median follow-up period of 2.8 years. As with the relationship between statins and pneumonia risk, the possibility of 'confounding by indication' and the 'healthy user effect' were considered separately in a series of sensitivity analyses. The results suggested that the observed protective effects of statins on pneumonia mortality may be true. ACE inhibitor use was associated with a 38% decrease in 30-day mortality but no association was found with long-term all-cause mortality following a pneumonia diagnosis. To investigate whether the observed effects of ACEIs were merely reflections of co-prescription with statins, an additional multivariate regression model was created which included all the four exposure drugs, to take into account co-prescription. The results were similar for models with and without co-prescription of other drugs. No significant impact on either short or long-term pneumonia mortality was observed for histamine-2 receptor antagonists or proton pump inhibitors.

8.3 Clinical and Public Health implications

8.3.1 Incidence study: Pneumonia incidence in primary care

This study showed pneumonia incidence rate in the UK general practice population is currently 233 per 100,000 person-years. This is lower than that quoted in the British Thoracic Society guidelines,[39] but still suggests that an average GP practice with 10,000 registered patients could expect about 23

cases of pneumonia in a year. Incidence rates remained fairly stable over the study period and no perceptible trends were noted. A slight upward trend in incidence was observed from 2000 to 2003 which may reflect changes in coding practices. Nevertheless, it would be worth monitoring future trends given recent evidence of increase in pneumonia hospital admissions in England.[115]

8.3.2 Mortality study: Mortality in pneumonia cases compared to the general population

Pneumonia is a significant problem in primary care because it is associated with both increased short-term and long-term mortality. The 30-day prognosis in pneumonia cases is very poor with an over forty-fold increased mortality risk as compared to controls. Even in the long-term pneumonia appears to be an independent predictor of mortality irrespective of age, sex or coexisting comorbidity. While older and more deprived patients with coexisting comorbidities are especially at risk, pneumonia may be an important predictor of mortality in younger patients who are not typically classified as 'high risk'.

8.3.3 The impact of statins, ACE inhibitors, PPIs and histamine 2 receptor antagonists on the risk of acquiring pneumonia

The results of this study add to the evidence on the potential of current statin and ACE inhibitor use to prevent pneumonia and the increased risk of pneumonia with PPI use. It is however important to distinguish between observed statistical associations and causality. A limitation of observational studies is that they cannot establish causality as an observed association

could be because of chance, confounding or bias. While this study evidence is not sufficient to recommend the use of these drugs for patients at increased risk of pneumonia as a preventive measure, this added benefit should be considered when rationalising drug treatment for patients already on these drugs or those who have other indications for prescribing of these drugs. Statins are already being prescribed in general practice as both a primary and secondary prevention measure in patient groups with elevated cardiovascular disease risk [116] [117] and statins could potentially also reduce the pneumonia burden in primary care. However, clinical trials will be needed to determine which individual statin will be best for this purpose and provide evidence on suitable dosage, duration, safety and target patient group. The results also show that people prescribed a PPI are at an increased risk of acquiring pneumonia. PPIs are prescribed commonly in general practice, and often without a firm diagnosis, so even a potentially small increase in pneumonia risk could have considerable impact on the burden of community-acquired pneumonia. Clinicians therefore should carefully consider their decision to prescribe a PPI especially in patients who may already be at an increased risk of pneumonia.

8.3.4 The impact of statins, ACE inhibitors, PPIs and histamine 2 receptor antagonists on pneumonia mortality

These study findings support previous research that statins may be associated with a lower risk in both short and long-term mortality following pneumonia. Statins are already being prescribed in general practice as both a primary and secondary prevention measure in patient groups with elevated

cardiovascular disease risk [116] [117] and they could potentially also reduce the pneumonia mortality. There are two possible prescribing policy implications arising from this: first, that statins be prescribed as a secondary preventive measure in pneumonia patients. As pointed out above, it will be necessary to conduct clinical trials on statins in pneumonia patients to determine whether the observed decrease in mortality can be demonstrated in experimental studies as well before national prescribing guidelines can be changed. Clarity will also be needed on the best statin to use, dose, and duration. The second implication is regarding prescribing frameworks for end-of life care. There has been much debate about the benefits versus harm of polypharmacy in end-of-life patients. Some clinicians are in favour of reducing medications in these cases and the decision to discontinue a drug must be informed by the evidence on potential harms and benefits.[118] [119] The findings of this study suggest that it may be worth continuing statins in these patients. This study also found a lower risk of short-term mortality in pneumonia cases who were current ACEI users. Once again, as in the case of statins, there may be a case for continuing with ACEIs in patients at high risk of pneumonia complications and mortality.

8.4 Recommendations for further studies

Some of the limitations encountered during this research could be addressed in future studies. This study defined pneumonia on the basis of a list of Read codes recorded in general practice. One of the limitations was that radiological confirmation of pneumonia was not available. A validation study for pneumonia diagnoses used in general practice would form a useful reference

for future studies on pneumonia. It was not possible to determine the exact duration of exposure and the mean daily dose using individual drugs within the drug classes of interest. An attempt was made to approximate these variables but it resulted in an enormous loss of statistical power because of small numbers and missing data. This meant that it was not possible to look at dose-dependent relationships between pneumonia and the various drug exposures in this study. This information would be useful for clinicians and formulating prescription guidelines. Another limitation of using prescription data from THIN is that there is no certainty that the drugs were actually taken by the patient. The next step would be to ascertain exposure in a more robust manner, possibly by linking with pharmacy databases to determine how many prescriptions were actually filled, and following-up patients. There is also the difficulty of exposure ascertainment for gastric acid suppressants because of their availability as non-prescription medications and the potential association of these drugs with pneumonia should be reinvestigated with more accurate ascertainment of exposure to these drugs.

The findings of this research in turn can be used as a basis for further research. The pneumococcal vaccine for older people (above 65 years) was introduced in a phased manner from August 2003, and since September 2006, the revised childhood immunisation schedule came into effect, and includes a pneumococcal vaccine for infants at two, four and thirteen months.[120] This study provides methodology and baseline data which can be used to evaluate the impact of the pneumococcal vaccination policy on pneumonia incidence in the future. In addition, future research should

investigate whether the pneumococcal vaccine for older people has had any impact on health inequalities and decreased the socio-economic gradient observed for pneumonia incidence. One of the findings of this study was the slight peak in incidence of acute lower respiratory infections and pneumonia in women aged 30-39 years and one of the possible explanations was that women in this age group are exposed to a greater risk of chest infections from their children. It would be interesting to study whether there is any secondary impact of the childhood pneumococcal vaccine on pneumonia incidence in women aged 30-39 years.

This study found a protective effect of statins with regards pneumonia but before any conclusions can be drawn regarding their potential use in the prophylaxis of pneumonia, a randomised controlled trial would be needed. Such an experimental study design would also be able to determine the suitable dose and duration of statins required for adequate pneumonia prevention. Lastly, this study found an association between prescriptions for ACE inhibitors and a decrease in pneumonia incidence and short-term mortality. The possible mechanisms by which ACE inhibitors could prove beneficial in pneumonia are not fully understood. The earlier view that the cough reflex mediated by ACE inhibitors was responsible for the observed effects could explain the decreased risk of aspiration pneumonia, but does not explain the decrease in mortality. Recent literature has suggested that ACE inhibitors prevent endothelial dysfunction which has a crucial role in the pathophysiology of septic shock, which could influence pneumonia

outcomes.[63 66] Further work is needed to understand the possible pleiotropic effects of ACEIs in respiratory disease pathophysiology.

References

1. Hoare Z, Lim WS. Pneumonia: update on diagnosis and management *British Medical Journal* 2006;332:1077-1079.
2. Blasi F, Aliberti S, Pappalettera M, Tarsia P. 100 years of respiratory medicine: Pneumonia. *Respiratory Medicine* 2007;101:875-881.
3. File TM, Garau J, Low DE, Torres A. *Lectures in Respiratory Tract Infections: Community-Acquired Pneumonia*. London: Current Medicine Group, 2007.
4. BTS. British Thoracic Society Guidelines for the management of community acquired pneumonia in adults. *Thorax* 2001;56(suppl 4):1-64.
5. Macfarlane J, Colville A, Guion A, Macfarlane R, Rose D. Prospective study of aetiology and outcome of adult lower-respiratory tract infections in the community. *Lancet* 1993;341:511-514.
6. Lim WS, Macfarlane JT, Boswell TCJ, Harrison TG, Rose D, Leinonen M, et al. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. *Thorax* 2001;56:296-301.
7. Scott JAG, Hall AJ, Muyodi C, Lowe B, Ross M, Chohan B, et al. Aetiology, outcome, and risk factors for mortality among adults with acute pneumonia in Kenya. *The Lancet* 2000;355:1225-1230.
8. McPhee SJ, Ganong WF, editors. *Pathophysiology of Disease: An Introduction to Clinical Medicine*. New York London: McGraw-Hill, 2006.
9. Fleisher GR, Ludwig S, Henretig FM, Ruddy RM, Silverman BK. *Textbook of Pediatric Emergency Medicine*: Lippincott Williams and Wilkins, 2005.
10. File TM. Community-acquired pneumonia. *The Lancet* 2003;362:1991-2001.
11. Mortensen EM, Coley CM, Singer DE, Marrie TJ, Scott Obrosky D, Kapoor WN, et al. Causes of death for patients with community-acquired pneumonia: Results from the Pneumonia Outcomes Research Team cohort study. *Archives of Internal Medicine* 2002;162:1059-1064.
12. NHS. Pneumococcal vaccine: http://www.immunisation.nhs.uk/Vaccines/Pneumococcal/Pneumococcal, 2008.
13. HPA. Pneumococcal vaccination recommendations: http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1195733781639?p=1203008863948, 2008.
14. Bourke A, Dattani H, Robinson M. Feasibility study and methodology to create a quality-evaluated database of primary care data. *Informatics in Primary Care* 2004;12:171-7.
15. EPIC. THIN data from EPIC: A guide for researchers, 2007.
16. EPIC. THIN DATA. *Epiclink* 2006(5):1.
17. Lis Y, Mann RD. The VAMP Research multi-purpose database in the U.K. *J Clin Epidemiol* 1995;48(3):431-43.

18. Walley T, Mantgani A. The UK General Practice Research Database. *Lancet* 1997;350(9084):1097-9.
19. EPIC. The General Practice Research Database - A Guide for Researchers. 2001.
20. GPRD. GPRD-Excellence in Public Health Research, 2008.
21. Hansell A, Hollowell J, Nichols T, McNiece R, Strachan D. Use of the General Practice Research Database (GPRD) for respiratory epidemiology with the 4th Morbidity Survey in General Practice (MSGP4). *Thorax* 1999;54:413-419.
22. EPIC. THIN data statistics. *Epiclink* 2004(3).
23. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf* 2006.
24. BNF. *British National Formulary 50*. London: British Medical Association & Royal Pharmaceutical Society of Great Britain, 2005.
25. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Disease* 1987;40(5):373-383.
26. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *Journal of Clinical Epidemiology* 1992;45(6):613-619.
27. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson Comorbidity Index predicted in-hospital mortality. *Journal of Clinical Epidemiology* 2004;57:1288-1294.
28. de Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity: a critical review of available methods. *Journal of Clinical Epidemiology* 2003;56:221-229.
29. Morris R, Carstairs V. Which deprivation? A comparison of selected deprivation indexes. *Journal of Public Health Medicine* 1991;13(4):318-326.
30. Townsend P. Deprivation. *J. Social Policy* 1987;16:125-146.
31. Adams J, Ryan V, White M. How accurate are Townsend Deprivation scores as predictors of self-reported health? A comparison with individual level data. *Journal of Public Health* 2004;2004(Nov):1-6.
32. MacIntyre CR, McIntyre S, Cagney M. Community-based estimates of incidence and risk factors for childhood pneumonia in Western Sidney. *Epidemiol Infect* 2003;131:1091-1096.
33. Farr BM, Woodhead M, Macfarlane JT, Bartlett CLR, McCracken JS, Wadsworth J, et al. Risk factors for community-acquired pneumonia diagnosed by general practitioners in the community. *Respiratory Medicine* 2000;94:422-427.
34. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiology* 1992;45(6):613-619.
35. Smeeth L, Donnan PT, Cook DG. The use of primary care databases: case-control and case-only designs. *Family Practice* 2006;doi:10.1093/fampra/cml025.
36. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. *Statistics in Medicine* 2005;http://statistics.open.ac.uk/sccs.

37. Myles PR, McKeever T, Hoare Z, Smith C, Hubbard R. The incidence of pneumonia in the United Kingdom: data from a computerized general practice database. *Epidemiol Infect* 2008.
38. Holmes WF, Woodhead MA. Providing better care for patients who may have pneumonia. *Thorax* 1999;54(10):925-928.
39. Macfarlane J, Boldy D. 2004 update of BTS guidelines: what's new? *Thorax* 2004;59:364-6.
40. BTS. British Thoracic Society Guidelines for the Management of Community Acquired Pneumonia in Childhood. *Thorax* 2002;57(Supplement 1):il-24.
41. Foy HM, Conney MK, Allan I. Rates of pneumonia during influenza epidemics in Seattle, 1964 to 1975. *JAMA* 1979;241:253-8.
42. Jokinen C, Heiskanen L, Juvonen H, Kallinen S, Karkola K, Korppi M, et al. Incidence of community-acquired pneumonia in the population of four municipalities in Eastern Finland. *American Journal of Epidemiology* 1993;137(9):977-988.
43. Almirall J, Bolibar I, Vidal J, Sauca G, Coll P, Niklasson B, et al. Epidemiology of community-acquired pneumonia in adults: a population based study. *Eur Respir J* 2000;15:757-763.
44. Woodhead M, Macfarlane J, McCracken J, Rose D, Finch R. Prospective study of the aetiology and outcome of pneumonia in the community. *Lancet* 1987;1(8534):671-4.
45. Houston MS, Silverstein MD, Suman VJ. Community-acquired lower respiratory tract infection in the elderly: a community-based study of incidence and outcome. *Journal American Board Family Practitioners* 1995;8(5):347-56.
46. Almirall J, Morato I, Riera F, Verdaguer A, Priu R, Coll P, et al. Incidence of community-acquired pneumonia and chlamydia pneumoniae infection: a prospective multicentre study. *Eur Respir J* 1993;6(1):14-8.
47. Lewis JD, Bilker WB, Weinstein RB, Strom BL. The relationship between time since registration and measured incidence rates in the General Practice Research Database. *Pharmacoepidemiology and drug safety* 2005;14:443-451.
48. Macfarlane J, Holmes W, Gard P, Macfarlane R, Rose D. Prospective study of the incidence, aetiology and outcome of adult lower respiratory tract illness in the community. *Thorax* 2001;56(2):109-114.
49. Skull SA, Andrews RM, Byrnes GB, Campbell DA, Nolan TM, Brown GV, et al. ICD-10 codes are a valid tool for identification of pneumonia in hospitalized patients aged ³65 years. *Epidemiol Infect* 2008;136:232-240.
50. ONS. Life expectancy and healthy life expectancy at birth: by gender: Social Trends 31, 2002.
51. Kapur N, Hunt I, Lunt M, McBeth J, Creed F, Macfarlane G. Primary care consultation predictors in men and women: a cohort study. *British Journal of General Practice* 2005;55(511):108-113.
52. Scaife B, Gill P, Heywood P, Neal R. Socio-economic characteristics of adult frequent attenders in general practice: secondary analysis of data. *Family Practice* 2000;17(4):298-304.
53. Campbell S, Roland M. Why do people consult the doctor? *Family Practice* 1996;13(1):75-83.

54. Walters S, Phupinyokul M, Ayres J. Hospital admission rates for asthma and respiratory disease in the West Midlands: their relationship to air pollution levels. *Thorax* 1995;50:948-954.
55. Farr BM, Bartlett CLR, Wadsworth J, Miller DL. Risk factors for community-acquired pneumonia diagnosed upon hospital admission. *Respiratory Medicine* 2000;94(10):954-963.
56. Vrbova L, Mamdani M, Moineddin R, Jaakimainen L, Upshur REG. Does socioeconomic status affect mortality subsequent to hospital admission for community acquired pneumonia among older persons? *Journal of Negative Results in BioMedicine* 2005;4(4).
57. Loeb MB. Community-Acquired Pneumonia in Older People: The need for a broader perspective. *Journal of the American Geriatrics Society* 2003;51(4):539-543.
58. Griffiths C, Golblatt P, Fitzpatrick J. Chapter 13: Geographic variations in health: main findings and implications for the future. *Geographical variations in health- Decennial supplement DS16*, 2001.
59. Myles PR, Hubbard RB, McKeever TM, Pogson Z, Smith CJP, Gibson JE. Risk of community-acquired pneumonia and the use of statins, ace inhibitors and gastric acid suppressants: a population-based case-control study. *Pharmacoepidemiology and drug safety* 2009;18:269-275.
60. Haldar K. Targeting the host to control an infection disorder. *Archives of Internal Medicine* 2008;168(19):2067-2068.
61. Stancu C, Sima A. Statins: mechanism of action and effects. *J. Cell. Mol. Med.* 2001;5(4):378-387.
62. Frost FJ, Petersen H, Tollestrup K, Skipper B. Influenza and COPD mortality protection as pleitropic, dose-dependent effects of statins. *Chest* 2007;131:1006-1012.
63. Wiel E, Pu Q, Leclerc J, Corseaux D, Bordet R, Lund N, et al. Effects of the angiotensin-converting enzyme inhibitor perinopril on endothelial injury and hemostasis in rabbit endotoxic shock. *Intensive Care Medicine* 2004;30:1652-1659.
64. Hothersall E, McSharry C, Thomson NC. Potential therapeutic role for statins in respiratory disease. *Thorax* 2006;61:729-734.
65. El Solh AA, Saliba R. Pharmacologic prevention of aspiration pneumonia: a systematic review. *The American Journal of Geriatric Pharmacotherapy* 2007;5:352-362.
66. Gryglewski RJ. The Sir Hans Krebs Lecture: Pharmacology of vascular endothelium *The FEBS Journal* 2005;272:2956-2967.
67. Rang HP. *Rang and Dale's Pharmacology*. 6th ed. Philadelphia: Churchill Livingstone Elsevier, 2007.
68. Laheij R, Sturkenboom M, Hassings R, Dieleman J, Stricker B, Jansen J. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004;292(16):1955-1960.
69. Gulmez SE, Holm A, Frederiksen H, Jensen TG, Pedersen C, Hallas J. Use of proton pump inhibitors and the risk of community-acquired pneumonia. *Archives of Internal Medicine* 2007;167:950-955.
70. Sataloff RT, Laheij RJ, Sturkenboom MC, Dieleman J, Stricker BH, Jansen JB. Community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2005;293(7):795-796.

71. Schleinger RG, Fedson DS, Jick SS, Jick H, Meier C. Statins and the risk of pneumonia: a population-based, nested case-control study. *Pharmacotherapy* 2007;27(3):325-332.
72. van de Garde EMW, Hak E, Souverein PC, Hoes AW, van den Bosch JMM, Leufkens HGM. Statin treatment and reduced risk of pneumonia in patients with diabetes. *Thorax* 2006;61:957-961.
73. Ohkubo T, Chapman N, Neal B, Woodward M, Omae T, Chalmers J. Effects of an angiotensin-converting enzyme inhibitor-based regimen on pneumonia risk. *Am J Respir Crit Care Med* 2004;169(9):1041-1045.
74. Okaishi K, Morimoto S, Fukuo K, Niinobu T, Hata S, Onishi T. Reduction of risk of pneumonia associated with use of angiotensin I converting enzyme inhibitors in elderly inpatients. *Am J Hypertens* 1999;12(8 Pt 1):778-783.
75. Takahashi T, Morimoto S, Okaishi K, Kanda T, Nakahashi T, Okuro M, et al. Reduction of pneumonia risk by an Angiotensin I-Converting Inhibitor in elderly Japanese inpatients according to insertion/deletion polymorphism of the Angiotensin I-Converting Enzyme Gene. *American Journal of Hypertension* 2005;18:1353-1359.
76. Mortensen EM, Restrepo MI, Anzueto A, Pugh J. The impact of prior outpatient ACE inhibitor use on 30-day mortality for patients hospitalised with community-acquired pneumonia. *BMC Pulmonary Medicine* 2005;5(12).
77. Majumdar SR, McAlister FA, Eurich DT, Padwal RS, Marrie TJ. Statins and outcomes in patients admitted to hospital with community acquired pneumonia: population based perspective. *BMJ* 2006;333(7576):999.
78. Laheij R, Van Ijzendoorn M, Janssen M, Jansen J. Gastric acid-suppressive therapy and community-acquired respiratory infections. *Aliment Pharmacol Ther* 2003;18(8):847-851.
79. Canani RB, Cirillo P, Roggero P, Romano C, Malamisura B, Terrin G, et al. Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. *Pediatrics* 2006;117:817-820.
80. Sarkar M, Hennessy S, Yang Y. Proton-pump inhibitor use and the risk for community-acquired pneumonia. *Annals of Internal Medicine* 2008;149:391-398.
81. Van de Garde EMW, Souverein PC, van den Bosch JMM, Deneer VHM, Leufkens HGM. Angiotensin-converting enzyme inhibitor use and pneumonia risk in a general population. *Eur Respir J* 2006;27:1217-1222.
82. Etminan M, Zhang B, Fitzgerald M, Brophy JM. Do angiotension-converting enzyme inhibitors or angiotensin II receptor blockers decrease the risk of hospitalization secondary to community-acquired pneumonia? A nested case-control study. *Pharmacotherapy* 2006;26(4):479-482.
83. Schneeweiss S, Maclure M. Use of comorbidity scores for control of confounding in studies using administrative databases. *International Journal of Epidemiology* 2000;29:891-898.

84. Smeeth L, Douglas I, Hubbard R. Commentary: We still need observational studies of drugs- they just need to be better. *International Journal of Epidemiology* 2006;35:1310-1311.
85. Farrington CP, Nash J, Miller E. Case series analysis of adverse reactions to vaccines: a comparative evaluation. *American Journal of Epidemiology* 1996;143(11):1165-73.
86. Gibson JE, Hubbard RB, Smith CJP, Tata LJ, Britton JR, Fogarty AW. Use of self-controlled analytical techniques to assess the association between use of prescription medications and the risk of motor vehicle crashes. *American Journal of Epidemiology* 2009;doi: 10.1093/aje/kwn364.
87. Myles PR, Hubbard R, Gibson JE, Pogson Z, Smith CJP, McKeever TM. Pneumonia mortality in a UK general practice population cohort. *European Journal of Public Health* in press.
88. Kalin ME, Ortquist A, Almela M, Aufwerber E, Dwyer R, Henriques B, et al. Prospective study of prognostic factors in community-acquired bacteremic pneumococcal disease in 5 countries. *Journal of Infectious Diseases* 2000;182:840-7.
89. Hirani N, Macfarlane J. Impact of management guidelines on the outcome of severe community acquired pneumonia. *Thorax* 1997;52:17-21.
90. McNabb WR, Shanson DC, Williams TDM, Lant AF. Adult community-acquired pneumonia in central London. *Journal of the Royal Society of Medicine* 1984;77:550-555.
91. Macfarlane JT, Finch R, Ward MJ, Macrae AD. Hospital study of adult community-acquired pneumonia. *Lancet* 1982;2(8292):255-8.
92. Lim WS, Macfarlane JT. Defining prognostic factors in the elderly with community acquired pneumonia: a case controlled study of patients aged >=75 yrs *Eur Respir J* 2001;17:200-205.
93. Venkatesan P, Gladman J, Macfarlane JT, Barer D, Berman P, Kinnear W, et al. A hospital study of community acquired pneumonia in the elderly. *Thorax* 1990;45:254-258.
94. Garcia-Vidal C, Fernandez Sabe N, Carratala J, Diaz V, Verdaguer R, Dorca J, et al. Early mortality in patients with community-acquired pneumonia: causes and risk factors. *ERJ Express* 2008.
95. White RJ, Blainey AD, Harrison KJ, Clarke SKR. Causes of pneumonia presenting to a district general hospital. *Thorax* 1981;36:566-570.
96. BTS. Community-acquired pneumonia in adults in British hospitals in 1982-1983: A survey of aetiology, mortality, prognostic factors and outcome. *Quarterly Journal of Medicine* 1987;62(239):195-220.
97. Myles PR, McKeever T, Hoare Z, Smith C, Hubbard R. The incidence of pneumonia in the United Kingdom: data from a computerized general practice database. *Epidemiol Infect* in press.
98. Mortensen EM, Kapur WN, Chang CH, Fine MJ. Assessment of mortality after long-term follow-up of patients with community-acquired pneumonia. *Clinical Infectious Diseases* 2003;37:1617-24.
99. Marrie TJ, Carriere KC, Jin Y, Johnson DH. Factors associated with death among adults <55 years of age hospitalized for community-acquired pneumonia. *Clinical Infectious Diseases* 2003;36:413-421.

100. Kothe H, Bauer T, Marre R, Suttorp N, Welte T, Dalhoff K. Outcome of community-acquired pneumonia: influence of age, residence status and antimicrobial treatment. *Eur Respir J* 2008;32:139-146.
101. Hedlund JU, Ortquist AB, Kalin ME, Granath F. Factors of importance for the long term prognosis after hospital treated pneumonia. *Thorax* 1993;48:785-789.
102. Fine MJ, Stone RA, Singer DE, Coley CM, Marrie TJ, Lave JR, et al. Processes and outcomes of care for patients with community-acquired pneumonia. *Archives of Internal Medicine* 1999;159:970-980.
103. Koivula I, Sten M, Makela PH. Prognosis after community-acquired pneumonia in the elderly: a population-based 12-year follow-up study. *Archives of Internal Medicine* 1999;159:1550-1555.
104. Hak E, Bont J, Hoes AW, Verheij TJM. Prognostic factors for serious morbidity and mortality from community-acquired lower respiratory tract infections among the elderly in primary care. *Family Practice* 2005;22:375-380.
105. van de Nadort C, Smeets HM, Bont J, Zuithoff NPA, Hak E, Verheij TJM. Prognosis of primary care patients aged 80 years and older with lower respiratory tract infection. *British Journal of General Practice* 2009;59:261-265.
106. Janssen F, Peeters A, Mackenbach JP, Kunst AE. Relation between trends in late middle age mortality and trends in old age mortality- is there evidence for mortality selection? *J Epidemiol Community Health* 2005;59:775-781.
107. Lewis JD, Brensinger C. Agreement between GPRD smoking data: a survey of general practitioners and a population-based survey. *Pharmacoepidemiology and drug safety* 2004;13:437-441.
108. Mant J, Murphy M, Rose P, Vessey M. The accuracy of general practitoner records of smoking and alcohol use: comparison with patient questionnaires. *Journal of Public Health Medicine* 2000;22(2):198-201.
109. Myles PR, Hubbard R, Gibson JE, Pogson Z, Smith CJP, McKeever TM. The impact of statins, ACE inhibitors and gastric acid suppressants on pneumonia mortality in a UK general practice population cohort. *Pharmacoepidemiology and drug safety* 2009;10.1002/pds.1769
110. Mortensen EM, Restrepo MI, Anzueto A, Pugh J. The effect of prior statin use on 30-day mortality for patients hospitalised with community-acquired pneumonia. *Respiratory Research* 2005;6(1):82.
111. Chalmers JD, Singanayagam A, Murray MP, Hill AT. Prior statin use is associated with improved outcomes in community-acquired pneumonia. *The American Journal of Medicine* 2008;121:1002-1007.
112. Suissa S. Immortal time bias in observational studies of drug effects. *Pharmacoepidemiology and drug safety* 2007;16:241-249.
113. Thomsen RW, Riis A, Kornum JB, Christensen S, Johnsen SP, Sorensen HT. Preadmission use of statins and outcomes after hospitalization with pneumonia. *Archives of Internal Medicine* 2008;168(19):2081-2087.
114. Rafailidis PI, Matthaiou DK, Varbobitis I, Falagas ME. Use of ACE inhibitors and risk of community-acquired pneumonia: a review. *Eur J Clin Pharmacol* 2008;64:565-573.

115. Trotter CL, Stuart JM, George R, Miller E. Increasing Hospital Admissions for Pneumonia, England. *Emerging Infectious Diseases* 2008;14(5):727-733.
116. NICE. Technology appraisal 94: Statins for the prevention of cardiovascular events, 2006.
117. DH. *Coronary heart disease: national service framework for coronary heart disease- modern standards and service models*, 2000.
118. Holmes HM. Reconsidering medication appropriateness for patients late in life. *Archives of Internal Medicine* 2006;166:605-609.
119. Holmes HM. Rational prescribing for patients with a reduced life expectancy. *Clinical Pharmacology and Therapeutics* 2008;85(1):103-107.
120. Pebody RG, Hippisley-Cox J, Harcourt S, Pringle M, Painter M, Smith G. Uptake of pneumococcalpolysaccharide vaccine in at-risk populations in England and Wales 1999-2005. *Epidemiol Infect* 2008;136:360-369.

Appendices

Appendix 1: Drug exposures considered as covariates

Drug Family	Generic drug name	Percent
Nitrates	Amyl Nitrite	2.0
	Isosorbide mononitrate	46.0
	Glyceryl Trinitrate	30.0
	Isosorbide dinitrate	20.0
	Pentaerythritol tetranitrate	2.0
Ace-2 inhibitors	Candesartan	14.8
	Eprosartan	8.8
	Valsartan	24.7
	Losartan	12.0
	Irbesartan	8.8
	Olmesartan	8.8
	Telmisartan	8.8
Beta blockers	Acebutalol	2.0
	Atenolol	14.0
	Bisoprolol	9.0
	Carvedilol	7.8
	Co-tenidone	5.0
	Labetalol	7.0
	Metoprolol	8.0
	Oxprenolol	8.0
	Pindolol	2.0
	Propranolol	24.0
	Sotalol	6.0
	Timolol	1.6
Calcium channel blockers	Amlodipine	6.6
	Diltiazem	30.0
	Felodipine	7.6
	Nifedipine	25.0
	Nimodipine	0.8
	Nisoldipine	1.2
	Verapamil	20.0
	Others	8.8
Fibrates	Bezafibrate	32.0
	Ciprofibrate	3.8
	Clofibrate	3.8
	Fenofibrate	38.0
	Gemfibrozil	22.6
Antacids	Aluminium Hydroxide	12.0
	Magnesium trisilicate	8.0
	Magnesium oxide	5.9
	Aluminium hydroxide/Magnesium carbonate/magnesium hydroxide	10.0
	Activated dimethicone/aluminium hydroxide mixture	7.8
	Others	56.0
Oral and inhaled steroids	Beclometasone	25.5
	Betametasone	2.3
	Budesonide	8.2
	Ciclesonide	0.9
	Cortisone acetate	3.2
	Deflazacort	1.4
	Dexamethasone	8.6
	Fluticasone	12.0
	Hydrocortisone	5.0
	Methylprednisalone	5.0
	Mometasone Furoate	0.9
	Prednisolone	16.0
	Prednisone	4.1
	Salbutamol+Beclometasone	1.4
	Triamcinolone	3.0

Appendix 2: Charlson Comorbidity Index

A. Calculating the Charlson Index Score: Weighted index of comorbidity

Assigned weights for diseases	Diseases/Conditions
1	Myocardial infarct Congestive heart failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic pulmonary disease Connective tissue disease Ulcer disease Mild liver disease Diabetes
2	Hemiplegia Moderate or severe renal disease Diabetes with end organ damage Any tumour Leukaemia Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumour AIDS

Code lists were assembled from list of Read codes (July 2005). No duplicates were allowed within code lists but there could have been duplicates across code lists. There were no duplicates across differently scored code lists. The presence of any of these conditions at anytime before the pneumonia diagnosis (index date of corresponding matched case) was counted towards the comorbidity burden. However some conditions were only counted if they occurred in the year before pneumonia diagnosis such as mild liver disease and acute events like myocardial infarction.

B. DEFINING COMORBID CONDITIONS FOR CALCULATING CHARLSON COMORBIDITY INDEX: READ CODES MAPPED TO ICD-9 CODES

1. Myocardial infarction

410- 410.9 Acute myocardial infarction

Includes:

- cardiac infarction
- coronary (artery):
- embolism
- occlusion
- rupture
- thrombosis
- infarction of heart, myocardium, or ventricle
- rupture of heart, myocardium, or ventricle
- ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction
- any condition classifiable to 414.1-414.9 specified as acute or with a stated duration of 8 weeks or less
- The following fifth-digit subclassification is for use with category 410:
- 0 episode of care unspecified
- Use when the source document does not contain sufficient information for the assignment of fifth-digit 1 or 2.
- 1 initial episode of care
- Use fifth-digit 1 to designate the first episode of care (regardless of facility site) for a newly diagnosed myocardial infarction. The fifth-digit 1 is assigned regardless of the number of times a patient may be transferred during the initial episode of care.
- 2 subsequent episode of care
- Use fifth-digit 2 to designate an episode of care following the initial episode when the patient is admitted for further observation, evaluation or treatment for a myocardial infarction that has received initial treatment, but is still less than 8 weeks old.

412 Old myocardial infarction*

- Healed myocardial infarction
- Past myocardial infarction diagnosed on ECG [EKG] or other special investigation, but currently presenting no symptoms

2. Congestive Heart Failure

428- 428.9 Heart failure

- Code, if applicable, heart failure due to hypertension first (402.0-402.9, with fifth-digit 1 or 404.0-404.9 with fifth-digit 1 or 3)

Excludes:

- rheumatic (398.91)
- that complicating:
- abortion (634-638 with .7, 639.8)
- ectopic or molar pregnancy (639.8)
- labor or delivery (668.1, 669.4)

3. Peripheral vascular disease

443.9 Peripheral vascular disease, unspecified*

- Intermittent claudication NOS
- Peripheral:
- angiopathy NOS
- vascular disease NOS
- Spasm of artery

Excludes:

- atherosclerosis of the arteries of the extremities (440.20-440.22)
- spasm of cerebral artery (435.0-435.9)

441- 441.9 Aortic aneurysm and dissection*

Excludes:

- syphilitic aortic aneurysm (093.0)
- traumatic aortic aneurysm (901.0, 902.0)

441.0 Dissection of aorta

441.00 Unspecified site

441.01 Thoracic

441.02 Abdominal

441.03 Thoracoabdominal

441.1 Thoracic aneurysm, ruptured

441.2 Thoracic aneurysm without mention of rupture

441.3 Abdominal aneurysm, ruptured

441.4 Abdominal aneurysm without mention of rupture

441.5 Aortic aneurysm of unspecified site, ruptured

- Rupture of aorta NOS

441.6 Thoracoabdominal aneurysm, ruptured

441.7 Thoracoabdominal aneurysm, without mention of rupture

441.9 Aortic aneurysm of unspecified site without mention of rupture

- Aneurysm
- Dilatation of aorta
- Hyaline necrosis of aorta

785.4 Gangrene*

Gangrene:

- NOS
- spreading cutaneous
- Gangrenous cellulitis
- Phagedena
- Code first any associated underlying condition

Excludes:

- gangrene of certain sites
- gangrene with atherosclerosis of the extremities (440.24)
- gas gangrene (040.0)

V43.4 Blood vessel replaced by prosthesis*

Procedure 38.4 Resection of vessel with replacement

- lower limb arteries
- Femoral (common) (superficial)
- Popliteal
- Tibial

4. Cerebrovascular disease

430-438 Cerebrovascular disease†

Includes:

- with mention of hypertension (conditions classifiable to 401-405)
- Use additional code to identify presence of hypertension

Excludes:

- any condition classifiable to 430-434, 436, 437 occurring during pregnancy, childbirth, or the puerperium, or specified as puerperal (674.0)
- iatrogenic cerebrovascular infarction or hemorrhage (997.02)

430 Subarachnoid hemorrhage

- Meningeal hemorrhage
- Ruptured:
- berry aneurysm
- (congenital) cerebral aneurysm NOS

Excludes:

- syphilitic ruptured cerebral aneurysm (094.87)

431 Intracerebral hemorrhage

Hemorrhage (of):

- basilar
- bulbar
- cerebellar
- cerebral
- cerebromeningeal
- cortical
- internal capsule
- intrapontine
- pontine
- subcortical
- ventricular
- Rupture of blood vessel in brain

432 Other and unspecified intracranial hemorrhage

433 Occlusion and stenosis of precerebral arteries

The following fifth-digit subclassification is for use with category 433:
0 without mention of cerebral infarction
1 with cerebral infarction

Includes:

- embolism of basilar, carotid, and vertebral arteries
- narrowing of basilar, carotid, and vertebral arteries
- obstruction of basilar, carotid, and vertebral arteries
- thrombosis of basilar, carotid, and vertebral arteries

Excludes:

- insufficiency NOS of precerebral arteries (435.0-435.9)

434 Occlusion of cerebral arteries

The following fifth-digit subclassification is for use with category 434:
0 without mention of cerebral infarction
1 with cerebral infarction

436 Acute, but ill-defined, cerebrovascular disease
Apoplexy, apoplectic:
- NOS
- attack
- cerebral
- seizure
- Cerebral seizure

Excludes:
- any condition classifiable to categories 430-435
- cerebrovascular accident (434.91)
- CVA (ischemic) (434.91)
- embolic (434.11)
- hemorrhagic (430, 431, 432.0-432.9)
- thrombotic (434.01)
- postoperative cerebrovascular accident (997.02)
- stroke (ischemic) (434.91)
- embolic (434.11)
- hemorrhagic (430, 431, 432.0-432.9)
- thrombotic (434.01)

437 Other and ill-defined cerebrovascular disease

438 Late effects of cerebrovascular disease

Note: This category is to be used to indicate conditions in 430-437 as the cause of late effects. The "late effects" include conditions specified as such, or as sequelae, which may occur at any time after the onset of the causal condition.

5. Dementia

290- 290.9* Dementia
Excludes:
- dementia due to alcohol (291.0-291.2)
- dementia due to drugs (292.82)
- dementia not classified as senile, presenile, or arteriosclerotic (294.10-294.11)
- psychoses classifiable to 295-298 occurring in the senium without dementia or delirium (295.0-298.8)
- senility with mental changes of nonpsychotic severity (310.1)
- transient organic psychotic conditions (293.0-293.9)

290.0 Senile dementia, uncomplicated
Senile dementia:
- NOS
- simple type

Excludes:
- mild memory disturbances, not amounting to dementia, associated with senile brain disease (310.1)
- senile dementia with:
- delirium or confusion (290.3)
- delusional [paranoid] features (290.20)
- depressive features (290.21)

290.1 Presenile dementia
Brain syndrome with presenile brain disease
Excludes:
- arteriosclerotic dementia (290.40-290.43)
- dementia associated with other cerebral conditions (294.10-294.11)

290.2 Senile dementia with delusional or depressive features
Excludes:
senile dementia:
- NOS (290.0)
- with delirium and/or confusion (290.3)

290.3 Senile dementia with delirium
Senile dementia with acute confusional state
Excludes:
senile:
- dementia NOS (290.0)
- psychosis NOS (290.20)

290.4 Vascular dementia
Multi-infarct dementia or psychosis
Use additional code to identify cerebral atherosclerosis (437.0)
Excludes:
suspected cases with no clear evidence of arteriosclerosis (290.9)

290.40 Vascular dementia, uncomplicated
Arteriosclerotic dementia:
- NOS
- simple type

290.41 Vascular dementia with delirium
Arteriosclerotic dementia with acute confusional state

290.42 Vascular dementia with delusions
Arteriosclerotic dementia, paranoid type

290.43 Vascular dementia with depressed mood
Arteriosclerotic dementia, depressed type

290.8 Other specified senile psychotic conditions
Presbyophrenic psychosis

290.9 Unspecified senile psychotic condition

5. Chronic pulmonary disease
490-496* Chronic obstructive pulmonary disease and allied conditions

490 Bronchitis, not specified as acute or chronic
Bronchitis NOS:

- catarrhal
- with tracheitis NOS
- Tracheobronchitis NOS

Excludes:
bronchitis:

- allergic NOS (493.9)
- asthmatic NOS (493.9)
- due to fumes and vapors (506.0)

491 Chronic bronchitis

Excludes:

chronic obstructive asthma (493.2)

491.0 Simple chronic bronchitis

- Catarrhal bronchitis, chronic
- Smokers' cough

491.1 Mucopurulent chronic bronchitis

Bronchitis (chronic) (recurrent):

- fetid
- mucopurulent
- purulent

491.2 Obstructive chronic bronchitis

Bronchitis:

- emphysematous
- obstructive (chronic) (diffuse)

Bronchitis with:

- chronic airway obstruction
- emphysema

Excludes:

- asthmatic bronchitis (acute) (NOS) 493.9
- chronic obstructive asthma 493.2

491.20 Without exacerbation

Emphysema with chronic bronchitis

491.21 With (acute) exacerbation

- Acute exacerbation of chronic obstructive pulmonary disease [COPD]
- Decompensated chronic obstructive pulmonary disease [COPD]
- Decompensated chronic obstructive pulmonary disease [COPD] with exacerbation

Excludes:

chronic obstructive asthma with acute exacerbation 493.22

491.22 With acute bronchitis

491.8 Other chronic bronchitis

Chronic:

- tracheitis
- tracheobronchitis

491.9 Unspecified chronic bronchitis

493 Asthma

Excludes:
wheezing NOS (786.07)
The following fifth-digit subclassification is for use with category 493.0-493.2, 493.9:

- 0 unspecified
- 1 with status asthmaticus
- 2 with (acute) exacerbation

494 Bronchiectasis

- Bronchiectasis (fusiform) (postinfectious) (recurrent)
- Bronchiolectasis

Excludes:

- congenital (748.61)
- tuberculous bronchiectasis (current disease) (011.5)

495 Extrinsic allergic alveolitis
Includes:

- allergic alveolitis and pneumonitis due to inhaled organic dust particles of fungal, thermophilic actinomycete, or other origin

500-505* Pneumoconioses and other lung diseases

500 Coal workers' pneumoconiosis

- Anthracosilicosis
- Anthracosis
- Black lung disease
- Coal workers' lung
- Miners' asthma

501 Asbestosis

502 Pneumoconiosis due to other silica or silicates

- Pneumoconiosis due to talc
- Silicotic fibrosis (massive) of lung
- Silicosis (simple) (complicated)

504 Pneumonopathy due to inhalation of other dust

505 Pneumoconiosis, unspecified

506.4 Chronic respiratory conditions due to fumes and vapors

- Emphysema (diffuse) (chronic) due to inhalation of chemical fumes and vapors
- Obliterative bronchiolitis (chronic) (subacute) due to inhalation of chemical fumes and vapors

- Pulmonary fibrosis (chronic) due to inhalation of chemical fumes and vapors

6. Rheumatologic disease (connective tissue disease)

710.0* Systemic lupus erythematosus
- Disseminated lupus erythematosus
- Libman-Sacks disease
- Use additional code to identify manifestation, as:
- endocarditis (424.91)
- nephritis (583.81)
- chronic (582.81)
- nephrotic syndrome (581.81)

Excludes:
- lupus erythematosus (discoid) NOS (695.4)

710.1* Systemic sclerosis
- Acrosclerosis
- CRST syndrome
- Progressive systemic sclerosis
- Scleroderma
- Use additional code to identify manifestation, as:
- lung involvement (517.2)
- myopathy (359.6)

Excludes:
- circumscribed scleroderma (701.0)

710.4* Polymyositis

714.0* Rheumatoid arthritis
Arthritis or polyarthritis:
- atrophic
- rheumatic (chronic)

Excludes:
- juvenile rheumatoid arthritis NOS (714.30)

714.1* Felty's syndrome
Rheumatoid arthritis with splenoadenomegaly and leukopenia

714.2* Other rheumatoid arthritis with visceral or systemic involvement
Rheumatoid carditis

714.81* Rheumatoid lung
- Caplan's syndrome
- Diffuse interstitial rheumatoid disease of lung
- Fibrosing alveolitis, rheumatoid

725* Polymyalgia rheumatica

7. Peptic ulcer disease

531-534.9

531 Gastric ulcer

Includes:

ulcer (peptic):

- prepyloric
- pylorus
- stomach

Use additional E code to identify drug, if drug-induced

Excludes:

- peptic ulcer NOS (533.0-533.9)

531.0 Acute with hemorrhage

531.1 Acute with perforation

531.2 Acute with hemorrhage and perforation

531.3 Acute without mention of hemorrhage or perforation

531.4* Chronic or unspecified with hemorrhage

531.5* Chronic or unspecified with perforation

531.6* Chronic or unspecified with hemorrhage and perforation

531.7* Chronic without mention of hemorrhage or perforation

531.9 Unspecified as acute or chronic, without mention of hemorrhage or perforation

532 Duodenal ulcer

Includes:

- erosion (acute) of duodenum
- ulcer (peptic):
- duodenum
- postpyloric
- Use additional E code to identify drug, if drug-induced

Excludes:

- peptic ulcer NOS (533.0-533.9)

532.0 Acute with hemorrhage

532.1 Acute with perforation

532.2 Acute with hemorrhage and perforation

532.3 Acute without mention of hemorrhage or perforation

532.4* Chronic or unspecified with hemorrhage

532.5* Chronic or unspecified with perforation

532.6* Chronic or unspecified with hemorrhage and perforation

532.7* Chronic without mention of hemorrhage or perforation

532.9 Unspecified as acute or chronic, without mention of hemorrhage or perforation

533 Peptic ulcer, site unspecified
Includes:
- gastroduodenal ulcer NOS
- peptic ulcer NOS
- stress ulcer NOS
- Use additional E code to identify drug, if drug-induced

Excludes:
peptic ulcer:
- duodenal (532.0-532.9)
- gastric (531.0-531.9)

533.0 Acute with hemorrhage
533.1 Acute with perforation
533.2 Acute with hemorrhage and perforation
533.3 Acute without mention of hemorrhage and perforation
533.4* Chronic or unspecified with hemorrhage
533.5* Chronic or unspecified with perforation
533.6* Chronic or unspecified with hemorrhage and perforation
533.7* Chronic without mention of hemorrhage or perforation
533.9 Unspecified as acute or chronic, without mention of hemorrhage or perforation

534 Gastrojejunal ulcer
Includes:
ulcer (peptic) or erosion:
- anastomotic
- gastrocolic
- gastrointestinal
- gastrojejunal
- jejunal
- marginal
- stomal

Excludes:
- primary ulcer of small intestine (569.82)

534.0 Acute with hemorrhage
534.1 Acute with perforation
534.2 Acute with hemorrhage and perforation
534.3 Acute without mention of hemorrhage or perforation
534.4* Chronic or unspecified with hemorrhage
534.5* Chronic or unspecified with perforation
534.6* Chronic or unspecified with hemorrhage and perforation
534.7* Chronic without mention of hemorrhage or perforation
534.9 Unspecified as acute or chronic, without mention of hemorrhage or perforation

8. Mild liver disease

571.2* Alcoholic cirrhosis of liver
- Florid cirrhosis
- Laennec's cirrhosis (alcoholic)

571.5* Cirrhosis of liver without mention of alcohol
Cirrhosis of liver:
- NOS
- cryptogenic
- macronodular
- micronodular
- posthepatitic
- postnecrotic
- Healed yellow atrophy (liver)
- Portal cirrhosis

571.6* Biliary cirrhosis
Chronic nonsuppurative destructive cholangitis
Cirrhosis:
- cholangitic
- cholestatic

571.4* Chronic hepatitis
Excludes:
viral hepatitis (acute) (chronic) (070.0-070.9)

571.40* Chronic hepatitis, unspecified

571.41* Chronic persistent hepatitis

571.49* Other
Chronic hepatitis:
- active
- aggressive
- Recurrent hepatitis

9. Diabetes

250-250.3* Diabetes mellitus
Excludes:
- gestational diabetes (648.8)
- hyperglycemia NOS (790.6)
- neonatal diabetes mellitus (775.1)
- nonclinical diabetes (790.29)

250.0* Diabetes mellitus without mention of complication

- Diabetes mellitus without mention of complication or manifestation classifiable to 250.1-250.9
- Diabetes (mellitus) NOS

250.1* Diabetes with ketoacidosis

Diabetic:

- acidosis without mention of coma
- ketosis without mention of coma

250.2* Diabetes with hyperosmolarity

- Hyperosmolar (nonketotic) coma

250.3* Diabetes with other coma

- Diabetic coma (with ketoacidosis)
- Diabetic hypoglycemic coma
- Insulin coma NOS

Excludes:

- diabetes with hyperosmolar coma (250.2)

250.7* Diabetes with peripheral circulatory disorders

Use additional code to identify manifestation, as
diabetic:

- gangrene (785.4)
- peripheral angiopathy (443.81)

9. Diabetes with chronic complications

250.4-250.6* Diabetes with renal, ophthalmic, or neurological complications

250.4 Diabetes with renal manifestations

Use additional code to identify manifestation, as:

- chronic kidney disease (585.1-585.9)

diabetic:

- nephropathy NOS (583.81)
- nephrosis (581.81)
- intercapillary glomerulosclerosis (581.81)
- Kimmelstiel-Wilson syndrome (581.81)

250.5 Diabetes with ophthalmic manifestations

Use additional code to identify manifestation, as:
diabetic:

- blindness (369.00-369.9)
- cataract (366.41)
- glaucoma (365.44)
- macular edema (362.07)
- retinal edema (362.07)
- retinopathy (362.01-362.07)

250.6 Diabetes with neurological manifestations
Use additional code to identify manifestation, as:
diabetic:

- amyotrophy (358.1)
- gastroparalysis (536.3)
- gastroparesis (536.3)
- mononeuropathy (354.0-355.9)
- neurogenic arthropathy (713.5)
- peripheral autonomic neuropathy (337.1)
- polyneuropathy (357.2)

10. Hemiplegia or paraplegia

344.1* Paraplegia
Paralysis of both lower limbs
Paraplegia (lower)

342-342.9* Hemiplegia
342 Hemiplegia and hemiparesis
Excludes:

- congenital (343.1)
- hemiplegia due to late effect of cerebrovascular accident (438.20-438.22)
- infantile NOS (343.4)

342.0 Flaccid hemiplegia
342.1 Spastic hemiplegia
342.8 Other specified hemiplegia
342.9 Hemiplegia, unspecified

11. Renal disease
582-582.9* Chronic glomerulonephritis
Includes:

- chronic nephritis

582.0 With lesion of proliferative glomerulonephritis
Chronic (diffuse) proliferative glomerulonephritis

582.1 With lesion of membranous glomerulonephritis

- Chronic glomerulonephritis:
- membranous
- sclerosing
- Focal glomerulosclerosis
- Segmental hyalinosis

582.2 With lesion of membranoproliferative glomerulonephritis

- Chronic glomerulonephritis:
- endothelial
- hypocomplementemic persistent
- lobular
- membranoproliferative
- mesangiocapillary
- mixed membranous and proliferative

582.4 With lesion of rapidly progressive glomerulonephritis

- Chronic nephritis with lesion of necrotizing glomerulitis

582.8 With other specified pathological lesion in kidney

582.81 Chronic glomerulonephritis in diseases classified elsewhere
Code first underlying disease, as:

- amyloidosis (277.3)
- systemic lupus erythematosus (710.0)

582.89 Other
Chronic glomerulonephritis with lesion of:

- exudative nephritis
- interstitial (diffuse) (focal) nephritis

582.9 Chronic glomerulonephritis with unspecified pathological lesion in kidney

Glomerulonephritis: specified as chronic
NOS specified as chronic
hemorrhagic specified as chronic
Nephritis specified as chronic
Nephropathy specified as chronic

583-583.7 * Nephritis and nephropathy

583.0 With lesion of proliferative glomerulonephritis

Proliferative:

- glomerulonephritis (diffuse) NOS
- nephritis NOS
- nephropathy NOS

583.1 With lesion of membranous glomerulonephritis

Membranous:

- glomerulonephritis NOS
- nephritis NOS
- Membranous nephropathy NOS

583.2 With lesion of membranoproliferative glomerulonephritis
Membranoproliferative:
- glomerulonephritis NOS
- nephritis NOS
- nephropathy NOS
- Nephritis NOS, with lesion of:
- hypocomplementemic persistent glomerulonephritis
- lobular glomerulonephritis
- mesangiocapillary glomerulonephritis
- mixed membranous and proliferative glomerulonephritis

583.4 With lesion of rapidly progressive glomerulonephritis
Necrotizing or rapidly progressive:
- glomerulitis NOS
- glomerulonephritis NOS
- nephritis NOS
- nephropathy NOS
- Nephritis, unspecified, with lesion of necrotizing glomerulitis

583.6 With lesion of renal cortical necrosis
- Nephritis NOS with (renal) cortical necrosis
- Nephropathy NOS with (renal) cortical necrosisc
- Renal cortical necrosis NOS

583.7 With lesion of renal medullary necrosis
- Nephritis NOS with (renal) medullary [papillary] necrosis
- Nephropathy NOS with (renal) medullary [papillary] necrosis

583.8 With other specified pathological lesion in kidney
583.81 Nephritis and nephropathy, not specified as acute or chronic, in diseases classified elsewhere
583.89 Other
Glomerulitis, glomerulonephritis, nephritis, nephropathy etc. with lesions of either exudative nephritis or interstitial nephritis

583.9 With unspecified pathological lesion in kidney
- Glomerulitis NOS
- Glomerulonephritis NOS
- Nephritis NOS
- Nephropathy NOS

Excludes:
- nephropathy complicating pregnancy, labor, or the puerperium (642.0-642.9, 646.2)
- renal disease NOS with no stated cause (593.9)

585* Chronic kidney disease (CKD)
Includes:
- Chronic uremia

585.1 Chronic kidney disease, Stage I
585.2 Chronic kidney disease, Stage II (mild)
585.3 Chronic kidney disease, Stage III (moderate)
585.4 Chronic kidney disease, Stage IV (severe)
585.5 Chronic kidney disease, Stage V
585.6 End stage renal disease
585.9 Chronic kidney disease, unspecified
- Chronic renal disease
- Chronic renal failure NOS
- Chronic renal insufficiency

586* Renal failure, unspecified
Includes:
- Uremia NOS

Excludes:
- following labor and delivery (669.3)
- posttraumatic renal failure (958.5)
- that complicating:
- abortion (634-638 with .3, 639.3)
- ectopic or molar pregnancy (639.3)
- uremia:
    - extrarenal (788.9)
    - prerenal (788.9)

588- 588.9* Disorders resulting from impaired renal function

588.0 Renal osteodystrophy
- Azotemic osteodystrophy
- Phosphate-losing tubular disorders
- Renal:
    - dwarfism
    - infantilism
    - rickets

588.1 Nephrogenic diabetes insipidus
Excludes:
diabetes insipidus NOS (253.5)

588.8 Other specified disorders resulting from impaired renal function
Excludes:
secondary hypertension (405.0-405.9)

588.9 Unspecified disorder resulting from impaired renal function

12. Any malignancy, including leukaemia and lymphoma

13. Moderate or severe liver disease

572.2* Hepatic coma
- Hepatic encephalopathy
- Hepatocerebral intoxication
- Portal-systemic encephalopathy

572.3* Portal hypertension

572.4* Hepatorenal syndrome

Excludes:
that following delivery (674.8)

572.8* Other sequelae of chronic liver disease

456.0* Esophageal varices with bleeding

456.1* Esophageal varices without mention of bleeding

456.2* Esophageal varices in diseases classified elsewhere

Code first underlying disease, as:
- cirrhosis of liver (571.0-571.9)
- portal hypertension (572.3)

456.20* With bleeding

456.21* Without mention of bleeding

14. Metastatic solid tumour

15. AIDS

042 Human immunodeficiency virus [HIV] disease
- Acquired immune deficiency syndrome
- Acquired immunodeficiency syndrome
- AIDS
- AIDS-like syndrome
- AIDS-related complex
- ARC
- HIV infection, symptomatic

Excludes:
- asymptomatic HIV infection status (V08)
- exposure to HIV virus (V01.79)
- non-specific serologic evidence of HIV (795.71)

Appendix 3: Search terms based on ICD-9 codes for identification of specific comorbid conditions

Condition	ICD-9 code	Description
Ischaemic Heart Disease	410-410.9 412	Acute myocardial infarction Old myocardial infarction
Chronic Pulmonary Disease	490-496 500-505 506.4	Chronic obstructive pulmonary disease Pneumoconioses and other lung diseases Chronic respiratory conditions due to fumes and vapours

Appendix 4: Publications based on this thesis

1. Myles, P.R., McKeever, T.M., Pogson, Z., Smith, C.J.P., Hubbard, R.H. (2008). The incidence of pneumonia in the UK- Data from a computerized general practice database. Epidemiology and Infection doi:10.1017/S0950268808001428

2. Myles,P.R., Hubbard, R.B., McKeever, T.M., Pogson, Z., Smith, C.J.P., Gibson, J.E. (2009). 'Risk of Community-acquired pneumonia and the use of statins, ACE inhibitors and gastric acid suppressants: A population based case-control study'. Pharmacoepidemiology and Drug Safety 18, 269-275

3. Myles,P.R., Hubbard, R.B., McKeever, T.M., Pogson, Z., Smith, C.J.P., Gibson, J.E. (*in press*). 'The impact of statins, ACE inhibitors and gastric acid suppressant on pneumonia mortality in a UK general practice population cohort'. Pharmacoepidemiology and Drug Safety

4. Myles, P.R., Hubbard R.B., Gibson, J., Pogson, Z., Smith, C.J.P., McKeever, T.M. (*in press*). 'Pneumonia mortality in a UK general practice population'. European Journal of Public Health.