An analysis of the variation in event rates, case fatality and mortality of Acute Coronary Syndrome across English districts 2006-2010

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Submitted for fulfilment of the requirements for Doctor of Philosophy (PhD)
Declaration of originality

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Abstract

Ischaemic heart disease (IHD) is a leading cause of hospitalisation, mortality and healthcare spending in the industrialised world. Wide temporal, spatial and social class variations show that high IHD mortality is not inevitable. The temporal decline in IHD in the UK and other industrialised countries since the 1960’s and 1970’s has been decomposed into that caused by reductions in population risk which affect event rate versus that caused by changes in case fatality which can potentially be ameliorated by the health system. The persistent Northern excess in IHD mortality in England has not been studied in the same way. This is because there is no national database of IHD events and thus no systematic way to assess sub-national variation.

I focused on the acute, life-threatening component of IHD – acute coronary syndrome (ACS). I constructed a national data set of ACS events using routine hospitalisation and mortality data and estimated ACS event rates, mortality and case fatality for each of the 354 English Local Authority Districts using a Bayesian spatial model to smooth away unwarranted variability. I decomposed spatial variation in ACS mortality into its constituent components of event rates and case fatality.

60-80% of the between district variation in mortality is due to variation in event rates depending on age and sex, and an additional 15-30% is due to variation in case fatality. Further, the proportion of events resulting in an out-of-hospital ACS death has more impact on differences in case fatality than do deaths following hospitalisation.

These findings have important implications for directing health policies aimed at reducing ACS burden and addressing regional inequalities in health in England.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACS</td>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td>AMI</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>ARIC</td>
<td>Atherosclerosis risk in communities</td>
</tr>
<tr>
<td>BRHS</td>
<td>British Regional Heart Study</td>
</tr>
<tr>
<td>BYM</td>
<td>Besag, York, Mollié</td>
</tr>
<tr>
<td>CAR</td>
<td>Conditional auto-regressive</td>
</tr>
<tr>
<td>CCG</td>
<td>Clinical commissioning group</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CIPS</td>
<td>Continuous inpatient spell</td>
</tr>
<tr>
<td>CPRD</td>
<td>Clinical practice research datalink</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>DIC</td>
<td>Deviance information criterion</td>
</tr>
<tr>
<td>ED</td>
<td>Enumeration district</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>FCE</td>
<td>Finished consultant episode</td>
</tr>
<tr>
<td>GBD</td>
<td>Global burden of disease</td>
</tr>
<tr>
<td>GOR</td>
<td>Government Office Region</td>
</tr>
<tr>
<td>GRACE</td>
<td>Global Registry of Acute Coronary Events</td>
</tr>
<tr>
<td>HES</td>
<td>Hospital Episode Statistics</td>
</tr>
<tr>
<td>HSCIC</td>
<td>Health and Social Care Information Centre</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>IHD</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>IMD</td>
<td>Index of Multiple Deprivation</td>
</tr>
<tr>
<td>INLA</td>
<td>Integrated nested Laplace approximation</td>
</tr>
<tr>
<td>LSOA</td>
<td>Lower Super Output Area</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------------------------------------</td>
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<tr>
<td>MCMC</td>
<td>Markov chain Monte Carlo</td>
</tr>
<tr>
<td>MeSH</td>
<td>Medical Subject Headings</td>
</tr>
<tr>
<td>MINAP</td>
<td>Myocardial Ischaemia National Audit Project</td>
</tr>
<tr>
<td>MONICA</td>
<td>Multinational Monitoring of Trends and Determinants in Cardiovascular Disease</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>NHLI</td>
<td>National Heart and Lung Institute</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
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<tr>
<td>ONS</td>
<td>Office for National Statistics</td>
</tr>
<tr>
<td>PCT</td>
<td>Primary Care Trust</td>
</tr>
<tr>
<td>RSS</td>
<td>Residual sum of squares</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST elevation myocardial infarction</td>
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<tr>
<td>NSTEMI</td>
<td>Non ST elevation myocardial infarction</td>
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<tr>
<td>STward</td>
<td>Standard table ward</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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To the boys who pick me up from work,

Idris, Ilyās and Muhammed Umar
Chapter 1: Introduction

1.1 Rationale

Ischaemic heart disease (IHD) is one of the leading causes of hospital admissions, mortality and healthcare spending in industrialised countries.\(^{(1)}\) There has been a dramatic decline in IHD mortality over the last 30-40 years \(^{(2–4)}\) such that death rates are now one-third of what they were in the early 1980’s. Despite this, IHD is the number one cause of death in men in England, and the second most common cause of death in women.\(^{(5)}\)

![Ischaemic heart disease spectrum](image)

**Figure 1.1.** The clinical spectrum of ischaemic heart diseases (IHD). AMI = acute myocardial infarction. ACS = acute coronary syndrome.

The primary focus for this thesis is the acute life-threatening portion of the IHD spectrum – known as acute coronary syndrome (ACS) (Figure 1.1). ACS is made up of acute myocardial infarction (AMI) and acute non-AMI ACS (see Chapter 2.2.1). IHD spectrum diseases fall under the broader umbrella of cardiovascular diseases (CVD). Whilst this thesis focuses on ACS, CVD and IHD are more often referenced in the literature and are relevant to setting the context for the work.
The decline in IHD mortality has been heavily investigated but it is still not entirely clear what precipitated it and what drives its rate.(6) The first step in investigations which tackle the problem systematically is to look at the trends in IHD incidence and in case fatality. If declines in incidence are comparable to declines in mortality, then mortality declines are attributed to a reduction of population risk. Conversely, if the reduction in incidence is zero then mortality declines must be due to improved survival. An intermediate situation implies contributions from both improved risk and better treatment or survival.(7,8) Further investigation focuses on uncovering specific risk factors, risk reduction programmes and treatment strategies which parallel the fall in incidence and case fatality and may account for the changes seen.(6,9,10)

Treatment for IHD and specifically for ACS has changed radically in the last 4-5 decades. The introduction of resuscitation (1960), thrombolysis (1986), (11) angioplasty (1993), (12) and the use of aspirin (13) and anti-platelet agents (14) have transformed our ability to manage an acute event. However, all of these interventions are critically dependent on the speed with which the patient can reach the healthcare service.(15) The fundamental factor of delay between the patient experiencing symptoms and calling for help has changed little since the 1980’s,(16–18) but there have been significant improvements in the interval between the first call for help and the initiation of treatment (Chapter 9).(19,20)

The spatial variation in IHD mortality in England is perhaps as dramatic as the temporal decline, but the reasons for it are less well investigated. There is a 2-3 fold excess in all-cause mortality in the North of England compared to the South, and this is largely driven by the Northern excess in IHD mortality (21) which has been persistent over the last 4-5 decades.(22) The damning Black and Acheson reports of the 1980’s and 1990’s highlighted the extent of regional variation and the lack of improvement over a twenty year period.(23,24) This led to the UK government
setting explicit goals to reduce regional inequalities in health.(25,26) The management of ACS is one of the most highly protocol driven areas within medicine. National guidelines, introduced by the Department of Health under the National Service Framework for Coronary Heart Disease in 2000,(25) provide overall recommendations on how patients should be managed in England, and these have been supplemented with more exact directions produced by the National Institute for Health and Care Excellence (NICE)(27,28). Thus variations in care under the National Health Service (NHS) should be minimal, although this is by no means certain.

Previous studies have attempted to correlate the regional variation in IHD mortality with potential risk factors ranging from blood pressure and socioeconomic status to hardness of the water supply.(29–32) However the primary step of decomposing the variation in mortality into that driven by incidence or events rates vs. that driven by case fatality has never been undertaken. There is no national registry that covers all AMI and non-AMI ACS events and it is currently not possible to determine whether and how event rates or case fatality for ACS vary by area.

This thesis aims to fill that gap by using routine data to create a national database from which all ACS events can be identified and case fatality assessed. I aim to look at how differences in event rates vs. case fatality drive the spatial variation in ACS mortality and further, whether it is hospital case fatality or out-of-hospital deaths which have the greater impact on total case fatality.

1.2 Aims and objectives

The aims of the study were:
To build a national database of all ACS events and to capture and quantify the variation in event rates, case fatality and mortality across Local Authority Districts in England.

The objectives set to fulfil this aim were:

a) To systematically identify ACS events from routinely collected administrative data.

b) To make comprehensive and comparable estimates of ACS event rates, total and hospital case fatality, mortality and proportion of out-of-hospital deaths, along with uncertainty estimates for each English district.

c) To decompose the variation in ACS mortality into that driven by variation in underlying event rates vs. by case fatality.

d) To decompose variation in case fatality into variation in hospital case fatality vs. out-of-hospital mortality.

1.3 Structure

The outputs of the thesis are in two parts:

Part I is an analysis of mortality in England which describes the spatial variation in total CVD mortality, and sets the epidemiological context for further work.

Part II is an analysis of ACS event rates, case fatality and mortality in England. Hospitalisation and mortality data were linked for this analysis. An ACS cohort was constructed and spatial variations in ACS mortality were decomposed into their constituent parts.
Chapter 2 provides an historical introduction to IHD and ACS describing how our understanding, of the conditions, ability to diagnose them, and methods of recording have evolved over time.

Chapter 3 surveys the current literature on variations in mortality, incidence, event rates, total and hospital case fatality, and proportion of out-of-hospital deaths.

Chapter 4 is a spatial analysis of mortality data for CVD from 1982-2006 and sets the context for analysis of linked data. This has been published as Asaria P et al. Trends and inequalities in cardiovascular mortality across 7932 English electoral wards 1982 – 1986: Bayesian spatial analysis. Int J Epidemiol 2012; 41(6):1737-49

Chapter 5 compares trends in CVD, IHD and ACS mortality and defines the primary outcomes and age groups which are analysed in Part II.

Chapter 6 describes the data sources available for making population estimates of ACS events in England, and describes what is known on the completeness and validity of the data.

Chapter 7 explains the linkage of hospitalisation and mortality data and the preliminary analyses which were carried out in order to determine which episodes and events to include and exclude from the case definition.

Chapter 8 estimates event rates, mortality and case fatality for each English district. I present results on the contribution of event rate vs. case fatality to between district variation in mortality. Chapter 9 analyses the role of hospital case fatality and proportion of events that result in out-of-hospital death in determining total case fatality by district.
Chapter 10 reflects on the findings of the research and considers the policy implications in terms of public health surveillance, health system accountability and social constructs of disease. Further avenues of research are outlined.
Chapter 2: From angina to ACS – the construction of a very British disease

2.1 The identification of a new disease

On 21 July 1768 William Heberden addressed the Royal College of Physicians:

“There is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, which deserves to be mentioned more at length and of which I do not recollect any mention among medical authors...”

Heberden stood as a fellow of thirty years standing, at the apogee of the British medical establishment. As a classicist, he had a good knowledge of Greek, Latin and Hebrew, whilst his position in the College drew him into a network of physicians spanning Europe and the Americas. With these qualifications, Heberden was still unable to identify historical or contemporary examples of the constellation of symptoms that he characterised. It was almost as if his description of cardiac chest pain marked the birth of IHD as a significant disease; even naming its symptoms in terms that are still current - as angina pectoris.(33,34) His landmark presentation, based on his observation of symptoms in a series of 100 patients, continues:

“Those who are afflicted with it are seized, while they are walking and more particularly when they walk soon after eating with a painful and most disagreeable sensation in the breast, which seems as if it would take their life away if it were to increase or to continue; the moment they stand still, all this uneasiness vanishes. In all other respects, the patients are, at the beginning of this disorder perfectly well ...

After it has continued for some months, it will not cease so instantaneously upon standing still; and it will come on not only when the persons are walking, but when they are lying down and oblige them to rise up out of their beds every night for many months together...
The os sterni (sternal notch) is usually pointed to as the seat of this malady, but it seems sometimes as if it was under the lower part of it, and at other times under the middle or upper part, but always inclining more to the left side, and sometimes there joined with it a pain about the middle of the left arm”

Heberden’s comprehensive description is not only intelligible to current clinical practice - covering what might be called stable and unstable angina as well as myocardial infarction - but is also, significantly, easily appreciated by the lay eighteenth century reader; often from the same social background as their physician. Thus at its birth, IHD was not the abstracted product of specialist knowledge, but the lived patient experience.

Angina pectoris was identified increasingly frequently in eighteenth century Britain, but contemporaneous texts from France (including that of Napoleon’s physician another eminent and well-read practitioner), Germany, the Netherlands and New England make no mention of angina or its equivalent until half a century later. It seems that IHD was effectively born in Britain in the midst of the upheavals of its industrial and agrarian revolutions.(35)

The question of the locus of the angina rapidly became a matter of debate amongst British physicians following its first description. In the very first edition of the New England Medical Journal, John Warren summarised the work of Jenner, Hunter, Fothergill, Wall and Heberden; noting the clinic-pathological correlation of the symptoms Heberden described with coronary calcification, although only identifying four cases of angina in contemporary New England practice.(36)

The coronary theory of angina only gained widespread support in the nineteenth century, due in part to the inconsistency of the presence and extent of coronary calcification; some symptomatic
patients had little or no atheroma whilst others had so much their arteries appeared to be “tubes of bone.” (34) By 1912, Obrastow, Straschenko and Herrick, using clinical-pathological studies, elucidated that coronary thrombosis, rather than gradual atheromatous occlusion, was the catastrophic final cause of myocardial infarction. Survival from such a calamitous event was assumed to be due to the presence of excellent collateral circulation in the hearts of some patients. (35)

It was not until the 1980’s, after the birth of angiography, that de Wood et al performing cardiac catheter studies in the first few hours after the onset of an acute myocardial infarction, demonstrated that the coronary arteries could recannalise and the thrombus could pass allowing the patient to recover. (37) This marked a paradigm shift – acute myocardial infarction was no longer inevitably fatal in all but the lucky few with excellent circulation. There was a subsequent explosion in the search for therapies aimed at clot dissolution and removal.

It is interesting to note that a disease entity as seemingly established as IHD, is in fact a relatively new phenomenon and that our understanding of its pathophysiology is based on recent findings. The acceptance of the coronary theory marked the transition of IHD to one in which the condition was defined and validated by pathologist rather than the patient. The introduction of diagnostics based on the electrocardiogram (ECG) and enzyme tests characterised a further transition; shifting definition even further from the patient’s account and placing it firmly in the hands of the validating expert.
2.2 Current understanding of ACS

IHD has both acute and chronic manifestations. ACS is the acute, life-threatening end of the IHD spectrum while stable angina (chest pain on exertion which resolves with rest), old myocardial infarction and ischaemic cardiomyopathy mark the more chronic forms (Chapter 1.1).

The term ACS has only come into use in the last 20-25 years, with the first PubMed citation appearing in an abstract in 1986.(39) Modern conceptions of ACS rely on the acute occlusion theory, whilst chronic, gradual narrowing of the coronary arteries thought to be the mechanism underlying stable angina, which may or may not precede an ACS event (see Figure 2.1).(40) Chronic narrowing does not predict the time to an acute life-threatening event, nor does it predict

Figure 2.1. Chronic ischaemic heart disease (IHD) (left), and acute coronary syndrome (ACS) (right). Adapted from Watkins et al. 2006, Nature reviews, Genetics(38)
which artery will be blocked during an acute episode; in two-thirds of cases the acutely obstructed artery is not the one to have been most narrowed previously. It does however indicate persons in whom the risk of an acute event is high.

Coronary arteries sit on the outer (epicardial) surface of the heart and are the nutrient arteries to the heart muscle. With increasing age, and as a result of exposure to smoking, high blood pressure and other risk factors, ‘vulnerable plaques’ filled with lipid can develop in these arteries (Figure 2.1). The plaques make the internal wall of the artery friable allowing it to erode or fissure in response to physical, chemical, mechanical or psychological stress. Eroded walls provide a strong stimulus for the blood to clot. The resulting thrombus occludes the artery leading to restriction of blood flow and ischaemia (oxygen starvation) in the heart muscle. Irreversible damage starts to occur after about 15 minutes of restriction in blood supply. This initially affects heart muscle cells on the inner surface of the heart furthest away from the artery resulting in non-ST-elevation infarction (NSTEMI). As the ischaemia progresses, cell death spreads through the full thickness of the heart muscle and ST-elevation infarct (STEMI) ensues. The ST nomenclature describes electrical changes that can be seen in the ST-segment of the ECG trace (the horizontal segment following the main upstroke) during the process of ischaemia and infarction (Figure 2.2). When restriction of the blood supply is prolonged, or a particularly critical pathway is disrupted by the infarction, then the episode may lead to death. In milder cases, the acute thrombus may cause only sub-total restriction of blood flow; these events are hypothesised to be the cause of episodes of unstable angina.
ACS as currently understood, thus refers to four conditions; STEMI, NSTEMI, unstable angina and death as a result of ischaemia (Figure 2.2).(39) Frequently only the three non-fatal components are discussed in cardiology literature.(40,42,43) The evolution in our understanding of ACS over the last fifty years frames the interventions and treatment aimed at reducing mortality. These include the use of reperfusion therapies (thrombolysis or primary angioplasty) to remove the acute occlusive thrombus, anti-platelet agents such as aspirin, clopidogrel and heparins to prevent further clot formation, and the use of statins, beta-blockers and ACE inhibitors to reduce background risk of narrowing and plaque formation (Figure 2.3).
Acronyms refer to trials which provided evidence for mortality benefits of the treatments described: TIMI = thrombolysis in myocardial infarction, GISSI = Italian group for the study of survival in myocardial infarction, ISIS = International study of infarct survival, SAVE = Survival and ventricular enlargement, 4S = Scandinavian Simvastatin survival study, CURE = Clopidogrel in unstable angina to prevent recurrent events.

### 2.2.1 Clinical definition of ACS

The current clinical criteria for diagnosing AMI are outlined in the third revision of the universal definition of myocardial infarction published by the task force of the European Society of Cardiology, the American College of Cardiology, the American Heart Association and the World Heart Federation (ESC/ACC/AHA/WHF) in 2012 (Table 2.1).(45) Clinical guidelines
concentrate on diagnosing AMI in patients who present for investigation. Dying heart muscle cells leach their contents (enzymes) into the blood, and these are used as markers of myocardial infarction in diagnostic blood tests. The diagnosis of unstable angina (non-AMI ACS) is based on clinical judgement, as by definition, enzymes are not raised (Figure 2.2). Over time newer, more sensitive assays which are more specific to cardiac cell death have been developed.(46) As a result a smaller percentage of patients are now diagnosed with unstable angina (chest pain accompanied by a negative enzyme test), and more and more are labelled as having NSTEMI. As enzyme assays evolve even further, the diagnosis of unstable angina may disappear altogether.

<table>
<thead>
<tr>
<th>Diagnostic criteria for AMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rise and or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) with at least one of the following :</td>
</tr>
<tr>
<td>Symptoms of ischaemia</td>
</tr>
<tr>
<td>ECG changes indicative of new ischaemia</td>
</tr>
<tr>
<td>Development of pathological Q waves on the ECG</td>
</tr>
<tr>
<td>Imaging evidence of new loss of myocardium or wall motion abnormality</td>
</tr>
<tr>
<td>Sudden cardiac death with symptoms suggestive of myocardial ischaemia and new ECG changes indicative of ischaemia, but death occurred before biomarkers were available</td>
</tr>
</tbody>
</table>

Table 2.1. Diagnostic criteria for clinical definition of AMI. Adapted from Thygesen et al. 2012 Eur Heart J.(45)

Current diagnostic guidelines rely heavily on the assessment of a cardiac enzyme named troponin. Any rise in troponin level no matter how small is thought to indicate a potential AMI. However, as the sensitivity of troponin testing has increased, its specificity has declined; conditions which are not primarily AMI may also demonstrate a rise in troponin levels (e.g. pulmonary embolism, severe sepsis and renal failure). It is unclear whether this occurs because the heart is ‘stressed’ in some way during these events or due to some other mechanism of release. A diagnosis of AMI is therefore only made when the rise in troponin levels occurs in
conjunction with supporting features such as chest pain or changes in the ECG or heart imaging (Table 2.1), or by direct visualisation of a clot in the coronary artery at angiography. Interventions are directed primarily at treating AMI which is due to plaque rupture and/or clot formation (Type 1 AMI). Other types of AMI which may be due to imbalance of oxygen demand and supply to the heart (Type 2 AMI), and troponin release which is secondary to some other condition such as sepsis, may receive risk factor modification but are not subject to reperfusion therapy.(45)

Troponin based diagnostic criteria for AMI were laid out in 2000 and updated in 2007 and again in 2012.(45,47,48) The time span of the ACS data used in this thesis is 2006-2010; a point in time when troponins had already been established as the cornerstone of clinical diagnosis.(47) In addition the National Service Framework for Coronary Heart Disease which aimed to standardise the management of IHD across England had been published by the Department for Health in 2000,(25) and additional specific guidance on thrombolysis,(49) primary angioplasty and stenting(50) and risk factor modification were available from the National Institute for Health and Care Excellence (NICE). Thrombolysis was commonly used to treat STEMI and primary angioplasty was being rolled out across the country as an alternative, improved method of revascularisation (Figure 2.3).(51)

2.2.2 Epidemiological definition of ACS

Epidemiological definitions of ACS date back to World Health Organization (WHO) criteria formulated in the 1950’s. These focus on case ascertainment of AMI, ignoring the more uncertain category of non-AMI ACS. Assessment of the cause of out-of-hospital death, where neither ECG nor biomarkers are available for diagnosis, are not covered well by the clinical
criteria described in section 2.2.1. By contrast, epidemiological classifications pay particular attention to the ascertainment of out-of-hospital deaths which constitute 50-75% of the overall AMI burden.(52)

Epidemiological classifications tend to rely on retrospective review of hospital and death records. They divide AMI into definite, probable and possible subtypes depending on the evidence available.(53) Incidence and case fatality rates are then calculated with explicit documentation of the subsets of AMI (definite, possible and probable) which have been included. The WHO criteria have been updated most recently in 2010 to take into account the new, troponin-based universal definition of AMI.(53) For out-of-hospital deaths however, epidemiological definitions do away with the emphasis on troponin, stating only that there should be ‘naked-eye’ appearances of fresh AMI or recent coronary occlusion at necropsy.(53) In practice autopsy rates are low and most fatal cases of AMI in both the epidemiological and clinical literature are now based on presumptive diagnoses indicating possible or probable AMI. Non-AMI ACS does not feature in the current WHO definitions (53) but is mentioned in the 2003 American Heart Association (AHA) guidelines on case definition in ACS for epidemiological and clinical studies.(52)

2.3 Assignment and coding of causes of hospitalisation and death

In 1837, the UK government passed the Births and Deaths Registration Act, mandating registration of death and subsequently requiring that a cause of death be entered onto the death certificate.(54) William Farr, the Superintendent of Statistics to the General Registrar’s Office at that time insisted on this change and pushed it through. He was strongly convinced of the utility of having cause of death statistics to address concerns about the spread of infectious diseases and
plague and to monitor the mortality in the newly industrialised towns of Northern England during the Victorian era.

The Victorian concern with poverty led to the high mortality in Northern towns being viewed as a product of poor air and a ‘miasma’ which promoted disease. This led to social and sanitary reforms aimed at improving working and living conditions. With increasing industrialisation, the ‘miasma’ theory gave way to the more mechanistic ‘germ theory of disease’ which pointed at a single organism rather than a social cause as the basis of disease. A similar transition subsequently occurred over the twentieth century for coronary disease, which came to be seen as the biological end point of an individual lifestyle of overconsumption leading to ‘fatty change’ in the hearts of persons who over-indulged, rather than as a social problem of poor environment, poor opportunity or lack of access to medical care. (55)

Farr went on to advocate for international standardisation of the statistical nomenclature for causes of death. In keeping with the spirit of the age, he developed a mechanistic cause-of-death nomenclature which was heavily dependent on the anatomical localisation of the supposed cause. His nomenclature was presented to the first international statistical congress in 1853 and was adopted by the congress in favour of a more aetiological, symptom-based system devised by Marc D’Espine. Had an alternative classification system based on risk factors and social conditions for high mortality been adopted over an anatomically precise system, we may have seen a very different conception of the primary drivers of IHD mortality and may have placed more value on the patient’s symptomatic description, over and above that of the troponin result, than is currently the case.
Farr’s nomenclature of causes subsequently became the basis of the first International List of Causes of Death in 1900.(56) This international classification was expanded to include the classification of morbidity as well as death and evolved into the International Classification of Diseases (ICD).

Arteriosclerosis was introduced into the classification in 1911, and rapidly began to replace ‘old age’ as a cause of death in certification. Rules for assigning causes of death were changed such that “heart (disease was preferred) to respiratory disease if the two appear on the same certificate.”(55) This contributed to soaring numbers of deaths attributed to cardiac causes in the early twentieth century.(54,55,57)

The symptoms of IHD which have not changed since Heberden’s account in the eighteenth century have become increasingly difficult to identify in our current recording of the disease. ICD coding is still primarily anatomical, prioritising the localisation of the infarct to a particular site in the heart rather than patient symptoms. Furthermore, current ICD classifications capture neither the troponin level nor the ECG changes used in clinical diagnosis.(58) There is thus a disconnect between the patient’s account, the diagnostic tests recorded in the medical notes, and the final ICD code. Despite these limitations the ICD system is almost universally deployed for hospital and mortality coding, making it indispensable for capturing population wide data on causes of morbidity and death.

2.4 Summary

This chapter outlines the history of IHD which parallels the social transformation of Britain from an agrarian to an industrialised society. It demonstrates that our understanding of IHD which is frequently taken as a given, has in fact been socially constructed and is trapped within the
confines of the classifications we have chosen to adopt. Contemporary concepts of ACS diagnosis and assignment of ACS ICD codes, which will inform the analysis in Part II, have been reviewed.
Chapter 3: Literature review

3.1 Overview

This is a selective review of the current literature on trends in mortality, incidence, event rates total case fatality and hospital case fatality for IHD and ACS. Age, sex and socioeconomic patterns are examined first, then temporal trends in high income countries over the last century are described, and the recent declines in the UK, USA, Australia, New Zealand and Western Europe are explored. Finally geographical variations in event rates and mortality are reviewed.

3.1.1 Terminology

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Formula</th>
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</thead>
<tbody>
<tr>
<td>Event rate</td>
<td>Number of events / Population</td>
</tr>
<tr>
<td>Mortality / Death rate</td>
<td>Number of deaths / Population</td>
</tr>
<tr>
<td>Total case fatality</td>
<td>Number of deaths / Number of events</td>
</tr>
<tr>
<td>Hospital case fatality</td>
<td>Deaths following admission / Number of admissions</td>
</tr>
<tr>
<td>Proportion of out-of-hospital deaths</td>
<td>Deaths without prior admission / Number of deaths</td>
</tr>
<tr>
<td>Out-of-hospital deaths as a proportion of all events</td>
<td>Deaths without prior admission / Number of events</td>
</tr>
</tbody>
</table>

Figure 3.1. Health outcomes referenced in the literature.

There is a great deal of variability in the nomenclature of IHD spectrum diseases (Figure 1.2). ACS (encompassing AMI and non-AMI ACS) is a relatively new term for acute IHD (see Chapter 2.2); older literature often refers to coronary heart disease (CHD), and the terms IHD and CHD are sometimes used interchangeably to imply acute IHD. Recent ICD terminology
(ICD-9 and ICD-10) refers only to IHD. Health outcomes commonly referenced in the literature are shown in Figure 3.1.

3.2 Methods

I searched the Ovid MEDLINE database (1946 to present) using the Medical Subject Headings (MeSH) terms “acute coronary syndrome/or coronary artery disease/or myocardial infarction” in conjunction with either “Mortality” or “Cause of Death” or “Hospital Mortality” or “Survival Rate” or “Incidence”.

A further search was performed for the same conditions in conjunction with the terms “Registries” or “medical record linkage/medical record systems, computerised/electronic health records” or "quality of health care/guideline adherence/outcome assessment (health care)/program evaluation/benchmarking/quality assurance, health care/guidelines as topic/practice guidelines as topic/quality indicators, health care/standard of care/utilization review/health care quality, access, and evaluation/delivery of health care/health services research”.

Reports to the Government, publications from the Department of Health and the Office for National Statistics and grey literature were also reviewed, using searches on Google Scholar, or through follow-up of links and mentions in peer-reviewed publications.

3.3 Results

IHD was the leading cause of death worldwide in 2010 causing over 7 million deaths.(59)
### 3.3.1 Age and sex patterns

IHD mortality increases exponentially with age, with a rise of about 2.5 fold in men and 3.5 fold in women per decade above the age of 45 worldwide.\(^{(2,60–62)}\) In the UK and other high income countries with an aging population, 60-80% of IHD deaths now occur in people over the age of 75.\(^{(63,64)}\) In parallel with mortality, IHD event rates also rise steeply with age, with approximately half to three quarters of IHD events occurring in those over 65 years.\(^{(64,65)}\)

A male excess is present, both in IHD event rates \(^{(65–68)}\) and mortality in the order of 1.4-3.6 times that seen in women. This varies widely by country, cohort and year, indicating that the male preponderance is not inevitable and that environmental factors are largely responsible.\(^{(6,62,69,70)}\) The male to female gap in IHD mortality in England has narrowed in recent years.\(^{(69,71)}\)

Case fatality for IHD also increases with age,\(^{(61,65,72)}\) with some studies reporting higher hospital associated case fatality \(^{(73)}\) and lower proportions of out-of-hospital death in women than men,\(^{(74)}\) although this finding is not universal.\(^{(65)}\)

### 3.3.2 Socioeconomic status

In the early 1900’s IHD was a disease of the upper classes.\(^{(23)}\) In the US, where ethnicity is often used as a proxy for socioeconomic status, the mortality for IHD in white males actually rose between 1920-1947, whilst mortality in non-white males and females declined.\(^{(75)}\) The trend reversed mid-century and studies from the second half of the twentieth century consistently find mortality to be higher in lower socioeconomic groups \(^{(4,21,23,76)}\) and in more deprived areas.\(^{(77)}\)
3.3.3 Mortality

Accurate diagnosis of AMI as a cause of death, especially for out-of-hospital deaths where there is no ECG or blood enzyme result, is difficult. Many studies implicitly acknowledge this by reporting rates of definite AMI for hospitalised events but total IHD mortality. This strategy allows persons whose deaths may have been coded to more chronic manifestations of IHD because an AMI could not be confirmed, to be picked up.(64,78–80)

IHD mortality statistics rely on accurate certification of cause of death. Cause of death reporting has been in use in England since the 1850’s (Chapter 2.3). Other countries have varying degrees of completeness in vital registration procedures,(81) for example cause of death coding only became comprehensive in the US in 1933.(82) The information available to the certifying physician and the number of causes permitted on the death certificate influence what is reported. Further, the coding rules which are used to determine the underlying cause of death can affect the frequency of attribution to underlying vs. intermediate causes (Chapter 2.3).(83)

A number of attempts have been made to assess the accuracy of death certification; these are often based on comparing physician assigned causes of death to the post-mortem cause assigned by a pathologist.(84) The General Register Office evaluated clinical and post-mortem diagnosis for deaths in a large study covering 75 NHS hospitals in England in 1959. They found close agreement in overall numbers of IHD deaths certified by physicians and pathologists, but poor agreement for individual cases. Physicians were found to assign cases which would have been classified as biliary, abdominal or respiratory deaths by pathologists to the IHD category. Pathologists by contrast, tended to assign patients with both malignancy and cardiac pathology to IHD deaths rather than cancer; overall over and under-assignment by each group balanced out.
Agreement on individual cases was better for younger than for older age groups, in whom physicians tended to under-report IHD.(85)

There is a high background rate of atheromatous change in the general population which has been found to be present even in cases where the cause of death is due to accident or war,(86,87) and this may lead to the overall level of agreement between clinical and pathological causes of death being over-estimated. Thus, the post-mortem diagnosis is not necessarily the more accurate one. IHD codes have previously been called a “convenient statistical wastepaper basket” for deaths which cannot be otherwise classified.(82) Some researchers have tried to take account of misclassification when looking at mortality patterns – an early example being the a paper by Samuel Preston entitled “Mortality patterns in national populations : with special reference to recorded causes of death” published in 1976.(88) More recently the Global Burden of Disease (GBD) studies have developed reassignment algorithms for what they term ‘garbage codes’, or codes of death which are patho-physiologically unlikely to be underlying causes of death. These deaths are reassigned to more likely causes depending on the probability of the end cause being the true cause of death.(89) The latest iteration of this GBD approach assigns 84% of deaths coded to cardiac conduction disorders, 38% of those coded to cardiogenic shock, 11% of those coded to cardiac arrest and 46% of those coded to hypertension to the IHD category, resulting in an overall 21.5% increase in IHD deaths. In England, where vital registration is stable, approximately 10-15% of all death codes need reassignment based on this method.(90) An alternative to reassignment is to use a multiple-cause rather than an underlying-cause approach; this may result in improvement of estimates of the overall burden of mortality associated with circulatory causes, but is not commonly practised.(85)
Despite its limitations, mortality, based on underlying cause of death, is the most frequently used measure in descriptive epidemiology. In England and Wales, death is the first presentation of coronary disease in 20% of fatal cases. (91) Approximately half to three-quarters of all coronary deaths have been reported to occur outside of the hospital, of which about 40% go un-witnessed. (92)

**3.3.3.1 Temporal trends in mortality**

Mortality from IHD rose dramatically from the early 1900’s to the middle of the twentieth century. (4,93) There was initial speculation that at least part of the rise was due to changes in certification and cause of death assignment such that strokes, nephritic and hypertensive diseases, which all appeared to be declining, were being recoded as IHD deaths. (82) However, further studies correcting for the changes in certification practice, and for the aging population profile confirmed the increase in IHD mortality. (3,93) IHD mortality trends for Europe mirrored those in the USA, but there were sharp declines during the war years in European countries worst affected by food rationing. This lead to the hypothesis that diet, and in particular saturated fat and cholesterol were implicated in the development of acute events. (94,95)

Sustained declines in IHD mortality began in the mid 1960’s in the USA, (96,97) followed somewhat later in mid-1970’s by the UK. (2,98) In Central and Eastern European countries IHD mortality increased through the 1970’s and 80’s and only began to decline in the early to mid-1990’s. (99) The situation in the countries of the former Soviet Union has been more complex, with marked fluctuations in the mortality trend following the collapse of the Soviet Union which appear to reflect economic changes and changes in alcohol policy. (6,100) IHD mortality declines
in the USA, UK and Western Europe are still ongoing, and the rate of decline accelerated in most sub-groups at the beginning of the twenty-first century.

Importantly, declines in IHD mortality in the USA and Western Europe commenced well before the widespread use of effective therapies such as thrombolysis (1986), beta-blockade (1985) and angioplasty (1993) at a time when there was still controversy over whether patients with AMI should be managed at home or treated in a hospital coronary care unit.

3.3.4 Incidence and event rates

Incidence is a composite measure of the occurrence of both fatal and non-fatal IHD events. It is often not feasible to determine whether an IHD event is a first occurrence, thus many studies report event (attack) rates, rather than true incidence of first ever events.

Incidence and event rates have been reported from prospective cohort studies, community based surveillance studies and registries and from national data linkage studies. Capture and validation of IHD events are key issues in reporting, and have a large impact on the extent to which studies may be compared.

3.3.4.1 Prospective cohort studies

Early prospective cohort studies often report the true incidence of a first ever IHD event based on the follow up of a disease free, healthy-volunteer cohort. Cohorts tend be composed of voluntary participants in a particular area or sharing a particular occupation and results are not easily generalisable to other populations. However, events in these studies are carefully validated using pre-defined clinical and pathological criteria. Cohort studies are therefore useful for providing insight into the aetiology and risk factors for IHD events.
The National Heart and Lung Institute’s (NHLI) seminal Framingham Heart Study (n=5209, enrolment=M and F 30-62 years, start year=1948) validated non-fatal events by review of medical records and ECG and enzyme tests, whilst fatal events were autopsied for confirmation. The Framingham Heart Study reported an AMI incidence of 740 per 100,000 in men aged 60-69 years during the 1960’s. Incidence rates in Framingham fell in all except the oldest age group over time such that by the 1990’s rates in 60-69 year old males were 550 per 100,000.(107)

This is confirmed by the more recent National Health and Nutrition Examination Survey (NHANES) epidemiological cohorts in the USA, which use data linkage supplemented with validation of events for follow up; they report the incidence of first AMI to be 500 cases per 100,000 in their 1982-1992 cohort.(108).

The British Regional Heart Study (BRHS, n=7735, enrolment=M 50-59 years, start year=1978-80) followed up disease free men in 24 towns representative of Great Britain. They reported event rates of 1,750 per 100,000 in men aged 60-64 years in the 1980’s falling to 1,000 per 100,000 for men who reached 60-64 years in the late 1990’s.(109)

3.3.4.2 Community based surveillance studies

Community based surveillance studies and registries are designed to cover the entire population of an area. They collect data from routine sources such as hospitalisation and death certificates (“cold pursuit”) and supplement these with various forms of active case finding for events which may have been missed (“hot pursuit”). Like cohort studies, they tend to validate both fatal and non-fatal events, using measures such as assessment of ECG and blood tests, post-mortem examinations and interviews of victims or victims’ relatives soon after the event in order to
document symptoms. They capture a snapshot of all validated events occurring in a specified population.

Early examples of community based surveillance projects are the Oxford Record Linkage Study (1962) (110) and the Rochester Epidemiology Project (1966). (111) Other commonly cited studies employing community surveillance methodology are the Minnesota Heart Survey, the Atherosclerosis Risk In Communities (ARIC) study, the Worcester Heart Attack Study, the Cardiovascular Health Study and the World Health Organization’s Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study. (78)

The overall IHD incidence or event rates reported by such studies in the USA and Western Europe remained stable or declined only slightly from the 1970’s to mid-1980’s, with more rapid declines taking place thereafter. Declines were most marked in men aged under 75 years, and the burden of events appeared to shift towards the elderly and to women over time. For example, the Rochester Epidemiology Project reported that the age-sex adjusted incidence of fatal AMI combined with death due to coronary disease in Olmsted County was almost 300 cases per 100,000 in 1979 declining to 280 cases per 100,000 by 1998. (Arciero et al., 2004) The Minnesota Heart Survey also showed declines in AMI incidence in the order of about 10% in 35-74 year olds between 1985-1997, (114) whilst the ARIC study (n=470,000, enrolment=M and F 35-84 years, start year=1987) found that the rate of hospitalisation for AMI in 35-74 year olds stayed approximately stable between 1987-1994, although the rate of out-of-hospital death from IHD declined. (115) The Worcester Heart Attack Study, similarly found stable rates of hospitalisation for AMI in the under 65s with increasing rates in those aged 65 years and over between 1975-1981, but a significant decline in out-of-hospital IHD deaths. (116) More recently, Yeh et al. followed the Kaiser Permanente population in Northern California from 1999-2008
and found that the age-sex adjusted incidence of AMI declined from 287 cases per 100,000 in 2000 to 208 per 100,000 in 2008.\(^{(117)}\)

In Europe, Russia, Australia, New Zealand and China the WHO Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) studies covering 32 populations in 21 countries \((n=5,725,762,\) enrolment=\(M\) and \(F\) 25-64 years, start year=1985-1990), reported widely varying IHD event rates in men aged 30-64 years during the mid-1980’s; 274 per 100,000 in France, 266 in Italy in comparison with 695 and 777 per 100,000 in the UK centres of Belfast and Glasgow. The UK centres thus recorded 2-3 fold greater incidence of IHD compared to southern Europe. There was no MONICA site in England itself.\(^{(7,118)}\)

IHD event rates in the French MONICA centres declined slightly in men from 1985-1993 and subsequently stabilised; there was no decline in women and some centres even demonstrated an increase.\(^{(119)}\) Similarly, in a follow-up study from a Swedish MONICA centre, event rates fell more dramatically in men than women between 1985 and 2004.\(^{(66)}\) The Stockholm Heart Epidemiology Program, another community based surveillance project in Sweden, also found declines in incidence in men with a slight increase in women in some groups.\(^{(120)}\) By contrast, a follow up study from the Finnish MONICA sites demonstrated a fall in event rates in both men and women between 1983-1997\(^{(121)}\), as did a follow up from the northern Italian MONICA site for the period 1985-2004.\(^{(103)}\)

In England, the Oxford Record Linkage Study found IHD incidence rates of 434 per 100,000 in men aged 30-69 years during the late 1960’s which fell to 292 per 100,000 by the mid-1990’s. Thus incidence rates in Oxfordshire in the 1990’s were closer to those of southern Europe than to those reported by the MONICA Belfast and Glasgow centres.\(^{(72,122)}\) More recently, the Oxford
Vascular Study, covering a much wider age range (n=91,106, enrolment=M and F, all ages, start year=2002-2005), reported coronary event rates in the early 2000’s of 290 per 100,000 (389 per 100,000 if all ACS events were included) in men, and 233 per 100,000 in women (273 per 100,000 for all ACS events), with almost three quarters of all events occurring in the over 65 age group.(65)

3.3.4.3 National linked database studies

Data linkage relies on correctly matching individuals who appear in routinely collected data for non-fatal events (for example hospital admission records, primary care records or national registries of AMI) to centrally held mortality databases containing death records. This allows health service encounters to be followed for mortality outcomes and identifies individuals who die without recent health service contact. Internal linkage of records within the database also allows episodes of health service contact to be grouped by patient, permitting patterns of readmission to be examined (see Chapter 7.2.1). National data linkage is a relatively recent phenomenon and is better established in Western European countries with small populations and single predominant health service providers.

National data linkage is amenable to time trend analysis as well as the study of sub-national geographical variation. The key limitation is the inability to verify events using standard clinical and diagnostic tools, thus forcing a reliance on clinical coding to identify events. In addition, data linkage studies do not undertake active case finding or “hot pursuit” of cases, and it is estimated that they may miss between 5-25% of events depending on the data source, ICD codes, and ascertainment criteria which are used to identify events.(65,123–127) (These limitations are more fully examined in Chapter 6.4).
Using data linkage methods, Sweden reported age standardised AMI event rates of approximately 987 per 100,000 for men in 1987 falling to 881 per 100,000 by 1995. Event rates fell in all age groups except the oldest ages, where they rose. Denmark started off with marginally higher rates of AMI than Sweden, but the overall incidence of AMI declined by about 6% in men in Denmark and 3% in men in Sweden bringing the two countries level by the late 1990’s.

Finland, which had some of the highest incidence and mortality for IHD during the initial MONICA study in the 1980’s, experienced particularly steep declines in incidence and mortality over subsequent years. By 1990 data linkage studies from Finland estimated the age standardised incidence of first AMI in men to be 500 per 100,000 falling to 340 per 100,000 by 2002. In the Netherlands, the age standardised incidence of first AMI in men (fatal and non-fatal) was reported as 630 per 100,000 in 1998 falling to 380 per 100,000 by 2007.

Scotland has had the facility to link hospital and mortality data since 1992 via the Scottish Record Linkage System and England has done so since 2005. Age standardised rates for first AMI in men in Scotland stood at 512 per 100,000 in the early 2000’s.

National data linkage studies thus provide evidence that incidence/event rates for AMI are falling over time, despite changes in diagnostic criteria which mean that more minor events are diagnosed and coded. However, during the 1980’s and 1990’s the rate of decline in incidence appeared to be less dramatic than the rate of decline in mortality (see Chapter 8.3.1 and Chapter 8.3.2), and in line with this, most studies report a larger fall in the incidence of fatal IHD events than in the incidence of non-fatal AMI.
Many data linkage studies have focused on incidence and mortality trends for hospitalised AMI only. (137–140) However these numbers are more impacted by variations in clinical practice and in diagnostic criteria. (141) In addition as 20% of all first AMI and 40-70% of all events are out-of-hospital deaths, incidence for hospitalised AMI cannot be used as a proxy estimate for overall incidence of AMI in a population. Follow-up of these studies does, however, provide useful data on case fatality for hospitalised AMI which is covered in the next section.

3.3.5 Case fatality

Following the decline in IHD mortality in the middle of the twentieth century there was much speculation around whether the improvements were a result of medical intervention or were attributable to secular changes in diet and lifestyle. This question was explicitly posed during the 1978 National Heart Lung and Blood Institute conference on the decline in coronary heart disease mortality in Bethesda, Maryland. (97) The WHO MONICA studies of the early 1980’s were set up to investigate the answer, decomposing the effects of event rates and case fatality on IHD mortality and hypothesising that reductions in case fatality were likely to be related to improved medical care whereas reductions in event rate were likely to reflect changes in public health and prevention. MONICA subsequently attributed approximately one third of the overall reduction in IHD mortality to improvements in case fatality, and the other two-thirds to declining event rates, although this varied from country to country. (7)

However, reductions in total case fatality need not necessarily reflect more effective medical practice but might also be due to declining severity of the underlying disease. Many recent studies have suggested that the severity of AMI is, in fact, changing over time. (117,142,143) Therapies such as lipid-lowering and anti-hypertensive medications are now used for primary as
well as secondary prevention affecting the initial risk of an AMI event as well as post-AMI outcomes. These therapies are in widespread use in some countries, making it difficult to separate the effects of medical intervention from those of broader societal changes in background risk due to diet or policy intervention or due to changes in individual lifestyle and behaviour. Early intervention during an acute event may also prevent ‘definite’ AMI from completing and presenting with classic ECG changes and enzyme release. These considerations increasingly blur the distinction between ‘treatment’ and risk reduction.

Case fatality for hospitalised and community based events is calculated using different denominators (Figure 3.1). Hospital based studies look at the proportion of those admitted with AMI who go on to die within 28-30 days from any cause, whilst community studies report total case fatality i.e. all AMI related fatal-events (deaths from any cause within 28-30 days of an AMI event in addition to deaths coded to AMI/IHD as an underlying cause) as a proportion of all events or as a proportion of all fatal events. Hospital case fatality has been reported to be higher in women than men and the proportion of out-of-hospital deaths higher in men than women although this is not universally so. Case fatality rates reported in the studies below refer to short term mortality, within 28-30 days of an event.

3.3.5.1 Total case fatality

Case fatality rates for AMI tend to be low in those aged less than 60-years (10-20%) rising dramatically with age to about 40-45% in the oldest age groups.

Declines in case fatality lagged behind declines in incidence by about 10 years. Total case fatality for AMI (in-hospital plus out-of-hospital deaths) stood in the region of 60% in the 1960’s in Oxfordshire. By the late 1980’s this figure was around 45% in the UK MONICA centres.
and by the late 1990’s it was reported as 42% in Oxfordshire.(72) By 2010, age-standardised total case fatality for AMI for the whole of England was reported to be 31%.(154) Similar results are reported for case fatality rates in the USA during the 1960’s (155) and for recent declines over time in Europe, Australia and New Zealand.(134,136)

Although declines in total case fatality appear to contribute significantly to the overall temporal trend in IHD, the MONICA studies, when restricted to economically comparable countries, found less variation in case fatality between countries than was found for event rates or mortality.(156)

### 3.3.5.2 Hospital case fatality

Hospital case fatality was about 20-25% in the early 1980’s in the USA, Canada, Western Europe, Australia and New Zealand and had fallen to 10-15% by the late 1990’s.(136,139,157–160) Studies in Norway,(138) Denmark,(68) Netherlands,(134) Sweden,(161) and the USA (162,163) show continuing falls into the 2000’s, with more pronounced reductions in younger (<65 years) vs. older people (>65 years).(138,164)

Declines in hospital case fatality were slower in some areas of the UK than others. The Nottingham Heart Attack Register reported no significant change in hospital case fatality for AMI between 1982-1992; case fatality hovered around 20% even though this was the period during which the use of aspirin, thrombolysis and beta blockers was rolled out.(165) Similarly hospital case fatality in the late 1980’s in Scotland was reported as around 23%,(74) but fell gradually to about 19% by the mid 1990’s. Case fatality for hospitalised events in Scotland declined more rapidly in men than women.(166) The Oxford Myocardial Infarction Study
(OXMIS) reported a marked decline in hospitalised case fatality between the late 1960’s when case fatality stood at 27% and the mid 1990’s when it had reduced to 15%.(72)

The Olmstead County Study (USA) reported low case fatality rates for hospitalised AMI of 12% in the early 1980’s without any significant decline by the early 1990’s(11%),(113) as did the Perth MONICA centre in Australia.(136) However other US community based studies, with higher baseline case fatality rates (around 18%) reported 30-50% declines in hospital case fatality similar to that seen in European countries, and reaching rates of around 10% in the late 1990’s and early 2000’s. (Worcester Heart Attack Study,(167,168) Minnesota Heart Survey(114,169)).

The Global Registry of Acute Coronary Events (GRACE) collected data from 200 hospitals in 28 countries in North and South America, Europe, Australia and New Zealand from 1999-2009. They report hospital case fatality of 7% for STEMI, 6% for NSTEMI and 3% for unstable angina in 2002.(164) By 2005 hospital case fatality for STEMI in GRACE was reported as 4.6% and in other ACS as 2.2%.(170)

### 3.3.6 Out-of-hospital mortality

AMI has a very high early mortality with approximately 45% of victims dying within the first hour of symptoms if no intervention is provided.(171) The proportion of all AMI events (fatal plus non-fatal) which occur as out-of-hospital deaths ranges from 20% in those aged <55 years to over 60% in those older than 85 years,(172,173) whilst the proportion of all fatal-IHD events which are out-of-hospital deaths is reported as 60-75%, and declines with age.(92,136,171,172,174,175) Ambulance based defibrillation and strategies targeted at reducing the delay between call for help and administration of reperfusion therapy have been used to
reduce out-of-hospital death. The overall mortality for both pre-hospital and post-admission deaths has fallen, but the ratio of pre to post admission deaths remains close to what it was in the 1970’s. The failure to improve the fraction of out-of-hospital deaths is thought to be largely due to the time that the patient waits before calling on help, which has remained constant at over 90 minutes over the last 30 years.(16–18,176) In order to improve the ratio, a larger proportion of patients who are dying early in the community, would need to be transferred to a hospital where they have a chance of treatment. Patient education campaigns targeted at early recognition of symptoms and community defibrillation by bystanders are now being introduced to see if time to first response can be reduced. A 25% survival rate from out-of-hospital cardiac arrest has been achieved with such measures in Norway.(177) Current estimates in the UK put out-of-hospital cardiac arrest survival rates at about 8.5%.(178)

3.3.7 Geographical variation

There is a long history of cross-country comparisons in IHD mortality. Central Asian Republics and Russia currently have the highest IHD morality rates.(179) IHD remains a leading cause of death both globally and in high income countries. The IHD mortality burden in high income countries is driven by an aging population and persists despite the declines in age-standardised IHD mortality.(1) Within Europe there is a recognised gradient in age standardised IHD mortality running from the North East to the South West, with the highest rates seen in Central and Eastern European countries and the lowest rates in France, Portugal, Italy and Spain.(180) A similar North East to South West gradient has also been reported within the UK which has one of the most marked internal geographical variations in mortality of any European country. In both Europe and the UK, the majority of the all-cause mortality differentials between regions are
driven by differences in IHD mortality; relative differences between areas in other causes of
mortality such as cancer are less pronounced than those for IHD. (77,181)

The regional differences in mortality within the UK, which shows a marked Northern excess,
have been persistent through the last century (182,183) and mirror historical patterns of
poverty. (23,24,184) These differences are analysed in finer detail for both younger and older
ages in Chapter 4. Previous geographical studies of within country variation in the UK have
focused primarily on separating contextual from compositional effects, trying to distinguish
whether the differing mortality seen between places result from the different kinds of populations
that live in these areas or are due to something intrinsically related to the area itself. Area and
area deprivation appear to have a small, but distinct independent effect once individual
socioeconomic status as measured by occupational class or educational attainment has been
accounted for. (185–188) The proposition that the area forms the individual rather than
individuals forming the area, has been less well examined. Geography captures more than a
simple aggregation of individual socioeconomic statuses, and reflects wider social and
environmental disadvantages faced by a community in terms of transport and leisure facilities,
community organisation, pollution and other factors which can affect health independently of the
characteristics of the people living an area. (189)

Regional differences are more pronounced in lower socioeconomic groups, whilst those of
higher socioeconomic status seem relatively insulated from the regional variations in
mortality. (185) Furthermore, similarly deprived areas in the North have higher mortality than in
the South. Socioeconomic and area deprivation gradients are more marked in men than in
women when all causes of death are considered, but for IHD the opposite is true –
socioeconomic gradients and area deprivation gradients for IHD mortality are more marked in
women than men. (186) It has been postulated that the persistent regional differences seen within socioeconomic groups and deprived areas may relate to regional differences in risk factor distribution, (32,190) health behaviours or even psychosocial stress. (191,192)

Variations in incidence and case fatality are much less well studied than variations in mortality especially at sub-national level. There is some indication from the MONICA studies that, at country level, incidence and mortality track together whilst case fatality is relatively unrelated. (156)

3.4 Conclusion

Declines in incidence/event rates for IHD started earlier and have been more rapid than declines in case fatality. They appear to contribute more to the downward trend in IHD mortality.

3.5 Summary

The temporal and regional variations in IHD mortality, event rates and case fatality reported in the literature have been surveyed. Within country studies of spatial variation in the UK tend to focus on IHD mortality alone, and its relationship to socioeconomic variables. This thesis will initially look at spatial mortality patterns in more detail and then go on to estimate within country variation in event rates and case fatality and assess their contribution to the variation in ACS mortality patterns in England.
Part I – CVD mortality
Chapter 4: Spatial variation in CVD mortality in England 1982-2006

This chapter presents the results of an investigation into temporal trends in CVD mortality. The analysis sets the epidemiological context for the remainder of the thesis.

4.1 Introduction

CVD mortality in England has declined by two-thirds since the early 1980’s. The geographical differential in CVD mortality between Northern and Southern England, as well as between areas of high and low deprivation, is well documented. Much less is known about mortality differentials at the small area administrative levels at which the majority of health services and health system factors operate. Currently, CVD networks to transfer patients to hospital care operate at local authority level or across Local Authority Districts, whilst primary care and CVD prevention operate at the level of the GP practice, or group of practices.

4.1.1 Previous work

Two recent studies have conducted cross-sectional ward-level analyses of IHD and all cause mortality in persons aged 65 years or less, but present only aggregate results. They report that associations with area deprivation account for approximately 45% of the variability among wards.(193,194) A further study looked at temporal trends in IHD mortality by quintile of area deprivation in both older and younger persons, but did not conduct spatial analysis. This study reported a reduction in absolute inequalities in IHD mortality between deprivation quintiles over time.(195) Other temporal analyses which have been conducted either for broader areas (county, parliamentary constituency or region) or for broader causes of death (all-cause mortality) find
increasing relative inequalities between geographical areas (196,197) and among places classified according to area deprivation (198,199) in persons aged less than 65 or 75 years.

4.1.2 Current analysis

I estimated CVD mortality at the fine granularity of electoral wards for both younger and older age groups. CVD mortality was chosen as ACS deaths which drive the overall CVD pattern (see Chapter 5) are too sparse to be modelled stably at ward level. I report ward level estimates with their uncertainty and examine changes in patterns of mortality since 1982 as well as the association of morality with area deprivation.

4.2 Methods

4.2.1 Units of analysis

Estimates of mortality were made at ward level separately for men and women aged 30-64 years and ≥65 years. Ward boundaries change over time; boundary data were obtained from the ONS and were fixed at their 2001 Standard Table (ST) limits. ST wards are produced by the merger of wards with populations less than 1000 residents or 400 households into larger receiving wards to avoid breaches of confidentiality.(200) All data were assigned to the 7932 ST ward boundaries. Further references to ward in this thesis, refer to ST wards. Five cross sectional analyses were undertaken to determine how stable the spatial pattern of CVD mortality was over time. Data were aggregated over the following 5 year intervals (1982-1986, 1987-1991, 1992-1996, 1997-2001, 2002-2006) in order to achieve sufficient samples for analysis in each age-sex-ward-time group.
4.2.2 Data

4.2.2.1 Mortality

Deaths from CVD causes ICD-9 codes 390-459 (1982-2000) and ICD-10 codes 100-199 (2001-2006) were extracted by age, sex and ward from national mortality records provided by the ONS.

4.2.2.2 Population

Population data by age and sex and ward were available directly from ONS for 2001 and all subsequent years. (201) For earlier years census data were available for census Enumeration District (ED) in 1981 and 1991. ED populations were divided equally among all postcodes in each ED; postcode populations were then aggregated to 2001 ST ward boundaries. For intervening years between 1982 and 2001, ONS population data were available at local authority district level. Census data for 1981, 1991 and 2001 were used to estimate the proportion of district population which falls into each ward within that district by sex and age group; the proportion for inter-censual years was calculated using linear interpolation between census years. The ratio of ward-to-district population, by sex and age group, was used to redistribute district population into wards for inter-censual years prior to 2001.

4.2.2.3 Area deprivation

The Index of Multiple Deprivation (IMD) 2007 was used as the main measure of area deprivation. (202,203) IMD incorporates 38 indicators of income, employment, health, education, housing and services, living environment/infrastructure and crime. Scores for each IMD domain are available at the Lower Super Output Area (LSOA) level and were transformed to ward-level domain scores by weighting using the LSOA:ward population ratio. Areas were grouped by IMD quintile, as the IMD score itself has little meaning, being a non-linear measure of area
deprivation. The health domain was removed from the deprivation score in this analysis in order to avoid circularity between outcomes and input covariates, although this had little impact on the final results.(204)

**4.2.2.4 Covariates**

Indicators of urbanicity and government office region (GOR) for each ward were available from ONS and were used as covariates to improve the efficiency of estimation of the posterior distribution.(205)

**4.2.3 Statistical analysis**

**4.2.3.1 Bayesian spatial model for disease mapping**

It is important to consider two issues specific to small area data before estimating disease rates: firstly, the numbers of deaths in a single small area are often sparse. Thus in areas with small populations, a small change in the number of deaths may result in a large apparent fluctuation in the crude disease rate (high sampling variability). The smaller the population in the area, the larger the problem of unstable rates will be, with maps of crude disease rates dominated both on the low and high sides by these smaller areas.(206,207) Second, there is often local spatial dependence between areas, such that rates in places which are close to each other are more similar than rates in areas at a distance from each other. Thus the data often exhibit a latent spatial process which is obscured by observational noise.(208)

Bayesian spatial models employ a hierarchical structure in an attempt to reduce this ‘noise’ and distinguish true spatial heterogeneity, taking into account the relatedness between areas. Commonly, the first level of the hierarchy models cases of disease in an area as being drawn from a Poisson distribution based on the assumption that occurrence is a rare event and
individual risks vary randomly within areas. The second level of the hierarchy models the mean of the Poisson estimate for each area as the national mean plus a random effect which allows each area to deviate from the national rate. The random effect has a latent spatial structure which can be captured by a number of possible priors, but the one which appears to perform best is the conditionally specified Markov random field first proposed by Besag, York and Mollie in 1991 (BYM prior). (209) Using the BYM prior, the random effect is partitioned into spatially structured and unstructured effects modelled by independent realisations from a ‘clustering’ prior and a ‘heterogeneity’ prior. (206, 209) The clustering prior estimates the rate or risk of disease in area \( i \) (\( \lambda_i \)) jointly with that of the surrounding areas, allowing each area estimate to ‘borrow strength’ from its neighbours. (210) The partitioning between the structured and unstructured effects determines the level of local vs. global smoothing. The model can be written as follows:

Observations in area \( i \) (\( Y_i \)) are drawn from a Poisson distribution \( Y_i \sim P(\lambda_i * n_i) \) where \( \lambda \) is the rate of disease and \( n \) is the population at risk. In the second level of the hierarchy:

\[
\log \lambda_i = \alpha + U_i + V_i
\]

(Model 1)

Where:

\( \alpha \) = intercept and represents the global (national) mean

\( U_i \) = spatially structured random effect

\( V_i \) = unstructured random effect
$U_i$ and $V_i$ are assumed to be independent of each other. $U_i$ has a Gaussian conditional autoregressive (CAR Normal) prior distribution which assumes that the values in areas which are adjacent to each other are similar (local smoothing), whilst $V_i$ is drawn from an independent normal prior distribution, and provides smoothing to the national mean. Finally, hyperpriors are set for the variances of $U_i$ and $V_i$. These are usually highly dispersed gamma distributions. Statistical inference is then performed either by sampling the posterior probability distribution using a Markov chain Monte-Carlo (MCMC) algorithm, usually in conjunction with a Gibbs sampler (211) or by using the Integrated Nested Laplace Approximation (INLA) approach.(212)

4.2.3.2 Estimation of age standardised mortality rates

Age standardised risks of CVD death in 30-64 year olds and in those aged 65 and over, relative to the national average, were estimated for each ward, sex and time-period using the BYM model. Ward level estimates were conditioned on urbanicity and government office region (GOR). Age standardisation was to the age structure of the English population over the entire time-period (1982-2006), to allow comparison between the results in each of the five cross sectional analyses. Relative risks were transformed back into rates per 100,000 persons by multiplying by the national average rate in each group. Results for each ward are reported with their posterior probability estimate. Posterior probabilities range between 0 and 1, with a value close to 0 indicating high confidence in an estimated rate which is smaller than the national average and a value close to 1 indicating high confidence in an estimated rate which is larger than the national average. A posterior probability of 0.5 indicates a rate which is indistinguishable from the national average.(213) A further analysis was undertaken including IMD quintile as an additional covariate to estimate the effects of adjustment for area deprivation.
on the spatial variability in CVD mortality. Simple correlations between IMD score and ward level CVD rates are also reported.

The models were fitted in R version 2.13 using the package Integrated Nested Laplace Approximation (INLA), which provides a computationally efficient approximation to the Markov-Chain Monte Carlo algorithm. Model fit was assessed according to the deviance information criteria (DIC) goodness of fit statistic. The results of this analysis have been published as Asaria P et al. Trends and inequalities in cardiovascular mortality across 7932 English electoral wards 1982-2006: Bayesian spatial analysis. Int J Epidemiol 2012;41(6):1737-49.

4.3 Results

In 2002-2006, 38% of deaths in men and 37% of deaths in women over 30 years of age were due to CVD. National CVD mortality in men aged 30-64 years was 120 per 100,000 and the corresponding rate in women was 45 per 100,000. In men aged 65 years and over national CVD mortality was 2234 per 100,000 with the corresponding rate in women being 1590 per 100,000. 1 in 5 wards had CVD mortality which was higher in women than in men for the 65+ age group.
Figure 4.1. Age–standardised CVD death rates by ward 2002-2006. (Standardised to the English population 1986-2006). Each colour pertains to one decile of wards (i.e. 793 wards).
There was a four-fold difference in CVD mortality between the highest and lowest percentile of wards in the 30-64 year age group and a twofold difference at older ages. A clear Northern excess in mortality was apparent along with an excess in some London wards at younger ages (Figure 4.1 and 4.2). CVD mortality was highest in and around metropolitan areas of Liverpool, Manchester, Nottingham, Burnley and Blackpool; in parts of Yorkshire, Leeds and Bradford; in and around Birmingham and in the London boroughs of Newham, Hackney, Haringey, Tower Hamlets and Waltham Forest. By and large, CVD mortality was low in Southern England with
the exception of parts of London and a few places along the Southern coast such as Plymouth. (See Appendix A for English geography). The spatial distribution of high and low mortality areas was less polarised in older adults (65 years and older) than in younger people (30-64 years old).

4.3.1 Declines in CVD mortality between 1982-1986 and 2002-2006

Figure 4.3. CVD death rates in 1982-1986 (top) and change in CVD mortality between 1982-1986 and 2002-2006 (bottom) for persons aged 30-64 years.
From 1982-1986 to 2002-2006 CVD mortality declined in all but 2% of wards in both younger (30-64 years) and older (≥65 year old) men and women. The rises seen in the remaining 2% of wards were mostly in women aged 65 years and older.

Total decline over these 25 years was in the order of 66% in 30-64 year olds and 50% in those aged 65 years and over. There were marked differences in the rate of decline between different areas. CVD mortality declined 4.5 times faster in men and 7 times faster in women in the best performing percentile of wards for those aged 30-64 years than in the worst performing percentile (Figure 4.3). In those aged 65 years and over the corresponding rates of decline were 5 times faster in men and 10 times faster in women in the best compared to the worst wards (Figure 4.4).

At younger ages (30-64 years) the fastest declines were seen in wards with the highest starting death rates in 1982-1986, whilst slowest declines were seen in some London wards which had average mortality in 1982-1986 (Figure 4.3); this led to the latter ‘falling behind’ in the mortality tables and resulted in them becoming high CVD mortality wards by 2002-2006. Wards with very low mortality in 1982-1986 experienced slower rates of decline but persisted as low mortality areas in 2002-2006. Overall the absolute inequality between wards decreased over this period, but the relative rankings of the wards remained largely constant with correlations between the 1982-1986 mortality levels and the 2002-2006 mortality levels at 0.65 in men and 0.71 in women.
Figure 4.4. CVD death rates in 1982-1986 (top) and change in CVD mortality between 1982-1986 and 2002-2006 (bottom) for persons aged 65 years and older.

For men aged 65 years and over, fastest declines were again seen in Northern wards with the highest starting CVD mortality, however for women in the same age group, there was no clear geographical pattern for wards with the highest CVD mortality (Figure 4.4). The relative rankings of high and low mortality wards over time changed more in the older compared to younger age groups; correlation between CVD death rates in 1982-1986 and 2002-2006 was only 0.45 in men in this age group and 0.28 in women.
4.3.2 CVD mortality and area deprivation

In 2002-2006 ward CVD mortality was strongly correlated with ward level IMD deprivation score in the 30-64 year olds. Correlations were less strong at older ages (Figure 4.5). These associations between community deprivation and CVD mortality are also apparent in geographical patterns of CVD mortality. After adjusting for GOR and urbanicity additional adjustment for ward IMD quintile reduced overall spatial variation in CVD mortality by 80% in men and women aged 30-64 years, and by 58% in men aged 65 years and over. Women aged 65 years and over experienced a much smaller reduction of only 42% (Figure 4.6).

Figure 4.5. Correlation between ward IMD deprivation score and CVD mortality.
Figure 4.6. Posterior standardised mortality ratio for CVD mortality 2002-2006 in a) men aged 30-64 years, b) women aged 30-64 years, c) men aged 65 years and over, d) women aged 65 years and over. Unadjusted estimates (top), adjusted for urbanicity and GOR (middle) and adjusted for urbanicity, GOR and IMD (bottom). Scale reflects decile of wards in the unadjusted estimates.
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<td>2.06</td>
<td>2.25</td>
<td>2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Women 30-64 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least deprived</td>
<td>69</td>
<td>54</td>
<td>42</td>
<td>34</td>
<td>26</td>
<td>43</td>
<td>62%</td>
</tr>
<tr>
<td>Q2</td>
<td>80</td>
<td>64</td>
<td>51</td>
<td>41</td>
<td>31</td>
<td>49</td>
<td>61%</td>
</tr>
<tr>
<td>Q3</td>
<td>90</td>
<td>72</td>
<td>59</td>
<td>48</td>
<td>37</td>
<td>53</td>
<td>59%</td>
</tr>
<tr>
<td>Q4</td>
<td>109</td>
<td>89</td>
<td>74</td>
<td>60</td>
<td>47</td>
<td>62</td>
<td>57%</td>
</tr>
<tr>
<td>Most deprived</td>
<td>140</td>
<td>123</td>
<td>105</td>
<td>90</td>
<td>71</td>
<td>69</td>
<td>49%</td>
</tr>
<tr>
<td>Q5-Q1 difference</td>
<td>71</td>
<td>69</td>
<td>63</td>
<td>56</td>
<td>45</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Q5/Q1 ratio</td>
<td>2.03</td>
<td>2.28</td>
<td>2.5</td>
<td>2.65</td>
<td>2.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Men ≥ 65 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least deprived</td>
<td>3,334</td>
<td>2,927</td>
<td>2,586</td>
<td>2,104</td>
<td>1,630</td>
<td>1,704</td>
<td>51%</td>
</tr>
<tr>
<td>Q2</td>
<td>3,482</td>
<td>3,085</td>
<td>2,700</td>
<td>2,208</td>
<td>1,759</td>
<td>1,723</td>
<td>49%</td>
</tr>
<tr>
<td>Q3</td>
<td>3,562</td>
<td>3,160</td>
<td>2,820</td>
<td>2,317</td>
<td>1,840</td>
<td>1,722</td>
<td>48%</td>
</tr>
<tr>
<td>Q4</td>
<td>3,718</td>
<td>3,294</td>
<td>2,977</td>
<td>2,468</td>
<td>1,991</td>
<td>1,727</td>
<td>46%</td>
</tr>
<tr>
<td>Most deprived</td>
<td>3,845</td>
<td>3,497</td>
<td>3,185</td>
<td>2,752</td>
<td>2,265</td>
<td>1,580</td>
<td>41%</td>
</tr>
<tr>
<td>Q5-Q1 difference</td>
<td>511</td>
<td>570</td>
<td>599</td>
<td>648</td>
<td>635</td>
<td>-124</td>
<td></td>
</tr>
<tr>
<td>Q5/Q1 ratio</td>
<td>1.15</td>
<td>1.19</td>
<td>1.23</td>
<td>1.31</td>
<td>1.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Women ≥ 65 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least deprived</td>
<td>2,848</td>
<td>2,506</td>
<td>2,242</td>
<td>1,892</td>
<td>1,582</td>
<td>1,266</td>
<td>44%</td>
</tr>
<tr>
<td>Q2</td>
<td>2,958</td>
<td>2,617</td>
<td>2,321</td>
<td>2,021</td>
<td>1,763</td>
<td>1,283</td>
<td>43%</td>
</tr>
<tr>
<td>Q3</td>
<td>2,959</td>
<td>2,639</td>
<td>2,369</td>
<td>2,021</td>
<td>1,727</td>
<td>1,232</td>
<td>42%</td>
</tr>
<tr>
<td>Q4</td>
<td>3,114</td>
<td>2,754</td>
<td>2,469</td>
<td>2,122</td>
<td>1,809</td>
<td>1,305</td>
<td>42%</td>
</tr>
<tr>
<td>Most deprived</td>
<td>3,163</td>
<td>2,855</td>
<td>2,585</td>
<td>2,258</td>
<td>1,985</td>
<td>1,178</td>
<td>37%</td>
</tr>
<tr>
<td>Q5-Q1 difference</td>
<td>315</td>
<td>349</td>
<td>343</td>
<td>366</td>
<td>403</td>
<td>-88</td>
<td></td>
</tr>
<tr>
<td>Q5/Q1 ratio</td>
<td>1.11</td>
<td>1.14</td>
<td>1.15</td>
<td>1.19</td>
<td>1.25</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4.1. Age standardised CVD mortality (deaths per 100,000) over time by ward IMD quintile, age group and sex.
Over time (1982-1986 vs. 2002-2006) the absolute differences in CVD mortality between wards in the most and least deprived quintile of IMD reduced by 24% in men and 37% in women in the 30-64 year age group. However, relative differences between quintiles increased as relative declines were, on average, faster in less deprived wards than in the more deprived wards. For the 65 years plus age groups both absolute and relative inequalities between wards in the highest and lowest quintiles of deprivation increased as absolute declines in mortality were on average slower in more deprived wards (Table 4.1).

Figure 4.7. CVD mortality over time. Each dot represents a ward. Colours are IMD quintiles for wards: dark blue = most deprived quintile and light blue = least deprived.
It is of note that in all age-sex groups in each time period differences between wards within a quintile were greater than the overall difference between quintiles. By 2002-2006 rates in the most deprived IMD quintile were equivalent to or lower than rates in the least deprived quintile in 1982-1986 (Figure 4.7).

4.4 Discussion

There has been a 50-66% decline in CVD mortality in England over the 25 years between 1982 and 2006. Not all wards and age groups benefited equally. Although the absolute inequality in CVD mortality between wards reduced at younger ages, relative declines have been faster in less deprived areas than in more deprived ones and the country has become more polarised. Women in older age groups have fared worst; in some wards their CVD mortality has actually risen.

In 2002-2006 CVD mortality in younger age groups (30-64 years) was correlated with area level deprivation, and areas with high mortality were clustered in a band across the north of England and in a few high mortality wards in London. The spatial clustering of high mortality wards and their relationship with deprivation is less clear for older ages.

4.4.1 Strengths

These results are based on national mortality data with complete coverage of the entire population of England. It is feasible to produce stable estimates at ward level for CVD mortality by sex and age group, by borrowing strength across areas, so long as the number of events in multiple area-age-sex-time groups is not near zero. Posterior probabilities for the estimates allow uncertainty to be quantified.
4.4.2 Limitations

The major limitations of the study arise from the nature of routine data. Although statistical uncertainty has been quantified other sources of error are less easy to assess. Causes of death in routine data are often not verified and may be subject to misclassification. IHD mortality in particular has often been used as the “wastepaper basket” cause of death code (see Chapter 3.3.3). Although this is unlikely to vary systematically by area and bias results, it may change the overall estimated mortality.

Population data were not available for wards in some years and had to be estimated from district level populations. There are multiple possible ways of doing this, and the final estimates may be influenced by the method used. Advantages and disadvantages of the differing approaches to the estimation of small-area populations are discussed by Littlefield 2005.(215)

It is not possible from a study such as this to be able to discern whether changes in ward level mortality are due to changes in the health of the population in the ward or due to change in the composition of the ward as a result of in or out-migration. Death data record usual ward of residence at time of death. Previous work has shown a healthy migrant effect in which healthier people tend to migrate to more prosperous areas resulting in worsening patterns of health in the areas they leave behind.(216,217) This study highlights the differences in mortality seen between areas but cannot determine why patterns are changing.

IMD scores for wards were held fixed over the period of analysis with IMD 2007 used throughout. This allowed quintiles to be compared over time. However, wards themselves may change deprivation quintile, although a comparison of older measures of deprivation with newer ones shows relatively high correlation between areas. (Correlation coefficients for IMD 2007
area deprivation score and Carstairs scores from 1981, 1991 and 2001 at district level are 0.92, 0.94 and 0.95 respectively).

In reporting results for 7932 wards it is hard to summarise the data and sometimes it is difficult to see the “wood for the trees”. Furthermore, it was not possible to generate age specific estimates as CVD mortality for younger age groups was near zero for many wards.

4.5 Conclusion

It is feasible to use routine mortality data to produce small area estimates of CVD mortality with clear indication of the certainty with which high and low mortality areas are identified. Historic spatial patterns of high and low mortality in England appear to persist into the twenty-first century despite the dramatic declines seen in overall CVD mortality.

4.6 Summary

This analysis examined the spatial pattern of CVD mortality and its persistence over time in younger and older ages. This sets the context for more detailed spatial analysis of AMI and ACS mortality. Ward level data necessarily include wards with a very limited set of events in some groups, and it may be better to perform district level analysis when narrower causes of death such as ACS and AMI are being examined.
Chapter 5: Comparison of trends in CVD, IHD and ACS mortality and selection of outcomes for further analysis

5.1 Introduction

This chapter describes the age patterns and time trends in CVD, IHD and ACS mortality data. Age categories and primary outcomes chosen for the analysis in Part II of the thesis are defined and justified.

5.2 Methods

In order to understand the mortality data better, I examined age and sex specific mortality rates for CVD, IHD and ACS in England in 2012. I also analysed temporal trends in CVD, IHD and ACS mortality from 1982 and 2012 in men and women aged 30 years and over. These are presented as directly standardised rates using the age structure of the English population from 1982-2012. ICD-9 and ICD-10 codes used to identify CVD, IHD and ACS deaths in the mortality data are given in Table 5.1. ICD-10 has been in use in England since 2002 prior to which ICD-9 coding was used.

Hospitalisation data were available for 2006-2010. I analysed temporal trends in ACS admissions over this period in men and women aged 30 years and over. These are presented as directly standardised rates using the age structure of the English population from 2006-2010. I also analysed the proportion of the ACS admission burden which was due to AMI vs. non-AMI ACS. I grouped admissions into continuous spells of care, prior to analysis. This was done to ensure that an admission for a single event was counted only once even if the patient was
transferred multiple times. The full details of the grouping algorithm are described in Chapter 7.2.1.1.3. References to admissions in this chapter refer to continuous spells. ICD-10 codes I21, I22, I200, I240 or I249 appearing as the primary diagnosis at any point during an admission were used to identify ACS. The choice of diagnostic codes for ACS is discussed in detail in Chapter 7.5.

<table>
<thead>
<tr>
<th>CVD subset</th>
<th>ICD9</th>
<th>ICD 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD</td>
<td>390-459</td>
<td>100-199</td>
</tr>
<tr>
<td>IHD</td>
<td>410-414</td>
<td>120-125</td>
</tr>
<tr>
<td>Stroke</td>
<td>430-438</td>
<td>160-169</td>
</tr>
<tr>
<td>Other CVD</td>
<td>390-405</td>
<td>100-115</td>
</tr>
<tr>
<td></td>
<td>415-429</td>
<td>126-152</td>
</tr>
<tr>
<td></td>
<td>440-459</td>
<td>170-199</td>
</tr>
<tr>
<td>ACS</td>
<td>410</td>
<td>121-122</td>
</tr>
<tr>
<td></td>
<td>411 except 4110</td>
<td>1201-1209</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1200</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1240</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1249</td>
</tr>
<tr>
<td>Other IHD</td>
<td>4110</td>
<td>1201-1209</td>
</tr>
<tr>
<td></td>
<td>412</td>
<td>123</td>
</tr>
<tr>
<td></td>
<td>413</td>
<td>1241-1248</td>
</tr>
<tr>
<td></td>
<td>414</td>
<td>125</td>
</tr>
<tr>
<td>AMI</td>
<td>410</td>
<td>121-122</td>
</tr>
<tr>
<td>Non-AMI ACS</td>
<td>411 except 4110</td>
<td>1200</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1240</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1249</td>
</tr>
</tbody>
</table>

Table 5.1. ICD-9 and ICD-10 codes used to identify CVD mortality and its subsets.
5.3 Results

5.3.1 Mortality data

5.3.1.1 Age and sex patterns

Death rates for CVD, IHD and ACS were close to zero in men until the age of 30 years and very low between 30-45 years, rising exponentially thereafter. For women the first deaths appeared at the age of 35 and the main rise began after the age of 55 (Figure 5.1). The analysis of CVD mortality in Chapter 4 was performed using broad age groups (30-64 years and 65 years and over). For ACS analysis in Part II of the thesis, I used 10 year age bands, and began at age 35 years (Chapter 7.2.1 and Chapter 8.2.2.1) as there were not enough deaths at younger ages to give stable estimates, especially in women.

![Figure 5.1. Age and sex specific death rates for CVD, IHD and ACS in England, 2012.](image-url)
5.3.1.2 Temporal trends

Figure 5.2. Age-standardised CVD death rate in England, 1982-2012.

Since 1982 total CVD mortality has fallen by 69% in men and 66% in women (Figure 5.2). This appears to be heavily driven by the trend in IHD mortality (Figure 5.3) which has fallen by 72% in both sexes; amounting to an absolute decline of 570 IHD deaths per 100,000 in men and 270 in women. Mortality from stroke and other CVDs has also declined but less rapidly than for IHD; stroke mortality fell by 68% in men and 66% in women, but absolute declines in stroke mortality were much smaller than for IHD as baseline stroke mortality in 1982 was lower than IHD mortality.
Figure 5.3. Age-standardised death rates for CVD subtypes in England, 1982-2012.
The most marked declines in IHD mortality were evident for ACS mortality. Mortality for other IHD subtypes remained relatively stable until early 2000’s although there has been some decline since (Figure 5.4). The fall in ACS mortality is the result of the decline in AMI mortality (Figure 5.5). Mortality from non-AMI ACS was extremely low and has remained virtually unchanged (Figure 5.5).
5.3.1.3 Breakdown of deaths by cause

In 2012, CVDs constituted 28% of all deaths in England, and ACS the largest single subset of CVD, accounted for 4.7% of all deaths (Figure 5.6). AMI deaths were 98.2% of all ACS deaths and non-AMI ACS contributed only 1.8%.
5.3.2 Admissions

5.3.2.1 Temporal trends

ACS admissions fell by 14.0% in men and 13.8% in women from 2006-2010. The fall in non-AMI ACS admissions (21.3% in men and 20.8% in women) was more marked than the fall in AMI admissions (10.0% in men and 9.2% in women) over this period (Figure 5.7).
Figure 5.7. Age-standardised admission rates for ACS subtypes in England 2006-2010

5.4 Discussion

CVD mortality has declined rapidly over the last 30 years and this decline is in large part driven by declines in IHD mortality, and in particular ACS mortality. ACS admissions have also declined, but less dramatically than ACS mortality. A sizeable portion of the decline in ACS admissions was due to decline in non-AMI ACS admissions. This may reflect improvements in the sensitivity of diagnostic testing, as a result of which events that would previously have been classified as non-AMI ACS may have shifted to the NSTEMI (AMI) category in recent years (see Chapter 2.2.1). However, it is evident that the decline is not simply a shift phenomenon because the rate of both AMI and non-AMI ACS admissions are falling.
ACS deaths have declined more rapidly than ACS admissions in recent years. Although the fall in mortality predates the introduction of newer policies and procedures for the treatment of ACS, it is likely that some of the continuing decline into the 2000’s can be attributed to more rapid diagnosis and more aggressive treatment as well as more systematic prevention.

AMI and non-AMI ACS result from the same underlying pathophysiology and are treated with the same drugs and interventions, although the urgency of treatment may differ (Chapter 2.2). ACS is the clinical and epidemiological entity of interest as it drives the temporal pattern of CVD decline. It is subject to highly protocolled clinical management and its treatment should be consistent across England. The spatial pattern of ACS in England and the variations in its occurrence and case fatality are unknown.

Figure 5.8. Trade-off between completeness of capture and diagnostic validity of ICD-10 ACS codes

ACS constitutes 16.3% of the overall CVD mortality burden and 11.6% of the CVD admissions burden. Only 1.2% of ACS deaths are due to non-AMI ACS causes. However non-AMI ACS accounts for over one third of all ACS admissions. The diagnosis of non-AMI ACS is based on clinical judgement (chapter 2.2.1). The validity of non-AMI ACS diagnoses is discussed further in Chapter 6.4.2. Figure 5.8 shows the trade-off between certainty of diagnosis and completeness of capture of ACS events. If I were interested only in ACS mortality, it may have been reasonable to omit non-AMI ACS due to the uncertainty in its diagnosis. However, non-AMI ACS events constitute a large portion of the ACS admissions burden. On the balance of these
considerations I decided analyse to analyse AMI as the primary outcome in Part II of the thesis, and to conduct sensitivity analyses for all ACS.

5.5 Conclusion

Declines in ACS mortality have driven the temporal pattern of CVD mortality in England over the last 30 years. Non-AMI ACS contributes very little to the ACS mortality burden but makes up approximately one third of the ACS admissions burden, however it’s coding validity is unknown (see Chapter 6.4.2).

5.6 Summary

ACS is the entity of clinical and epidemiological interest. However, due to the difficulty of establishing the validity of non-AMI ACS diagnoses, I have chosen to analyse AMI as the primary outcome in Part II of the thesis, and to consider all ACS in the sensitivity analysis. Age groups suitable for analysis have been discussed and selected.
Part II - ACS event rates, case fatality and mortality
Chapter 6: Data sources and preparation

6.1 Introduction

Population based cancer registries provide a great deal of information which informs national cancer control strategies. Begun in the 1950’s, the core activity of the population based registry is to record the occurrence of every case of disease over a specified period of time. The comparison of rates between places allows for unexpected accumulations to be observed, and hypotheses about possible causes to be generated. The aim is to recognise and reduce risks.(218) Since their conception population based registries have evolved and now report survival as well as incidence.(219) More recently they have been used to study the effects of various aspects of service provision for prevention, early diagnosis, treatment and care.(220)

A severe limitation in the national management of ACS is the lack of similar population-based information on occurrence and survival. ACS although it remains a leading cause of mortality, is now highly treatable. Community based studies, such as those discussed in Chapter 3.3.4.2 have taught us a great deal about the impacts of advances in ACS diagnosis and treatment, but are not geared to allow international or subnational comparisons.

6.1.1 Preparation of data

There are a number of technical and practical considerations which are common to all population based registries and these are discussed below.
6.1.1.1 Data linkage

In practice the majority of registry data are obtained from hospital and mortality records. An important first step in creating a registry cohort is to link the records pertaining to a single diagnosis together in order to avoid duplicate registration. As survival improves individuals may experience more than one diagnosis, (for example a patient may have more than one cancer or IHD event) and it is important to be able to generate incidence and survival statistics pertaining to a specific event.(220)

6.1.1.2 Case definition

It is not always immediately obvious what constitutes a case of disease. Cancer registries struggle with recording malignant tumours vs. in-situ carcinoma vs. benign tumours which may still cause death via pressure effects such as brain tumours. Furthermore, the point at which a condition becomes a case is somewhat arbitrary and depends on how diligently the diagnosis is sought out, and on the sensitivity of the test used. In diabetes care for example, impaired glucose tolerance may have been present for a number of years before it is detected unless a programme of regular testing has been implemented. Fatal events are more definitive in that they are not subject to variations in clinical practice, but they offer little opportunity for diagnosis; post-mortems are now rare, and causes of death are often assigned on the balance of probability (Chapter 2.2.2).(220)

6.1.1.3 Data quality

The completeness, validity and timing of registry data will influence the interpretation of the results. These should be quantified and stated explicitly.
6.2 Relevant data sources

This work aims to address the gap in population-based information for ACS in England. I aim to construct a population cohort for ACS and use it to describe and compare event rates, mortality and case fatality variations within England. Due to the expansion of routine recording of healthcare interactions, this should now be possible without a formal registration process. Relevant data sources which might be used for this purpose are discussed below.

6.2.1 National mortality data

The Office for National Statistics (ONS) collects information on each death from Local Registration Services in each Local Authority District and from the General Register Office in Southport. Age, sex, place of residence and causes of death for the deceased are then extracted from the death certificates. Since 1993, causes of death listed on the certificates have been coded automatically using software which converts text terms to ICD codes and uses pre-defined rules to assign underlying causes of death. Mortality data are based on the number of deaths registered in each year, around 3-4% of these will have occurred in a previous year and will have been registered with some delay.(221)

6.2.2 National admissions data

The hospital episode statistics (HES) database captures all episodes of care provided at NHS hospitals or at private institutions commissioned by the NHS in England. The primary purpose of HES is to measure hospital activity and reimburse hospitals for the care they deliver. HES data are split into admitted patient data, outpatient attendance data and emergency attendance data. Of these, admitted patient data are the most established. HES data record a series of finished consultant episodes (FCE). An FCE describes the period of time spent by the patient under the
care of a single hospital consultant. If the patient is transferred to the care of second consultant during the admission, or is transferred between hospitals, then a new FCE commences. Each FCE is assigned a primary diagnosis, and up to 19 secondary diagnoses using ICD-10 coding (Figure 6.1). Assignment of primary and secondary ICD codes is based on national rules and is carried out by trained clinical coders. FCEs also record the patient’s age, sex, postcode and a number of additional administrative fields (the HES data dictionary gives more detail).

![Figure 6.1. Structure of English HES data, showing the multiple finished consultant episodes (FCE) and diagnostic code positions available for analysis. The arrows indicate how continuous spells of care, which define a complete admission for each patient, can be constructed. AMI = acute myocardial infarction, ICD = international classification of diseases, MI = myocardial infarction, NOF = neck of femur, PVD = peripheral vascular disease.](image)

### 6.2.3 Primary care data

Data on health service encounters in primary care are collected locally and submitted to the national Health and Social Care Information Centre (HSIC) but are not made available to researchers as yet. Currently, the most comprehensive clinical information on primary care encounters is from the Clinical Practice Research Datalink (CPRD) (formerly known as the
General Practice Research Database). This resource provides anonymised extracts of diagnostic and other information from voluntarily participating general practices in England and covers about 10% of all practices.(224)

6.2.4 Hospital registry data

6.2.4.1 Myocardial Ischaemia National Audit Project

The Myocardial Ischaemia National Audit Project (MINAP) collects data from participating hospitals in England which treat patients with acute ischaemia. It was founded in 1998 as part of a clinical audit program to improve the management of heart attack. The data for STEMI are largely complete but it is estimated that about 50-60% of NSTEMI events are missing from the registry. Participation in MINAP is voluntary and there has been some variability in reporting over time. There is no clear estimate of the number of episodes of unstable angina recorded or missed by MINAP.(225,226) In addition MINAP does not record out-of-hospital AMI in which the patient died soon after the event and was therefore not admitted for angioplasty. Some researchers have attempted to overcome these limitations, by linking MINAP to GP data to generate GP based case fatality rates for AMI.(125) Given the current unavailability of comprehensive national GP data and the uncertainties in GP practice populations and the lack of clarity about hospital catchment areas, this can be somewhat problematic. In addition, out-of-hospital AMI deaths are not systematically captured by GP records.

6.2.4.2 Global Registry of Acute Coronary Events

The Global Registry of Acute Coronary Events (GRACE) was set up in 1999 to track outcomes for hospitalised ACS events, focusing on STEMI, Non-STEMI and unstable angina. The UK
contributes data from one hospital in Scotland to GRACE, but there are no GRACE sites in England.(227)

6.2.5 Defining a comprehensive dataset of ACS events

An important consideration for data sources to be included in the analysis of ACS events was that they provide unbiased, comprehensive national coverage in order that sub-national estimates could then be made. National mortality data for England are complete, with every death registered by law prior to burial/cremation. National hospital admissions data record all admissions to hospitals commissioned by the NHS but miss private hospitals which are independent providers. Overall, care funded fully by the private sector comprised only 3% of total healthcare expenditure for inpatient services in the UK during the time period of the analysis.(228) Furthermore, during the time period of the analysis (2006-2010) fully private institutions in England tended to provide elective and planned procedures, or out-of-hours GP services and minor injury services in urgent care centres, but did not provide treatment for major medical emergencies. Thus, if a patient with ACS presented to a private centre they would probably have been referred onto an NHS emergency unit. It is likely that few, if any, episodes of ACS were treated in fully private institutions over this period. In theory, linked HES and mortality data should thus capture the vast majority of ACS events (fatal and non-fatal). Patients with symptoms of ACS normally present directly to NHS hospital emergency services or present to the GP who institutes an immediate referral to the emergency services under the National Service Framework for cardiovascular disease.(229) However, some patients (with mild or short duration symptoms) may delay presentation perhaps visiting their GP days or weeks after the event, or not at all. These silent or unrecognised ACS events are by definition not captured. The only way to assess their number would be to have a system of ‘hot pursuit’ where GPs are
regularly contacted and the cohort is periodically screened with ECGs. There is currently little data on the contribution of these events to the overall ACS burden.

Primary care data may provide individual level clinical information on patient risk factors for ACS. However they are incomplete at present and practices that participate in the CPRD may perform systematically differently to nonparticipating practices. Finally, MINAP registry data could add information to help verify diagnoses and outcomes, but have variable coverage for non ST elevation events as discussed previously (Section 6.2.4.1).

On the balance of these considerations I decided to use linked national hospitalisation and mortality data to obtain an unbiased national dataset of ACS events. Linked data are used in Chapter 7 and the specifics of data linkage are covered in section 7.2.1.1.

6.3 Case definition

Both ONS mortality and HES use ICD-10 coding to record causes of admission and death. I based identification of AMI and non-AMI ACS on three sources: codes normally used by hospital based registries (MINAP and GRACE), discussions with the coding department at Imperial College NHS Trust, and on national guidance on clinical coding. Table 6.1 shows the final set of ICD-10 codes selected. I21 and I22 refer to AMI and subsequent myocardial infarction which occurs within 28 days of a previous AMI event. AMI occurring more than 4 weeks prior to a current event is coded as I25 (chronic ischaemic heart disease) and is not included as part of the ACS subset. I200 refers to unstable angina, I240 to coronary thrombosis not resulting in myocardial infarction (this can happen if reperfusion occurs very rapidly) and I249 (unspecified acute ischaemic heart disease). I249 is used by clinical coders when ACS has been mentioned in the medical notes but no further details are provided as to whether a STEMI,
NSTemi or unstable angina episode occurred. The mention of the terms ‘Query ACS’ or ‘Possible ACS’ in clinical notes is coded using symptom codes for ‘chest pain’ or ‘dyspnoea’ or similar depending on the presenting symptom, and does not form part of the ACS subset of codes. (PA personal communication with Sucharita Ray, Clinical Coding Auditor, Imperial College NHS Trust).

A further consideration for case ascertainment is the selection of FCEs and primary vs. secondary diagnoses which should be used to capture an event. It is unclear whether only diagnoses appearing in the first FCE of an admission should be used, or whether diagnoses from subsequent FCEs should also be included, and further whether cases should be defined only from primary diagnostic coding positions or from both primary and secondary codes. An empirical analysis of the data exploring the impacts of these possible methods of case ascertainment was undertaken prior to final estimation of event rates and is presented in Chapter 7.

<table>
<thead>
<tr>
<th>ICD-10 code bracket</th>
<th>ICD-10 expanded codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>I20</td>
<td>Angina Pectoris</td>
</tr>
<tr>
<td></td>
<td>120.0 Unstable Angina</td>
</tr>
<tr>
<td>I21</td>
<td>Acute Myocardial Infarction</td>
</tr>
<tr>
<td></td>
<td>121.0 Acute transmural infarction of anterior wall</td>
</tr>
<tr>
<td></td>
<td>121.1 Acute transmural infarction of inferior wall</td>
</tr>
<tr>
<td></td>
<td>121.2 Acute transmural infarction of other sites</td>
</tr>
<tr>
<td></td>
<td>121.3 Acute transmural infarction of unspecified site</td>
</tr>
<tr>
<td></td>
<td>121.4 Acute subendocardial myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>121.9 Acute myocardial infarction, unspecified</td>
</tr>
<tr>
<td>I22</td>
<td>Subsequent Myocardial Infarction</td>
</tr>
<tr>
<td></td>
<td>122.0 Subsequent myocardial infarction of anterior wall</td>
</tr>
<tr>
<td></td>
<td>122.1 Subsequent myocardial infarction of inferior wall</td>
</tr>
<tr>
<td></td>
<td>122.8 Subsequent myocardial infarction of other sites</td>
</tr>
<tr>
<td></td>
<td>122.9 Subsequent myocardial infarction of unspecified site</td>
</tr>
<tr>
<td>I24</td>
<td>Other Ischaemic Heart Disease</td>
</tr>
<tr>
<td></td>
<td>124.0 Coronary thrombosis not resulting in myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>124.9 Acute Ischaemic heart disease, unspecified</td>
</tr>
</tbody>
</table>
Table 6.1. ICD-10 codes used to identify ACS

6.4 Data quality

6.4.1 Completeness of capture

In theory linked HES and mortality data should capture all ACS events in the country except for silent myocardial infarction which is, by definition, not captured and admissions to fully private institutions outside of the NHS (section 6.2.5). Surprisingly, in practice, it appears that between 5-25% of all non-silent AMI that survive to reach hospital are missed by HES data; these figures are derived from small studies as there has been no comprehensive national study of the level of missingness. Herrett et al. (2013) identified a cohort of 13,380 patients who had a record of myocardial infarction in the CPRD database and had also had an acute hospital admission during the same time period. They found that the HES database recorded 12,189 (91.5%) of these as having had an AMI. However, they only counted HES records which documented AMI as the primary diagnosis in the first FCE of an admission, and may have missed a number of AMI recorded only in subsequent FCEs of an admission (see Chapter 6.2.2 and Figure 6.1 for structure of HES data).(125) My own analysis found that 14.6% of primary AMI diagnoses were recorded only in the second or subsequent FCE of an admission (Chapter 7.3.1). CPRD uses a different coding system to HES (READ instead of ICD coding). According to the authors of the study, a history of old myocardial infarction may be coded as an acute event by the CPRD database in some instances. This may account some of the excess events recorded by CPRD. Further work on the coding validity of READ and free-text diagnoses in the CPRD data are needed to verify if the additional events recorded by CPRD are truly acute events which have
been missed by HES (PA personal communication with Emily Herrett first author Herrett et al., 2013).

Silver et al 2009, identified 820 cases of AMI from the OXVASC prospective cohort study in Oxfordshire, which had been validated according to the clinical and diagnostic criteria of European Society of Cardiology. They looked only at the (final) discharge diagnoses in HES for these patients and found that was no mention of any form of IHD in 21.3%. Their failure to examine initial FCEs may be the reason for the large discrepancy. Interestingly, of the 820 cases of AMI in the OXVASC cohort, 17.6% occurred in patients who were already in hospital for other reasons.(126)

Finally Sapsford et al 2003, identified 2153 cases of validated AMI in hospitals in Yorkshire. Of these, the discharge (primary or secondary) diagnostic code in HES again failed to pick up 22.5% of cases. HES codes used for identification were limited to ICD-10 I21 and did not look at FCE prior to discharge. Identification via HES missed fewer cases than identification from a coronary care unit registry or from a biochemistry registry, and was less labour intensive. There did not appear to be any systematic bias in coding between the 20 hospitals which participated, and the authors concluded that HES coding represents a robust and acceptable basis for audit and comparison of rates between centres.(230) My methods of diagnostic capture described fully in Chapter 7.5 are more comprehensive than those used by the studies discussed above, but no active case finding over and above what was recorded in the routine hospitalisation and mortality data was undertaken for this thesis.
6.4.2 Validity

The accuracy of cause of death coding in England conforms to best practice globally. However, as discussed in Chapter 3.3.3, frequency of autopsy in England is low, and CVD deaths may be registered on the basis of a presumptive diagnosis, or may be assigned in favour of an alternative competing cause of death. (85) Previous analysis suggests that the validity of ICD codes in capturing cause of death is high when broad ICD categories, such as I00-I99 denoting all CVD are employed, but becomes less so at finer granularity such as that used for AMI and non-AMI ACS. (75)

McCormick et al 2014, undertook a systematic review and identified thirty studies which validated ICD coded diagnosis of AMI in administrative data (hospital or death records) against clinical review of patient records or AMI registry diagnosis. They analysed the sensitivity (ability of the ICD codes in administrative data to identify true positive cases), specificity (ability of the ICD codes in administrative data to exclude false positive cases) and positive predictive value (the likelihood that an ICD code for AMI corresponds to a true positive case). The ‘gold standard’ for case ascertainment was either the troponin-based Universal Definition of AMI (employed by AMI registries) or the old WHO-MONICA definition of AMI. In general, studies using the Universal Definition of AMI tended to produce higher positive predictive values (PPV) as these were more in line with current clinical practice, whereas those using the old WHO-MONICA definitions as the reference standard had poorer PPV performance. For hospitalisation data, ICD codes identifying definite AMI had an overall sensitivity and specificity greater than 83% and a PPV in excess of 92%. For mortality data, ICD codes performed less well with sensitivity of only 59% in identifying a WHO-MONICA defined ‘definite’ fatal AMI. ICD-10 codes appeared to have better validity than ICD-9 although only two studies on the former were
identified. The accuracy of ICD coding for unstable angina and other non-AMI ACS were not examined.(123)

Metcalf et al 2013, undertook a systematic review of ICD coding of AMI focusing only on hospitalisation data. Their aim was to identify the specific codes which performed best at capturing AMI. They identified 26 validation studies, two of which used ICD-10 coding, to validate AMI against a gold standard of patient record review or registry validated cases. Sensitivity of ICD coding in these was 79-95% and specificity was 89-92%. A further 63 studies were identified which used case definitions of AMI based on ICD-9 (53 studies) or ICD-10 (15 studies), but did not necessarily undertake any validation. Metcalf et al applied the commonly used ICD-9 and ICD-10 definitions for AMI to discharge data for patients at a Canadian hospital. True AMI in the discharge data were validated by direct review of patient records. They found ICD-9 codes 410.x0 in combination with 410.x1 had sensitivity of 84% in capturing AMI, and ICD-10 codes I21 or I22 had sensitivity of 81.8%. All code combinations examined had specificity of greater than 99%. The PPV (82%) was similar for ICD-9 and ICD-10 codes. Use of only the primary diagnostic field missed a variable proportion of cases depending on the code selected. For example, use of ICD-10 codes I21 or I22 in the primary diagnostic position captured only 58% of the cases identified when using IC10 I21 or I22 in any diagnostic position.(124)

No systematic review has looked at the validity of codes used to capture non-AMI ACS events. However, a small previous study suggests that the ICD-9 code for unstable angina has a positive predictive value of only 73%; sensitivity and specificity were not assessed.(164,231)
Overall, ICD-10 codes I21 and I22 appear reasonably sensitive and specific in capturing AMI events in hospitalisation data. The validity of codes used to capture unstable angina and non-AMI ACS is uncertain. The validity of cause of death coding is difficult to establish without new pathological studies. However, there is no evidence to suggest that validity varies systematically by area within England. No further work was undertaken during this thesis to re-assess the validity of ICD coding in HES and mortality data.

6.5 Conclusion

HES and ONS mortality data provide the most comprehensive and unbiased coverage of ACS events in England. They should capture all ACS except silent AMI or delayed presentations to the GP which don’t result in acute admission, which are likely to be few.

6.6 Summary

HES and ONS mortality data will be used to build the national database of ACS events. The sensitivity and validity of ICD-10 codes in admissions and mortality data for identifying ACS events was reviewed. Codes for AMI are sensitive and specific but the coding validity of non-AMI ACS has not been systematically assessed. Coding validity for mortality data is less good than for admissions data.
Chapter 7: Importance of timing of AMI and ACS diagnosis and capture of primary vs. secondary events

7.1 Introduction

AMI often occurs in the context of multi-morbidity and can itself be a comorbid condition, with another more significant diagnosis taking precedence. Primary ACS and in particular primary AMI, have been well studied, but little is known about ACS occurring with a delayed diagnosis, comorbid ACS or death from ACS following a non-ACS admission.

English HES data preserve detailed information about episodes of care under each physician responsible for the patient during an admission; it is possible to interrogate the timing of the episode and prioritisation of a diagnosis as primary vs. secondary. This contrasts with the grouped admissions data in which the entire admission record is summarised into a single discharge diagnosis, which are commonly used in other countries (USA, Canada, New Zealand). Grouping algorithms, which are primarily designed for hospital reimbursement purposes, may deprioritise or increase the priority of one diagnosis over another depending on financial and other considerations, and drop details about timing altogether. HES data are closer to those which might be obtained by a true surveillance study.

Exploiting the richness of the data, I examined the clinical trajectory of patients with delayed ACS diagnoses, those with comorbid diagnoses and those with a non-ACS diagnosis who went on to die of ACS within 28 days of admission, in order to better understand what should constitute a ‘case’ of ACS. I looked at how the inclusion or exclusion of these categories of patients would impact event rates, total and hospital case fatality and proportion of out-of-
hospital deaths. Due to the uncertainty around the validity of non-AMI ACS coding, primary results are reported for AMI events, and all ACS events are reported in the sensitivity analysis.

7.2 Methods

7.2.1 Data

I had access to hospital admissions data from 2006-2010. I linked these to mortality data to create a cohort of all ACS admissions and deaths in adults aged 35 years and over.

7.2.1.1 Data linkage

7.2.1.1.1 HES-mortality linkage

![Venn diagram](image)

**Figure 7.1. Intersection of hospitalisation and mortality data.**

A patient who experiences an ACS event may survive or die. He or she may thus appear in both the national hospitalisation and mortality data depending on his/her outcome (Overlap area in Figure 7.1). Furthermore, a patient who survives may experience more than one ACS event.
In order to avoid duplicate registration of an ACS event appearing in both data sets I applied for permission to link HES data to mortality (forward linkage) and to link mortality data to HES (backward linkage). Permission was sought via the Health and Social Care Information Centre (HSCIC); only permission for forward linkage has been granted to date. This meant that a number of additional steps had to be undertaken to identify out-of-hospital deaths.

The primary identifier in HES data is a unique HESID whilst that in mortality data is NHS number. Thus the two data sets cannot simply be linked together using a single unique identifier as is the case in some European countries. However, increasingly frequently, HES add on NHS number to their records, but ONS mortality does not do the converse.

The HSCIC links ONS mortality data to HES using multiple identifiers (date of birth, sex, and NHS number/postcode). A final link file containing all patients who have experienced both admission and death is supplied to the end user to facilitate forward linkage. The link file gives only HESID and cause of death for each individual appearing in HES (even though linkage is performed on the basis of multiple identifiers). Thus HES data can be readily linked to cause of death data using the link file, but deaths with a prior admission cannot be directly subtracted from the mortality master to obtain out-of-hospital deaths (Figure 7.2) as NHS numbers are not given in the link file.
For my analysis it was essential to know how many out-of-hospital deaths occurred. I therefore looked back through all HES records to see if an NHS number was associated with the HESID at any point in time. If so it was assigned to that HESID, and was used to subtract events with 28-day case fatality from the mortality master. If multiple NHS numbers were associated with a HESID the most recent assignment was used (0.1% of HES records). 3.7% of HES records were not associated with an NHS number at all and could not be subtracted directly. The remaining cases were grouped by age, sex and district of residence and subtracted from the mortality master on the basis of group totals. This identified a final mortality dataset for patients who died of ACS but had no admission in the preceding 28 days. The steps undertaken to identify out-of-hospital deaths are shown more fully in Figure 7.3.
Figure 7.3. Pre-processing of HES and mortality data to identify out-of-hospital deaths.

7.2.1.1.2 Linkage failure

The linkage performed by the HSCIC can sometimes fail. This is usually due to poor quality identifiers (age, sex, postcode, NHS number) in either ONS mortality or HES data.(232) Late registration of death may also result in a person being flagged as having died by the hospital admissions system, but failing to appear in the ONS mortality dataset. HSCIC provide a measure of goodness of match for each record indicating confidence that the ONS record has been correctly matched to a patient in HES (Figure 7.4); 91% of records have a good match the remainder are based on partial matching. Approximately 2.4% of records in HES are flagged as having died but have no corresponding record in the ONS mortality dataset and cannot be matched.(232) This adds additional error to the errors described in section 7.2.1.1.1 which are due to the mismatch between HESID and NHS number.
Figure 7.4. Goodness of match for ONS mortality records with patients in HES. Match rank 0 refers to patients flagged as dead in HES but with no corresponding record in ONS. Match rank 1 and 2 indicate good matches. Match ranks 3-7 indicate increasingly uncertain matches. Adapted from: A Guide to Linked ONS and HES Mortality data. HSCIC, 2013.(232)

7.2.1.3 Within-patient HES linkage

As described in Chapter 6.2.2 (Figure 6.1) the FCE is the basic unit of recording in HES. If a patient is transferred multiple times between consultants and hospitals during their admission and has multiple recordings of their diagnosis, it is important that this stream of activity is grouped into one encounter and not counted multiple times. Some previous studies have overcome this problem by using only the first FCE of an admission, but this may lead to incomplete capture of cases recorded only in the second or subsequent FCE.
99% of all hospitalisations have only a single admission and the majority (88.6%) have only a single FCE. However for ACS hospitalisations 20% consist of multiple admissions implying transfer between hospitals, and 62% had more than one FCE during the time period considered (2006-2010), implying transfer between two or more consultants (PA analysis of HES data 2006-2010). This likely reflects the fact that not all hospitals provided angiography and angioplasty which are the preferred modes of treatment in ACS, and patients were often transferred to centres which did provide these services. Thus aggregation of FCE into continuous spells of care is thus particularly important when analysing patients with ACS.

A number of institutions publish algorithms for grouping within patient HES data to produce continuous in-patient spells of care (CIPS) from FCEs.(233–235) All of these group FCEs occurring within two days of each other into a single ‘spell’ of care (Chapter 6.2.2., Figure 6.1). The algorithms all generate similar numbers of spells from raw HES data inputs.(235) I used the University of York Centre for Health Economics algorithm to group FCEs into CIPS such that each patient event was counted only once regardless of how many times the patient was transferred between consultant and hospitals (Diadone S. 2011, Linking patient episodes in the HES dataset). Figure 6.1 shows how the continuous in-patient spells of care were constructed. All further references to hospitalisations or admissions in this thesis pertain to continuous spells of care.

7.2.1.4 Readmission within 28 days

Following on from previous analyses,(7) I tracked ACS cases for outcomes to 28 days post event. Recurrent episodes of ACS within a 28 day period were counted as part of the same event. This was done to avoid over-inflating case fatality. For example, an ACS event occurring 22
days before death and 17 days before death would be counted as two fatal events if the 28 day rule was not applied – although an individual can in reality of course only die once.

7.2.2 Events

<table>
<thead>
<tr>
<th></th>
<th>ACS admission diagnoses</th>
<th>ACS mortality codes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>(%)</td>
</tr>
<tr>
<td>I21</td>
<td>291,110</td>
<td>51.9</td>
</tr>
<tr>
<td>I22</td>
<td>68,760</td>
<td>12.3</td>
</tr>
<tr>
<td>I200</td>
<td>195,917</td>
<td>35.0</td>
</tr>
<tr>
<td>I240</td>
<td>3,259</td>
<td>0.6</td>
</tr>
<tr>
<td>I249</td>
<td>1,354</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Table 7.1. Frequency and proportions of specific ACS codes in HES and mortality data.

ICD-10 codes I21 and I22 were used to capture AMI, and ICD-10 I200, I240 and I249 were used to capture non-AMI ACS events (see Chapter 6.3). The frequency and proportions of occurrence of these codes in the final dataset are given in Table 7.1. ACS events in the mortality data were extracted based on underlying cause of death.

In order to understand the types of ACS being captured, patients were grouped into four categories:

i) those with ACS as a primary condition diagnosed during the first physician encounter of an admission (recoded in ICD-10 code position 1 Figure 6.1)

ii) those with ACS as a primary condition (recoded in ICD-10 code position 1 Figure 6.1) diagnosed during any subsequent physician encounter of the admission
iii) those with ACS recorded as a comorbid/secondary condition (ICD-10 code position 2-20 Figure 6.1), but not as a primary diagnosis, during any physician encounter of the admission

iv) those admitted with a non-ACS diagnosis who died of ACS within 28 days

Patients were followed up for mortality outcomes for 28 days, and a final category of patients who died of ACS but had no preceding admission was also examined.

**7.2.3 Statistical analysis**

Event rates and case fatality were calculated for each group. In addition records of patients with delayed and comorbid diagnoses of ACS and those with a non-ACS admission who went on to die of ACS were tracked backwards within HES to explore their primary admission diagnoses. Deaths were broken down by cause to explore the effects of restricting case fatality to ACS deaths vs. all cause death.

The impacts of including patients with delayed ACS diagnoses, comorbid diagnoses and non-ACS diagnoses with ACS death with 28 days on crude national event rate (fatal and non-fatal events), total case fatality (fatal events/ all events) and proportion of out-of-hospital deaths was estimated.

**7.2.4 Sensitivity analysis**

Coding validity for non-AMI ACS is not established (Chapter 6.4.2), thus primary results are reported for AMI and results for all ACS are reported in the sensitivity analysis.

Previous studies have excluded events coded as non-emergency or admissions lasting less than one day as it was suspected that these may be cases where a patient was assessed for ACS but
was found not to have it.\textsuperscript{(154)} The cohort was restricted to those with emergency admissions and those with admissions greater than one day to assess this.

7.3 Results

7.3.1 Admissions

There were 359,870 admissions recording AMI as a primary or secondary diagnosis in the hospitalisation data (Table 7.2). Of these, 81\% recorded AMI as the main diagnosis and 6 out of 7 of these the primary AMI was diagnosed during the first physician encounter of the admission.

Delayed capture of AMI i.e. in the second or subsequent physician encounter during an admission formed a slightly higher proportion of admissions in women and in older age groups. Where the main diagnosis of AMI was recorded with delay, the primary diagnosis in the first encounter frequently captured precursors of AMI such as unspecified chest pain, unstable angina, atherosclerotic heart disease, precordial pain, dyspnoea and syncope.
| Age Group | Males | | | | | | Females | | | | | | All | | | | | |
|-----------|-------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|           | Total | Non-fatal | Fatal (%) | Total | Non-fatal | Fatal (%) | Total | Non-fatal | Fatal (%) | Total | Non-fatal | Fatal (%) | Total | Non-fatal | Fatal (%) | Total | Non-fatal | Fatal (%) | Total | Non-fatal | Fatal (%) |
| 35-44     | 9,339 | 9,179 | 160 (1.7) | 2,942 | 2,879 | 63 (2.1) | 3,884 | 3,587 | 297 (7.6) | 10,475 | 10,265 | 210 (2.0) | 14,364 | 14,130 | 234 (1.6) | 24,839 | 24,395 | 444 (1.8) |
| 45-54     | 37,222 | 36,324 | 898 (2.4) | 12,346 | 12,017 | 329 (2.7) | 14,592 | 14,130 | 462 (3.2) | 53,860 | 52,451 | 1,409 (2.7) | 76,682 | 74,882 | 1,800 (2.4) | 151,544 | 148,333 | 3,211 (2.1) |
| 55-64     | 43,522 | 41,545 | 1977 (4.5) | 4,886 | 4,613 | 255 (5.2) | 7,264 | 6,189 | 1075 (14.8) | 51,389 | 47,268 | 4,121 (8.7) | 98,677 | 91,457 | 7,220 (7.9) | 190,066 | 178,725 | 11,341 (6.0) |
| 65-74     | 46,137 | 42,004 | 4133 (9.0) | 6,969 | 6,163 | 806 (11.6) | 10,943 | 8,136 | 2807 (25.7) | 57,080 | 50,140 | 6,940 (13.9) | 107,227 | 98,274 | 8,953 (9.2) | 214,307 | 198,414 | 15,893 (8.2) |
| 75-84     | 45,730 | 37,709 | 8021 (17.5) | 8,845 | 7,089 | 1756 (19.9) | 15,411 | 9,676 | 5735 (37.2) | 91,261 | 75,418 | 15,843 (21.1) | 166,490 | 140,632 | 25,858 (18.3) | 336,741 | 291,044 | 45,697 (15.3) |
| 85+       | 22,052 | 16,083 | 5969 (27.1) | 4,797 | 3,349 | 1448 (30.2) | 8,909 | 4,797 | 4112 (46.2) | 30,051 | 22,872 | 7,179 (31.7) | 52,103 | 38,955 | 13,148 (33.9) | 82,154 | 61,827 | 20,327 (32.8) |
|           |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |
| All       | 307,496 | 267,832 | 39664 (12.9) | 52,374 | 43,618 | 8756 (16.7) | 86,874 | 59,393 | 27481 (31.6) | 594,370 | 508,225 | 86,145 (16.9) | 1,102,861 | 941,530 | 161,331 (17.1) | 2,207,231 | 1,849,755 | 357,476 (19.1) |

Table 7.2. AMI types in linked HES – mortality data by age and sex.
19% of admissions recorded AMI only as a secondary diagnosis. Comorbid AMI was significantly more common in older age groups; 1 in 4 AMI diagnoses in those over the age of 85 years fell into this category, compared to 12% of AMIs in the 35-44 year old age group. Frequently recorded primary diagnoses in persons with comorbid AMI were: atherosclerotic heart disease, pneumonia, COPD, atrial fibrillation, stroke, heart failure and fractured neck of femur (Figure 7.5).

![Diagram](image)

Figure 7.5. Primary causes of admission in patients with comorbid AMI and in patients with a non-AMI admission who went on to die of AMI within 28 days.

### 7.3.2 Hospital case fatality

Case fatality for patients with a primary diagnosis of AMI made during the first physician encounter and those with a slightly delayed diagnosis in subsequent encounters was similar, ranging from 1.7%-30% depending on age and sex (Figure 7.6). Case fatality for comorbid AMI however, was 2-3 times that for primary AMI.
Figure 7.6. Event rates and case fatality for primary AMI recorded during the first and subsequent physician encounters (left and middle) and for comorbid AMI diagnoses (right).

Two thirds of deaths within 28 days of an AMI admission were due to AMI (Figure 7.7), 7% were due to other IHD such as chronic ischaemic heart disease, 5.5% due to respiratory causes, and a further 4.6% due to other circulatory disease such as stroke and peripheral vascular disease.
7.3.3 Mortality

There were 135,950 AMI deaths in total. Just under half of these patients (49%) had an admission in the 28 days preceding death; 24% with a primary AMI diagnosis and 25% with no primary AMI diagnosis (Figure 7.8). Common causes of admission in persons with a non-AMI admission who went on to die of AMI were other circulatory diagnoses including atrial fibrillation and heart failure (34%), symptomatic diagnoses including chest pain and dyspnoea (28%), respiratory diagnoses (14%) and injuries in particular fractured neck of femur (9%) (Figure 7.5).

Figure 7.7. Primary causes of death in patients with a primary AMI admission who died within 28 days of admission.
7.3.4 National estimates

Crude national event rate (for non-fatal plus fatal AMI) was 288 per 100,000 if admissions were restricted to those with a primary diagnosis of AMI in the first physician encounter, as previous studies have done. Total case fatality was 36%, hospital case fatality 13%, and proportion of out-of-hospital deaths (defined as having no relevant recent admission) 73%. As the additional categories of AMI (those with delayed diagnosis, those with comorbid diagnosis and those with a non-AMI diagnoses who went on to die of AMI in 28 days) were included in the count of AMI admissions, the proportion of out-of-hospital deaths fell and the total event rate increased (Figure 7.9).
Figure 7.9. Incremental impact of counting admissions with delayed diagnosis of AMI, with comorbid AMI and with non-AMI diagnosis followed by AMI death on national estimates of event rate, total case fatality and hospitalised case fatality and proportion of out-of-hospital deaths, compared to baseline of primary AMI diagnosed during the first encounter.

7.4 Sensitivity analysis

7.4.1 ACS admissions

The inclusion of non-AMI ACS led to a 60% increase in the total number of admissions (primary and secondary) compared to AMI alone. Of the 722,014 ACS admissions 22% were comorbid diagnoses whilst the remainder were primary diagnoses. Event rates for primary diagnoses of ACS were 20-30% higher than those for AMI in men, and 30-50% higher in women. Case fatality for both primary and comorbid admissions was lower than for AMI, especially in women (Table 7.3).
### Table 7.3. Event rate and case fatality for ACS subtypes in linked HES-mortality data by age and sex 2006-2010. CI = confidence interval.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Event rate (CI) per 100,000</th>
<th>Case fatality (%)</th>
<th>Event rate (CI) per 100,000</th>
<th>Case fatality (%)</th>
<th>Event rate (CI) per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-44</td>
<td>88 (71-108)</td>
<td>1.13</td>
<td>13 (7-22)</td>
<td>3.41</td>
<td>1 (0-6)</td>
</tr>
<tr>
<td>45-54</td>
<td>284 (252-319)</td>
<td>1.62</td>
<td>47 (35-63)</td>
<td>4.43</td>
<td>2 (0-7)</td>
</tr>
<tr>
<td>55-64</td>
<td>507 (464-553)</td>
<td>3.2</td>
<td>107 (88-129)</td>
<td>8.68</td>
<td>7 (3-14)</td>
</tr>
<tr>
<td>65-74</td>
<td>812 (757-870)</td>
<td>6.58</td>
<td>222 (194-253)</td>
<td>15.42</td>
<td>24 (15-36)</td>
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<tr>
<td>75-84</td>
<td>1321 (1251-1394)</td>
<td>13.54</td>
<td>450 (409-494)</td>
<td>26.8</td>
<td>67 (52-85)</td>
</tr>
<tr>
<td>85+</td>
<td>2113 (2024-2205)</td>
<td>22.9</td>
<td>828 (773-886)</td>
<td>37.44</td>
<td>162 (138-189)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-44</td>
<td>26 (17-38)</td>
<td>1.48</td>
<td>4 (1-10)</td>
<td>6.01</td>
<td>0 (0-4)</td>
</tr>
<tr>
<td>45-54</td>
<td>92 (74-113)</td>
<td>1.69</td>
<td>16 (9-26)</td>
<td>6.62</td>
<td>1 (0-6)</td>
</tr>
<tr>
<td>55-64</td>
<td>183 (157-212)</td>
<td>3.12</td>
<td>41 (29-56)</td>
<td>10.58</td>
<td>3 (1-9)</td>
</tr>
<tr>
<td>65-74</td>
<td>409 (370-451)</td>
<td>6.62</td>
<td>116 (96-139)</td>
<td>16.12</td>
<td>10 (5-18)</td>
</tr>
<tr>
<td>75-84</td>
<td>837 (781-896)</td>
<td>13.11</td>
<td>296 (263-332)</td>
<td>25.15</td>
<td>39 (28-53)</td>
</tr>
<tr>
<td>85+</td>
<td>1445 (1371-1521)</td>
<td>22.26</td>
<td>613 (565-664)</td>
<td>34.4</td>
<td>105 (86-127)</td>
</tr>
</tbody>
</table>

CI: Confidence interval

### 7.4.2 ACS mortality

There were a total of 136,833 deaths which recorded ACS as an underlying cause (only 0.6% more than those which recorded AMI as an underlying cause). The proportions of these with and without a preceding primary ACS admission were similar to AMI.

### 7.4.3 Non-emergency and short stay admissions

Event rates for primary diagnoses of AMI were reduced by 1.2% if short stay admissions were excluded and by 5% if non-emergency admissions were excluded. Case fatality showed little change.
7.5 Discussion

Changes in case definition have dramatic impact on event rates, hospital case fatality and proportion of out-of-hospital deaths. The commonly used method of defining an AMI admission by extracting admissions with a primary diagnosis of AMI in the first physician encounter misses 14% of all AMI admissions with a primary diagnosis, and almost 20% of all admissions.(236,237) The definition of out-of-hospital death as one in which there has been no primary AMI admission in the last 28 days inflates the proportion of out-of-hospital deaths and reduces hospital case fatality.(154) These finding have four main implications:

First, we see that admissions in which the main diagnoses of AMI is delayed to the second or subsequent encounters often have precursor symptoms of recorded AMI in their first physician encounter. These probably represent cases of suspected AMI in which results of confirmatory tests were being awaited before a final diagnosis was assigned. Case fatality in these patients is similar to that for primary AMI diagnosed in the first physician encounter. Treatment with blood thinning and anti-platelet agents may have begun presumptively, prior to confirmation of diagnosis in these cases.

Second, patients with comorbid AMI have 2-3 times the case fatality of patients with primary AMI. They tend to be older and female and frequently have a ‘stressor’ condition such as fractured neck of femur or pneumonia recorded as the primary reason for admission. The universal definition of myocardial infarction sub-classifies AMI into Type 1 AMI where cardiac ischemia is caused by the formation of acute thrombus in the coronary arteries and Type 2 where it is caused by an imbalance in myocardial oxygen supply and demand. The majority of AMI recorded as comorbid events in our data appear to fall into the Type 2 category and are likely to
benefit from haemodynamic optimisation in the first instance, rather than routine ACS treatment. Further, previous audits show that the recording of secondary conditions, including AMI is much less consistent between hospital trusts than that of primary conditions.(238)

Third, surprisingly, about half of all patients with non-AMI admission who go on to die of AMI have precursor symptoms such as non-specific chest pain, dyspnoea or syncope recorded during admission, or have been admitted with a non-AMI circulatory condition which shares risk factors with AMI. These may represent a high risk group in which symptoms heralding a fatal AMI have been missed. It is unclear whether such cases should be classed as hospital associated rather than out-of-hospital deaths as they are currently, especially as 79% are still in the hospital at the time of death.

Fourth, non-AMI ACS almost doubles the number of admissions captured when using AMI codes only. Total and hospital case fatality for ACS are lower than that for AMI. The majority of non-AMI ACS, are coded as I200 (unstable angina) which is by definition troponin negative. Troponin negative events have better prognosis than those which are troponin positive ones.(239) Some poorly defined myocardial infarctions are also likely to be captured by the non-AMI ACS code I249 (acute ischaemic heart disease, unspecified). However the diagnostic and coding validity for non-AMI ACS are unknown (see Chapter 6.4.2), and the increase in completeness of capture may come at the expense of validity.

Finally the exclusion of short stay and non-emergency patients from the cohort has little impact on case fatality. It is now feasible to rapidly diagnose, treat and safely discharge a low risk patient who has had a true acute event, within 24-48 hours, and as such, exclusion of short-stay and non-emergency patients may lead to an underestimation of AMI event rates.(240,241)
Case definition is a trade-off between completeness of capture and fidelity to the condition under consideration (Figure 5.8 in Chapter 5.4). In the light of my findings I decided:

- To report primary results for AMI only
- To use all primary diagnoses of AMI in the first physician encounter, regardless of whether they occurred with delay or not, to capture AMI admissions
- To exclude admissions with only a comorbid diagnosis of AMI
- To use underlying cause of death to capture AMI deaths
- To perform sensitivity analyses in which patients with a comorbid AMI or non-AMI admission in the 28 days preceding AMI death are grouped with hospital case fatality rather than out-of-hospital deaths
- To report secondary results for ACS

### 7.5.1 Strengths

This is an empirical analysis of the data to inform case definition for AMI and ACS events. My results are based on a cohort that covers almost the entire population of England. Record linkage simultaneously captures hospitalised and out-of-hospital AMI, both fatal and non-fatal allowing the clinical trajectory of the condition to be fully followed. Previous studies in a few other countries where record linkage is feasible have produced estimates of AMI event rates, case fatality and proportion of out-of-hospital deaths, and other measures of quality of care.(64,67,68,242–246) HES data have the additional advantage of allowing the role of AMI with delayed and secondary diagnosis, which have previously been excluded, to be considered.
7.5.2 Limitations

The limitations largely pertain to the nature of routine data. Clinical criteria for case-ascertainment of AMI were defined for cohort studies, and do not translate well to routine ICD-10 coded data. ICD-10 codes do not record ECG or laboratory findings and do not distinguish between ST elevation and non-ST elevation myocardial infarction (Chapter 2.3). I was unable to verify AMI events against ECG and laboratory findings, and was forced to rely on the routine coding. The sensitivity, specificity and completeness of capture of HES and mortality data (Chapter 6.4), and the linkage process itself are imperfect (Chapter 7.2.1.1.2).

Although imperfect, the use of a national dataset, which captures events as comprehensively as possible for routine surveillance may allow us to draw conclusions about sub-national variation in event rates and case fatality, and may allow changes in the sub-national patterns to be tracked into the future.

7.6 Conclusions

Clear case definition is critical for event rates and case fatality to be interpreted correctly. All primary AMI diagnoses, regardless of whether they are captured during the first physician encounter or captured with some delay probably represent the same condition. Some non-AMI diagnoses resulting in AMI death within 28 days may also represent missed cases of AMI. AMI in the main probably represents a separate pathophysiological process (Type 2 AMI).

7.7 Summary

This chapter looked at timing and prioritisation of diagnostic codes in the HES data in order to decide which should be used to define a ‘case’ of AMI or ACS.
Chapter 8: Event rates, case fatality and mortality by English district

8.1 Introduction

Differentials in IHD mortality drive the Northern excess in mortality seen in England. These differentials are marked (2-3 fold) and persistent (Chapter 1.1).

Previous work has attempted to correlate these differentials across space to factors like IMD and smoking, but has not attempted to break them down into the two aspects of disease which make up the mortality burden; event rates and case fatality.

Mortality = event rates * case fatality

8.1.1 Previous work

Temporal declines have frequently been subjected to a decomposition analysis. The seminal example of this is from the WHO-MONICA studies which estimated that approximately two-thirds of the decline in IHD mortality between the 1980’s and the 1990’s was due to declines in occurrence or event rate and approximately one-third due to the improvement in case fatality.(7) More recently, using linked national data, it was estimated that just over 50% of the decline in national AMI mortality between 2002-2010 in England was due to a fall in event rates and just under 50% due to a fall in case fatality.(175) The contribution of event rates vs. case fatality to the temporal declines in IHD mortality varies between countries and between regions. For example, not all countries in the MONICA study experienced a fall in case fatality; in 12 of the 37 countries case fatality rose. In some places, such as Denmark, Sweden, Germany and Finland
this was offset by large falls in event rates, leading to a decline in overall IHD mortality, but in other countries (mostly in Eastern Europe), mortality increased.(7)

Overall studies have attributed a larger proportion of the temporal declines in IHD mortality to measures which affect the background rate of events, than to health system improvements which ameliorate the probability of death following an event. However, the rationale for distinguishing between prevention and treatment, first posed in the 1970’s before the tremendous advances in AMI care of the 1980’s and 1990’s (Figure 2.3, Chapter 2.2), is now somewhat outmoded. Treatment of an acute event now includes the prescription of anti-hypertensives, anti-platelet agents and lipid lowering agents which may themselves reduce the risk of a further event, and thus event rate. Primary prevention is no longer limited to lifestyle change, but extends to screening (247) and prescription of risk-modifying medication in persons deemed to be at high risk of a first event.(248) Thus, the question is not so much about the effectiveness of treatment, which is now well established, but about the relative burden which is due to event rates and case fatality.

The ability of a specific factor to explain the regional inequalities is dependent on the extent of the heterogeneity in that factor between places and the extent to which that heterogeneity is related to the variation in mortality. The variable which contributes the largest proportion to the total AMI burden may not be the one which is responsible for the relative inequalities between places.(249) For example, cholesterol levels are highly associated with IHD mortality; the British Regional Heart Study (BRHS) found cholesterol levels in British men to be elevated throughout the country, with little variation between towns during the 1970’s and 1980’s. Thus whilst high cholesterol levels explained the high mortality rates seen in British men, they did not explain the excess mortality seen in some towns vs. others.(31)
This analysis seeks to estimate the variation in event rates and case fatality across districts in England to assess their contribution to the spatial variation in AMI mortality. The analysis in Chapter 9 will further determine whether the spatial variation in case fatality is related to variation in case fatality for hospitalised AMI or to the proportion of events which result in out-of-hospital AMI death.

8.2 Methods

8.2.1 Data

8.2.1.1 Units of analysis

Mortality, event rates and case fatality were estimated for each of the 354 Local Authority Districts in England. Separate estimates were produced for males and females aged 45-54, 55-64, 65-74, 75-84, and 85 years and over. Estimates in 35-45 year olds were highly unstable and did not converge due to sparseness of data (see Chapter 5.3.1.1). This group was dropped from further analysis.

8.2.1.2 Events

I used linked national hospitalisation and mortality data for adults aged 45 years and over from 2006-2010 to identify AMI events. Linkage has been described in detail in Chapter 7.2.1.1, and inclusion and exclusion criteria for AMI events are described in Chapter 7.5. In brief, any hospitalisation with a primary diagnosis of AMI was counted as an AMI admission. AMIs diagnosed as secondary or comorbid events and non-AMI admissions were included only if they led to an AMI death within 28 days. Death from any cause within 28 days of AMI admission was
counted as part of AMI mortality in addition to all deaths coded to AMI. The data were grouped into three distinct, mutually exclusive and collectively exhaustive AMI categories:

A – hospitalised with AMI and survived to 28 days

B – hospitalised with AMI and died by day 28

C – died of AMI but not hospitalised for AMI in the 28 days preceding death

The three groups A, B and C represent different aspects of a single disease process and are likely to share commonalities as well as to exhibit some differences in their spatial distribution. The rates for these events were modelled using a Bayesian shared component model.

8.2.1.3 Population

Population data were from ONS and were based on decennial census counts available by age and sex in census years. ONS also produces annual Local Authority District level population estimates in inter-censal years based on a cohort component method, where the baseline population estimates are updated with population change due to births, deaths and net migration from other administrative sources. These can be subject to some error especially because migration is not precisely known. ONS district level population projections were revised to align them with the 2011 endpoint census estimates prior to use.

8.2.1.4 Area deprivation

IMD was used as the measure of area deprivation. The constituents of the IMD score are fully described in Chapter 4.2.2.3. Lower super-output area (LSOA) level scores were aggregated to district level using LSOA:district population ratios. IMD is a non-linear measure, thus districts were assigned to deciles or quintiles of IMD for analysis.
8.2.2 Sensitivity analysis

Non-AMI ACS forms 36% of the primary ACS admissions burden (see Chapter 5.4) and may therefore influence the results of the current analysis considerably. However, the diagnostic and coding validity of non-AMI ACS events (discussed in Chapter 6.4.2) is unknown. The primary analysis was thus performed for AMI events which are captured with high validity, and a sensitivity analysis is reported for all ACS events which include both AMI and non-AMI ACS.

8.2.3 Bayesian shared component models

If multiple health outcomes share a similar geographical pattern then joint modelling improves the precision of the estimation over separate analysis of each outcome, as strength can be borrowed between disease outcomes. Joint modelling also allows consistent estimation of the uncertainty across outcomes. The Besag, York and Mollie (BYM) model used in Chapter 4.2.3, has been extended by Knorr-Held and Best to a ‘shared component’ model for two diseases. The probability of an event is partitioned into a component which is shared between the two outcomes plus additional components which model heterogeneity from the shared pattern.

For example, in the case of two related outcomes $Y_1$ and $Y_2$, both of which are Poisson distributed, the number of observations of outcome 1 in area $i$ can be written as $Y_{1i} \sim P(\lambda_{1i} \times n_i)$, where $\lambda_1$ is the rate of disease 1 and $n$ is the population at risk. Similarly the number of observations of outcome 2 can be written as $Y_{2i} \sim P(\lambda_{2i} \times n_i)$ where $\lambda_2$ is the rate of disease 2. The shared component model can then be written as:
\[ \log(\lambda_{1i}) = \alpha_1 + \phi_i \]
\[ \log(\lambda_{2i}) = \alpha_2 + \phi_i \cdot \delta + \psi_{2i} \]

(Model 2a)

Where:

\( \alpha \) = intercept global (national) mean for each outcome

\( \phi \) = risk for outcome 1

\( \delta \) = weight parameter

\( \psi_{2i} \) = specific component for outcome 2

If \( \phi_i \) is the risk for outcome 1 in each area \( i \), then \( \psi_{2i} \) represents the difference in risk between outcome 2 and outcome 1 in each area. The weight term \( \delta \) is used to scale \( \phi \) to the appropriate magnitude for representing risks of outcome 2. An alternative specification expands model 2a to include a specific component for disease outcome 1 making it symmetric.(252) In this case:

\[ \log(\lambda_{1i}) = \alpha_1 + \phi_i \cdot \delta_1 + \psi_{1i} \]
\[ \log(\lambda_{2i}) = \alpha_2 + \phi_i \cdot \delta_2 + \psi_{2i} \]

(Model 2b)

Where:

\( \alpha \) = intercept global (national) mean for each outcome

\( \phi \) = shared component
\( \delta = \text{weight parameter} \)

\( \psi_1 = \text{specific component for outcome 1} \)

\( \psi_2 = \text{specific component for outcome 2} \)

\( \phi_i \) now represents the shared component of the risk for outcomes 1 and 2 in each area, and \( \delta_1 \) and \( \delta_2 \) scale the relative contribution of the shared term to each outcome. (The sum \( \sum_{k=1}^{n} \log \delta_k \) is constrained to equal zero in order to ensure identifiability). The disease specific components \( \psi_{1i} \) and \( \psi_{2i} \) can be viewed as the differential for each outcome from the shared pattern of risk \( \phi_i \). Prior distributions can then be assigned to the shared (\( \phi \)) and disease-specific (\( \psi \)) components, which may allow one or both components to exhibit spatial clustering.

Best and Hansell 2009,(254) made use of a shared component model, jointly estimating the geographical risk for lung cancer and chronic obstructive pulmonary disease (COPD) in England, both of which are largely driven by tobacco smoking. The shared component was interpreted to represent tobacco exposure whilst an additional specific component for COPD was used to identify high risk areas in which factors other than smoking may be important.(254) Held et al. 2005 extended the principle further to model multiple diseases. Their model includes a primary shared component for all diseases being analysed, and additional shared components for subsets of diseases thought to be aetiollogically related, as well as components specific to one or more individual diseases.(255) More recently Richardson et al. 2006 studied spatio-temporal differences in male and female lung cancer mortality by extending their models to include shared components across the two outcomes for both spatial and temporal risk, as well as an additional specific component to capture the female differential in spatio-temporal risk.(256) Tzala et al. 2008, similarly extended their models to explore the shared spatio-temporal risk for six cancers.
in Greece, adding further interaction terms and disease specific components to improve their estimates. In addition to providing better inference, shared component models potentially identify shared patterns of spatial variation between different health outcomes which could be indicative of regional differences in underlying risk or provision of health care services.

8.2.3.1 Model selection

Figure 8.1. A selection of the models tested for analysis of event rates, case fatality, hospital case fatality proportion of out-of-hospital deaths and mortality. BYM = Besag, York and Mollie prior. CAR = conditional auto-regressive prior. V = independent univariate normal prior. A = hospitalised with AMI and survived to 28 days. B = hospitalised with AMI and died by day 28. C = died of AMI but not hospitalised in the 28 days preceding death.

I used a shared, three component model to estimate rates for the three distinct categories of AMI A, B and C (where A = hospitalised with AMI and survived to 28 days, B = hospitalised with AMI and died by day 28 and C = died of AMI but not hospitalised for AMI in the 28 days preceding death). Various specifications of the shared three-component model were tried. Each had a shared component representing the common risk for all three AMI categories in each district and additional specific components allowing the risk for specific AMI categories to vary away from the shared pattern. The prior distributions for the shared and specific components were altered to try to produce stable estimates with maximum efficiency. As such, I wanted to choose a model which would smooth sufficiently to overcome ‘noise’ or random variation.
between districts without over-smoothing to the extent of obscuring true variation. Model were fitted using Markov-chain Monte-Carlo (MCMC) algorithms with two starting chains and convergence of the two chains was required to produce stable estimates.

A selection of the models tested is shown in diagrammatically in Figure 8.1 and the priors used for each model are given in the text underneath. All models had a spatially structured prior on the shared component (i.e. it was assumed that areas which are closer together are more similar in their common risk for all three AMI categories than areas which are further apart) Model 24 and Model 27 had additional spatially structured priors, either BYM or CAR, on the individual (category specific) components of risk. This led to an increase in the overall number of parameters to be estimated and made convergence problematic in some age-sex groups (e.g. 45-54 year old females where data were sparse). In addition I was concerned that these models may over-smooth; the shared component was already introducing some local smoothing and the additional spatial structures for each specific outcome were then forcing events within categories A, B and C to be overly similar to their neighbours. Model 3 and 23 had Gaussian normal prior distributions for the individual (category specific) components of risk. These two models performed similarly in terms of estimation efficiency and convergence but Model 3 gave more flexibility for estimation of category A. I looked for evidence of correlation between the variation in the specific components, but found little to endorse this (see example in Figure 8.2) – providing further support for the use of independent normal priors on the specific components. A number of other possible model were considered but were dropped due to computational limitations, failure of convergence or concerns about over vs. under smoothing.
Figure 8.2. Correlation between the variance of the specific components of model 3 (psi1, psi2, psi3) after the shared component has been taken into account (sample plot for males age 65-74 years).

Model 3 was chosen as the final model. Model 3 had a BYM prior on the shared component of the random effect, $\phi_i$, allowing local and global smoothing between areas, and independent normal priors on the specific components for each category $k$, ($\psi_{ki}$), allowing individual outcomes to vary away from the shared pattern in each area. The specification of Model 3 for categories A, B and C was:

$$\log(\lambda_{Ai}) = \alpha_A + \phi_i \ast \delta_A + \psi_{Ai}$$

$$\log(\lambda_{Bi}) = \alpha_B + \phi_i \ast \delta_B + \psi_{Bi}$$

$$\log(\lambda_{Ci}) = \alpha_C + \phi_i \ast \delta_C + \psi_{Ci}$$

(Model 3)

Where:

$i = 354$ local authority districts in England

$\alpha = \text{intercept global (national) mean event rate for each category}$

$\phi = \text{risk shared by all three outcomes with a BYM prior}$
\[ \delta = \text{weight parameter for each outcome, constrained in order to ensure identifiability} \]

\[ \psi = \text{individual (category specific) component of risk for each outcome} \]

8.2.3.2 Model fitting

The models were fitted using the Markov chain Monte-Carlo algorithm in WinBUGS 14 (http://www.mrc-bsu.cam.ac.uk/software/bugs/the-bugs-project-winbugs/) an open source software which performs Bayesian inference using Gibbs sampling. (257) Models were run via R3.12 using the package R2Winbugs. Models were checked for convergence using Brooks-Gelman-Rubin diagnostics as well as with graphical checks of the chains and their autocorrelations. All models were run with two chains and estimates of rates of A, B and C were based on a collection of 5000 samples following burn in and appropriate thinning.

8.2.4 Statistical analysis

The outcomes of interest for this analysis were:

Event rate: A+B+C

Mortality: B+C

Case fatality: (B+C)/(A+B+C)

Estimated rates for AMI categories A, B and C were combined at each McMC draw (i.e. for each of the 5000 iterations) to calculate the outcomes of interest above and their posterior probability distributions. Posterior probability values range from 0 to 1. A posterior probability value close to 0 indicates high confidence in an estimated rate which is smaller than the national average and a value close to 1 indicates high confidence in an estimated rate which is larger than the national
average. A posterior probability of 0.5 indicates a rate which is indistinguishable from the national average (see Chapter 4.2.4).

Both age specific and age-standardised results are reported Direct age standardisation was performed using the English population from 2006-2010 as the reference population. When reporting summary measures of case fatality, I standardised the results using age weights based on the number of events in each age bracket rather than population, since the number of events needs to be held constant when comparing case fatality between districts.

I assessed the contribution of event rates and case fatality to between district variations in mortality was assessed using Poisson regressions (Generalised Linear Models (GLM) with a log link). The response variable in the Poisson regressions was the count of AMI deaths in each district, offset by the district population. I assessed the deviance of the null model in which there are no covariates to predict district mortality and compared this with the deviance of a model in which a) event rate was used as a predictor and b) case fatality was used as a predictor. The percentage reduction in deviance for each model a) and b), when compared to that of the null model was interpreted as representing the variation in mortality explained by each predictor. Once the predictor which accounted for the greater part of the variation in mortality had been identified, I ran a multivariate analysis, adding the second predictor to the first to see how much additional variation in mortality could be explained, conditioning on the first predictor already being in the model.
8.3 Results

8.3.1 Event rates

There were a total of 536,404 AMI events in adults aged 45 and over from 2006-2010 of which 61% occurred in men. Just over two-thirds of these events (359,870) were admissions with a primary diagnosis of AMI.

![Graph showing age-standardised rates for AMI events, AMI events leading to death and deaths assigned to AMI for men and women, 2006-2010. Rates have been standardised to the overall structure of the English population, 2006-2010.](image)

Event rates started at 641 per 100,000 for men in 2006 and decreased to 542 per 100,000 by 2010, equivalent to a 15.4% decline (Figure 8.3). Corresponding figures for women were 307 per
100,000 in 2006 declining to 264 per 100,000 by 2010 (14% decline). Age specific event rates increased exponentially across 10 year age brackets starting at the national median of 189 (men) and 40 (women) per 100,000 in the 45-54 year age group and rising to 2219 (men) and 1520 (women) per 100,000 in the 85+ age bracket (Figure 8.4). There was wide variation in event rates between districts and this was especially marked for the open ended 85+ age group. This may reflect the variability in the population age structure in this group, where some areas have proportionately more 85-100 year olds compared to poorer areas in which the majority of the 85+ age group fall into the 85-90 year old category.

Figure 8.4. AMI event rates in men and women by age. Each dot represents the estimate for one district.
8.3.1.1 Event rates and area deprivation

Lowest median event rates were in the least deprived decile of IMD (491 (men) and 230 (women) per 100,000) and highest in the most deprived decile (692 (men) and 343 (women) per 100,000). However the difference across deciles was small except in the most deprived areas (deciles 9 and 10) and the variation within deciles was larger than the variation between deciles (Figure 8.5).

Figure 8.5. Age standardised AMI event rates for men and women by decile of district IMD deprivation score. Each dot represents the estimate for one district. Horizontal bars are the median values for districts in each decile.

8.3.1.2 Geography of AMI event rates

Event rates and their posterior probabilities for each district are shown in the middle panels of Figure 8.12a-j at the end of the chapter and Appendix A provides a map of English geography. Event rates were high in a swathe across England, running from the metropolitan areas around
Manchester and Merseyside through Derbyshire, Nottinghamshire, Leicestershire, Lincolnshire and down into Cambridgeshire and Suffolk especially at older ages. Rates were also high in a band across the North from Cumbria through to Durham and North Yorkshire. There were also consistent pockets of high rates in Cornwall. Areas with consistently low event rates ran along the south coast and through the South West covering Oxfordshire, Gloucestershire and Hampshire as well as East Riding of Yorkshire, Scarborough and York in the North.

Within London, the North West and North East had the highest event rates with rates in Newham and Waltham Forest particularly marked in younger ages but not in older age groups (75+). Westminster and Kensington and Chelsea as well as the south west of London (with the exception of Kingston-upon-Thames) had low event rates. Spatial patterns for event rate were similar to those of mortality and distinct from case fatality.

### 8.3.2 Mortality

There were a total of 165,561 fatal AMI (deaths following an AMI event and deaths assigned to AMI cause) in adults over the age of 45 from 2006-2010 (Figure 8.3). 56% of these deaths occurred in men. Age standardised AMI mortality started off at 227 (men) and 117 (women) per 100,000 in 2006 and declined by 26.4% (men) and 25.6% (women) over the 5 year period to reach 167 (men) and 87 (women) per 100,000 by 2010. Declines in mortality were more rapid than the corresponding declines in event rate (section 8.3.1). AMI mortality was highly correlated with deaths with AMI recorded as the underlying cause (deaths assigned to AMI in Figure 8.3). There was a 2.4 fold difference in AMI mortality between the 1st (best) and 99th (worst) percentile of districts in men and a 2.3 fold difference in women.
8.3.2.1 Mortality and area deprivation

As with CVD mortality, AMI mortality showed some correlation with IMD, although the variation within IMD deciles was larger than that between deciles (Figure 8.6). The correlation of AMI mortality with IMD was stronger than that of event rate or case fatality.

![Figure 8.6. Age standardised AMI mortality for men and women by decile of district IMD deprivation score. Each dot represents the estimate for one district. Horizontal bars are the median values for districts in each decile.](image)

8.3.2.2 Mortality and geography

District AMI mortality and the posterior probability for each estimate are shown in the left hand panels of the maps in Figure 8.12a-j at the end of the chapter. As with CVD mortality, there were high rates across the North East and North West of England and low rates in Southern England. In London, the North East had the highest mortality. Rates in Newham and Tower Hamlets were
particularly high, with Kingston-upon-Thames, Brent and Hounslow also coming into play as high mortality areas at older ages.

8.3.3 Case fatality

Median age-specific case fatality rates were similar in men and women, starting at 13.2% (men) and 13.1% (women) for ages 45-54 and rising to 50.3% in both men and women aged 85 and above (Figure 8.7).

![AMI case fatality in men and women by age. Each dot represents the estimate for one district.](image)

8.3.3.1 Case fatality and area deprivation

Once the number of events in each age group had been accounted for there was very little residual trend in case fatality by IMD decile (Figure 8.8); however the most deprived decile of districts did contain the areas with the highest event standardised case fatality in England.
Figure 8.8. Age standardised AMI case fatality for men and women by decile of district IMD deprivation score. Each dot represents the estimate for one district. Horizontal bars are the median values for districts in each decile.

8.3.3.2 Geography of case fatality

The spatial pattern of case fatality was quite distinct from that of event rates and mortality, and did not follow a clear North-South gradient. High and low case fatality areas were scattered throughout the country. Districts with the highest case fatality were in London (Southwark, Lambeth and Waltham Forest), the North West (Blackpool) and the West Midlands (Birmingham and Sandwell). Maps of age specific case fatality and its posterior probability are shown in the right hand panel of Figure 8.12a-j at the end of the chapter. Case fatality at the oldest ages (75-84 years and 85+ years) demonstrated more spatial structure than in middle age. Total case fatality in young women aged 45-54 years (Figure 8.12f) was low (~13%) and the
estimates were less certain than for other age groups as there are very few deaths. This is reflected in the flatter posterior probability maps for this group.

8.3.4 Contributions of event rates and case fatality to mortality

Event rates and case fatality were not correlated across districts (Figure 8.9a and 8.9b). Districts with high event rates inevitably fell into the highest decile of mortality regardless of whether their case fatality rates were high or low. Conversely districts with high case fatality sometimes fell into lower mortality deciles if event rates were low. Thus event rates appeared to have a greater influence on mortality than case fatality. This was borne out by the Poisson regression (Table 8.1). When event rate was used to predict the variation in mortality across districts the deviance in the null (no covariate) model was reduced by ~65-85% depending on age and sex. When case fatality was used to predict the mortality response, the deviance in the null model was reduced by ~1.5-55% depending on age and sex. When case fatality was added into a model already containing event rate, the contribution of case fatality to the variation in mortality was reduced for younger age groups (45-64 years) and increased at older ages, compared to a univariate model in which case fatality was the sole predictor. Overall case fatality explained 15-30% of deviance once event rates had been accounted for. As such, event rate was the more important explanatory variable and case fatality became useful when conditioned on event rate, but was poorly correlated with mortality by itself especially in older people (age 75+).
Figure 8.9a. Relationship between event rates and case fatality across English districts in men. Each dot represents one district. Districts are coloured by decile of district mortality. Black lines are national median values for district event rate and case fatality.
Figure 8.9b. Relationship between event rates and case fatality across English districts in women. Each dot represents one district. Districts are coloured by decile of district mortality. Black lines are national median values for district event rate and case fatality.
### Table 8.1. Poisson regression with AMI mortality as outcome variable. Univariate analysis 1 adjusted for event rate, univariate analysis 2 adjusted for case fatality and the multivariate analysis adjusted for both event rate and case fatality.¹

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Univariate analysis 1</th>
<th>Univariate analysis 2</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deviance explained by event rate (%)</td>
<td>Deviance explained by case fatality (%)</td>
<td>Deviance explained by case fatality in addition to that explained by event rate (%)</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-54</td>
<td>80.2</td>
<td>41.5</td>
<td>17.7</td>
</tr>
<tr>
<td>55-64</td>
<td>65.9</td>
<td>55.8</td>
<td>32.8</td>
</tr>
<tr>
<td>65-74</td>
<td>67.6</td>
<td>47.1</td>
<td>31.3</td>
</tr>
<tr>
<td>75-84</td>
<td>72.4</td>
<td>14.5</td>
<td>26.0</td>
</tr>
<tr>
<td>85+</td>
<td>80.2</td>
<td>1.5</td>
<td>16.8</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-54</td>
<td>83.8</td>
<td>10.6</td>
<td>1.3</td>
</tr>
<tr>
<td>55-64</td>
<td>81.3</td>
<td>23.1</td>
<td>15.3</td>
</tr>
<tr>
<td>65-74</td>
<td>80.2</td>
<td>24.5</td>
<td>17.7</td>
</tr>
<tr>
<td>75-84</td>
<td>72.3</td>
<td>5.0</td>
<td>25.3</td>
</tr>
<tr>
<td>85+</td>
<td>79.0</td>
<td>12.2</td>
<td>16.6</td>
</tr>
</tbody>
</table>

Figure 8.10a and 8.10b show similar plots of event rates against case fatality but coloured by district deprivation quintile. Low deprivation districts tended to cluster in the low event rate-low case fatality group (bottom left of plot). There were however, high deprivation districts with low event rates, low case fatality or both scattered throughout.

¹ model1 <- glm(DeathCount ~ 1 + EventRate + offset(log(DistrictPopulation)), family="poisson")
model2 <- glm(DeathCount ~ 1 + CaseFatality + offset(log(DistrictPopulation)), family="poisson")
model3 <- glm(Deathcount ~ 1 + EventRate + CaseFatality + offset(log(DistrictPopulation)), family="poisson")
Figure 8.10a. Relationship between event rates and case fatality across English districts in men. Each dot represents one district. Districts are coloured by quintile of district deprivation. Black lines are national median values for district event rate and case fatality.
Figure 8.10b. Relationship between event rates and case fatality across English districts in women. Each dot represents one district. Districts are coloured by quintile of district deprivation. Black lines are national median values for district event rate and case fatality.
8.4 Sensitivity analysis

<table>
<thead>
<tr>
<th></th>
<th>Event rate (per 100,000)</th>
<th>Case fatality (%)</th>
<th>Mortality (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AMI</td>
<td>ACS</td>
<td>AMI</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-54</td>
<td>188</td>
<td>276</td>
<td>13.24</td>
</tr>
<tr>
<td>55-64</td>
<td>359</td>
<td>523</td>
<td>18.31</td>
</tr>
<tr>
<td>65-74</td>
<td>617</td>
<td>881</td>
<td>26.73</td>
</tr>
<tr>
<td>75-84</td>
<td>1,184</td>
<td>1,564</td>
<td>39.64</td>
</tr>
<tr>
<td>85+</td>
<td>2,219</td>
<td>2,719</td>
<td>50.14</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-54</td>
<td>40</td>
<td>80</td>
<td>13.15</td>
</tr>
<tr>
<td>55-64</td>
<td>97</td>
<td>170</td>
<td>16.97</td>
</tr>
<tr>
<td>65-74</td>
<td>266</td>
<td>414</td>
<td>25.95</td>
</tr>
<tr>
<td>75-84</td>
<td>693</td>
<td>963</td>
<td>37.99</td>
</tr>
<tr>
<td>85+</td>
<td>1,521</td>
<td>1,871</td>
<td>50.16</td>
</tr>
</tbody>
</table>

Table 8.2. Event rates, case fatality and mortality for AMI and ACS by age and sex. Values are medians across all English districts.

Event rates for ACS were 37% higher in men than for AMI alone and 46% higher in women (Table 8.2). The proportionate increase in event rates when including non-AMI ACS was more marked for younger age groups and for women. Non-AMI ACS was rarely coded as a cause of death and thus mortality rates were almost the same for AMI and ACS; this resulted in ACS case fatality being 25-30% lower than case fatality for AMI. The correlation between event rates and area deprivation score increased markedly from 0.54 in men and women to 0.65 (CI 0.59-0.71) in men and 0.64 (CI 0.56-0.70) in women (Figure 8.11), but that for case fatality worsened a little. The overall relationship between event rates and case fatality was still poor, and event rates continued to explain the majority of the between district variation in mortality (Table 8.3).
Figure 8.11. Correlation between district ACS event rate and district IMD 2007 deprivation score (sensitivity analysis).
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Deviance explained by event rate (%)</th>
<th>Deviance explained by case fatality (%)</th>
<th>Deviance explained by case fatality in addition to that explained by event rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-54</td>
<td>73.4</td>
<td>22.1</td>
<td>23.2</td>
</tr>
<tr>
<td>55-64</td>
<td>57.7</td>
<td>44.8</td>
<td>40.2</td>
</tr>
<tr>
<td>65-74</td>
<td>63.1</td>
<td>39.6</td>
<td>35.3</td>
</tr>
<tr>
<td>75-84</td>
<td>68.6</td>
<td>29.0</td>
<td>30.3</td>
</tr>
<tr>
<td>85+</td>
<td>80.2</td>
<td>0.2</td>
<td>17.5</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-54</td>
<td>82.4</td>
<td>48.3</td>
<td>0.1</td>
</tr>
<tr>
<td>55-64</td>
<td>74.3</td>
<td>9.0</td>
<td>19.6</td>
</tr>
<tr>
<td>65-74</td>
<td>72.8</td>
<td>21.0</td>
<td>24.4</td>
</tr>
<tr>
<td>75-84</td>
<td>72.7</td>
<td>14.3</td>
<td>25.6</td>
</tr>
<tr>
<td>85+</td>
<td>80.8</td>
<td>6.8</td>
<td>15.8</td>
</tr>
</tbody>
</table>

Table 8.3. Results of Poisson regression with ACS mortality as outcome variable.²

8.5 Discussion

Event rates explained between two-thirds and four-fifths of the between district variation in AMI mortality – 3-5 times as much as was explained by case fatality. Once event rates were accounted for, case fatality showed little correlation with district IMD. The clinical and policy implications of these findings are discussed below.

First, event rates are the primary drivers of the persistent variation in AMI mortality between districts in England. Event rates can be influenced to some extent by primary and secondary

² model1 <- glm(DeathCount ~ 1 + EventRate + offset(log(DistrictPopulation)), family="poisson")
model2 <- glm(DeathCount ~ 1 + CaseFatality + offset(log(DistrictPopulation)), family="poisson")
model3 <- glm(DeathCount ~ 1 + EventRate + CaseFatality + offset(log(DistrictPopulation)), family="poisson")
prevention strategies, but they are also subject to the wider social determinants of health over which the NHS has little control. We can see this in the spatial distribution of districts with high event rates, which mirrors that of high mortality areas and reflects patterns of entrenched regional and local poverty. (258–262) The larger urban and metropolitan centres of the North West of England which have been repeatedly worst hit during recurrent recessions, and show the slowest post-recession recovery, demonstrate this well. For AMI, the relationship between event rates and IMD is weak for lower (less deprived) deciles of IMD, however the highest event rates are always found in the most deprived areas, and what correlation there is, is driven by areas with the highest deprivation scores. Interestingly, for non-AMI ACS there appears to be a stronger area deprivation gradient such that the correlation of all ACS with IMD is much better than for AMI alone. Local health authorities may benefit from knowing that AMI and ACS mortality will be impacted more by ameliorating event rates than by focusing on case fatality. Treatment of AMI and secondary prevention, will of course play a part in this strategy, given that one in six events is a recurrence, (175) but a narrow focus on hospital case fatality rates or hospital standardised mortality ratios is unlikely to address regional inequalities in AMI and ACS mortality.

Second, there is variability in case fatality across districts, but this does not appear to be systematic. Case fatality shows little relationship with IMD, suggesting that the NHS performs equally well in all areas. Universal health coverage and access to high quality care have been shown to mitigate inequalities in health. (263) There is evidence that use of general practice and some secondary care services is the same or higher in more deprived areas in England. (264) However, equality of access does not guarantee equality of health outcomes and individuals from
higher socioeconomic backgrounds still tend to benefit preferentially even in deprived areas. (265)

Factors such as the severity of the event, the delay between the patient first experiencing symptoms and calling for help, time taken for help to reach the patient, time taken to establish a diagnosis and the speed and appropriateness of treatment can all influence case fatality patterns. These factors themselves are influenced by the behaviours and beliefs of both patients and health care providers, as well as structural and infrastructure problems such as the quality of roads, and time needed to get to the nearest hospital with relevant facilities, which vary from place to place. The more geographically confluent areas of high case fatality in the oldest age groups may reflect, for example, local NHS policies on resuscitation in elderly patients with multiple comorbidities or a similar variation in practice. Of course they may also reflect a case mix of more severe events or events with more complex comorbidities in those areas. It is not possible to distinguish between the two without further study. As expected, case fatality for ACS is markedly lower than for AMI alone. It is well known that troponin negative events tend to have better outcomes than ones in which troponin is raised, (239) and this analysis has quantified that effect at population level.

This study draws attention to areas of particular interest where event rates are low but case fatality is high (Southwark and Lambeth) and others where event rates are high whilst case fatality is low (Ipswich). These are explored further in the next chapter to see if these case fatality patterns are related to hospital case fatality or to out-of-hospital deaths.
8.5.1 Strengths

This is the first decompositional analysis of the spatial variation in AMI mortality in England and provides new information into the drivers of this variation and how it might best be addressed. The results are based on nationwide data which cover the entire population. The Bayesian shared component model helped to borrow strength in places and across outcomes where numbers of events were small and subject to more sampling noise, producing more robust estimates and taking into account the correlations between outcomes. Furthermore, the uncertainty for each estimate has been quantified. The data sources used are updated at regular intervals and the analysis could be repeated to explore persistent spatio-temporal patterns or track the impacts of policy change as more data become available.

8.5.2 Limitations

The main limitations arise from the nature of routine data which are recorded for administrative rather than clinical or epidemiological purposes. Completeness of coverage and validity of coding have been discussed in Chapter 6.4. Silent and unrecognised AMI are inevitably missed by this type of analysis of routine data which does not undertake active case-finding (see Chapter 6.2.5). The inclusion of all ACS codes rather than just traditional AMI codes is likely to improve the comprehensiveness of AMI capture as some non-AMI ACS codes capture poorly coded AMI. However, this comes at the expense of validity (Chapter 5.4 and chapter 6.4.2). ICD-10 codes do not record information on ECG and enzyme tests in individuals making it impossible to verify events using routine data sources alone, and forcing a reliance on the final summary code assigned. Further, information on the validity of certification of causes of death comes from studies performed in the 1950’s-1970’s and needs to be updated. Finally, it was not possible to
assess how uneven coding practice is across the country; it may be that some areas record less serious events more consistently than others and that this accounts for a proportion of the variability in event rates and case fatality seen.

All models are to some extent imperfect and there are an infinite number of permutations and combinations of shared and specific components and their priors which may have fit these data. I made a pragmatic decision based on my clinical and epidemiological understanding of the disease entity, and on practical considerations about convergence.

Finally, the IMD area deprivation score is measured at LSOA level and aggregation to district level may cause dilution of the relationships seen between health outcomes and area deprivation for LSOAs. The scores themselves capture deprivation imperfectly, especially in older age groups and women.

**8.6 Conclusion**

Decompositional analysis of the spatial variation in AMI mortality shows that event rates drive the variation. The NHS performs reasonably robustly with no systematic differences seen in case fatality between deprived and less deprived areas. Focus on the wider determinants of health, outside the scope of the NHS, may be the key to reducing persistent geographical variation.
Figure 8.12a. Mortality, event rate and case fatality (top left to right) and corresponding posterior probabilities (bottom) for men aged 45-54 years. Boxed area = London
Figure 8.12b. Mortality, event rate and case fatality (top left to right) and corresponding posterior probabilities (bottom) for men aged 55-64 years. Boxed area = London.
Figure 8.12c. Mortality, event rate and case fatality (top left to right) and corresponding posterior probabilities (bottom) for men aged 65-74 years. Boxed area = London.
Figure 8.12d. Mortality, event rate and case fatality (top left to right) and corresponding posterior probabilities (bottom) for men aged 75-84 years. Boxed area = London.
Figure 8.12e. Mortality, event rate and case fatality (top left to right) and corresponding posterior probabilities (bottom) for men aged 85+ years. Boxed area = London.
Figure 8.12f. Mortality, event rate and case fatality (top left to right) and corresponding posterior probabilities (bottom) for women aged 45-54 years. Boxed area = London.
Figure 8.12g. Mortality, event rate and case fatality (top left to right) and corresponding posterior probabilities (bottom) for women aged 55-64 years. Boxed area = London.
Figure 8.12h. Mortality, event rate and case fatality (top left to right) and corresponding posterior probabilities (bottom) for women aged 65-74 years. Boxed area = London.
Figure 8.12i. Mortality, event rate and case fatality (top left to right) and corresponding posterior probabilities (bottom) for women aged 75-84 years. Boxed area = London.
Figure 8.12j. Mortality, event rate and case fatality (top left to right) and corresponding posterior probabilities (bottom) for women aged 85+ years. Boxed area = London.
Chapter 9: Hospital case fatality and proportion out-of-hospital deaths by English district

9.1 Introduction

Case fatality varies by 49% in men and 45% in women between the 1st percentile of districts with lowest case fatality and the 99th percentile with highest case fatality in England (Chapter 8.3.3). Total case fatality is affected by pre-hospital deaths and hospital case fatality.

Hospital case fatality has been the outcome measure in numerous previous studies addressing quality of care. This is partly because hospitalised patients admitted are a population in whom highly standardised treatments can be applied in a systematic manner, and whose outcomes can be measured accurately. Despite clinical guidelines specifying the best practice for treatment of AMI, the data show substantial variation in clinical practice between hospitals which may translate to variations in hospital case fatality. (266–268) For example, Krumholz et al. 2003 observed that patients with AMI in New England were prescribed beta blockers and aspirin more frequently and had reperfusion therapy less frequently than in other regions of the USA, These differences persisted after adjusting for patient case-mix and provider characteristics and was associated with a 30 day case fatality rate that was four percentage points lower than in other regions. (267)

The proportion of AMI deaths which occur prior to hospitalisation has been reported as being the same or larger than the proportion following admission. (154,171,174) AMI has very high mortality in the first few minutes and hours after onset. (171) Pre-hospital deaths or heralding signs of impending death are less easy to identify and intervene on as the victims are not being
monitored. In addition, it is not always clear which persons are at highest risk of pre-hospital death. Thus interventions to limit pre-hospital mortality have been less well studied and have been more difficult to implement systematically than those for reducing hospital case fatality. Strategies have mainly focused on reducing the high early mortality by reducing delay between symptom onset and treatment. These include public education campaigns to raise awareness of symptoms and empowering patients to call for help early,(269) making automated defibrillators available in public places, encouraging bystander resuscitation whilst waiting for help,(270) early use of ECG by ambulance staff to identify AMI, service reorganisation to allow ambulances to call ahead and alert hospitals that an AMI is on the way and reorganisations allowing ambulances to take patients directly to hospitals which can provide reperfusion,(51) monitoring and reduction of ambulance response times and hospital ‘door-to-reperfusion’ times. Service reorganisations have successfully reduced the time between hospitalisation and reperfusion considerably since the late 1990’s, and it is now less than 90 minutes in most areas of England,(15) but the average delay between onset of first symptoms and call for help is also 90 minutes.(16,18,176) Further, approximately 40% of pre-hospital AMI deaths are unwitnessed events which cannot be helped by a bystander.(92)

This analysis examines the variations in hospital case fatality and the proportion of AMI events which are out-of-hospital deaths, across districts in England. I also examine the relationship of these two factors with the variation in overall case fatality, as I did in Chapter 8.3.4 for event rate and case fatality in relation to AMI and ACS mortality.
9.2 Methods

This analysis used the data, and Bayesian shared component model described in Chapter 8 sections 8.2.1 to 8.2.3.

9.2.1 Statistical analysis

The outcomes of interest for this analysis were:

Hospital case fatality: \( \frac{B}{A+B} \)

Proportion of events resulting in out-of-hospital death: \( \frac{C}{A+B+C} \)

The estimates for AMI categories A, B and C (Model 3 Chapter 8.2.1.2) where:

A – hospitalised with AMI and survived to 28 days

B – hospitalised with AMI and died by day 28

C – died of AMI but not hospitalised for AMI in the 28 days preceding death

were combined at each McMC draw (i.e. each of the 5000 iterations for estimation) to calculate the above outcomes of interest and their posterior probability distributions. A posterior probability value close to 0 indicates high confidence in an estimated rate which is smaller than the national average and a value close to 1 indicates high confidence in an estimated rate which is larger than the national average. A posterior probability of 0.5 indicates a rate which is indistinguishable from the national average (see Chapter 4.2.4).

I report both age-specific and age-standardised results. When reporting age standardised results, I standardised total case fatality and proportion of events resulting in out-of-hospital death using
event weights, and hospital case fatality using admission weights. Event rates need to be held constant when comparing case fatality and proportion of all events which result in out-of-hospital death, and admissions need to be held constant when comparing hospital case fatality.

I used linear regression to assess the relationship of hospital case fatality and proportion of all events resulting in out-of-hospital death with total case fatality. Both the response variable (total case fatality) and predictor variables were logit transformed prior to regression. I compared the residual sum of squares (RSS) in the null model with no covariates to the RSS in a model in which a) proportion of all events resulting in out-of-hospital death was used as a predictor and b) hospital case fatality was used as a predictor. The reduction in RSS was interpreted as indicating the proportion of variance in total case fatality which could be explained by each predictor. Hospital case fatality and proportion of events which resulted in out-of-hospital death were highly collinear and it was thus not appropriate to include them in the same model. I therefore do not report the relative contribution of each predictor in a multivariate model, as the results are not readily interpretable.

**9.2.2 Sensitivity analysis**

In previous studies, patients who were hospitalised with a non-AMI diagnosis or a comorbid AMI diagnosis in the 28 days preceding AMI death have been counted with out-of-hospital deaths.(7,175) My initial analysis of national data demonstrated that over three quarters of such patients are actually still in the hospital at the time of their death (Chapter 7.3.3). This assignment has little bearing on estimates of total case fatality, but estimates of hospital case fatality and out-of-hospital deaths as a proportion of all events are significantly impacted by the assignment of these cases to group B vs. group C (Figure 9.1). I report baseline results for the
traditional grouping shown in Figure 9.1a, and also explore in sensitivity analysis the groupings shown in Figure 9.1b where only patients who truly had no admission in the 28 days preceding death were counted as having an out-of-hospital death.

![Figure 9.1. Grouping of AMI data for a) the primary analysis and b) the sensitivity analysis.](image)

Primary results are reported for AMI events and a second sensitivity analysis was conducted for all ACS events as before (Chapter 8.2.2).

### 9.3 Results

#### 9.3.1 Proportion of all events resulting in out-of-hospital death

Out-of-hospital deaths made up 11.2% of all events in men aged 45-54 years (median value for age group), rising to 31.0% of all events in men aged 85 years and over. The proportions were 1-2% lower for women in younger age groups, but by the time women reached the 85+ age group the fraction of out-of-hospital deaths as a proportion of all events in women was equal to that of men (Figure 9.2).
Figure 9.2. Proportion of all events resulting in out-of-hospital death by age. Each dot represents a district. Horizontal bars are district medians.

9.3.1.1 Out-of-hospital deaths and area deprivation

The proportion of all events which resulted in an out-of-hospital death did not correlate well with area deprivation score (correlation coefficient 0.21 in men and 0.11 in women). However, areas with the most extreme values for proportion of events leading to out-of-hospital death did fall into the most deprived decile of IMD (Figure 9.3).
9.3.1.2 Geography of out-of-hospital deaths

The spatial pattern for the proportion of events which resulted in out-of-hospital death was almost the inverse of the pattern seen for overall mortality in older age groups; there was an excess of out-of-hospital deaths in South Western rural areas of England (Devon, Cornwall, Dorset and Somerset) for ages 75-84 years and age 85+ (maps of proportion of all events resulting in out-of-hospital death are presented in Figure 9.9a-j middle panel at the end of this chapter). In younger age groups highest proportions of events leading to an out-of-hospital death were seen in the North West, the North East and in South Yorkshire.
9.3.2 Hospital case fatality

Age standardised hospital case fatality was 13.6% in men and 14.3% in women (median of district values). Age specific rates ranged from a median of 2.3% in men aged 45-54 years to 27.7% in men aged 85 years and over. The corresponding rates were approximately 1% higher in women below the age of 75 years but equivalent thereafter (Figure 9.4).

Figure 9.4. Hospital case fatality by age. Each dot represents a district. Horizontal bars are district medians.

9.3.2.1 Hospital case fatality and area deprivation

Hospital case fatality was marginally more correlated with IMD than proportion of all events which result in an out-of-hospital death, but overall the correlation was still poor (Figure 9.5).
9.3.2.2 Geography of hospital case fatality

There was a 1.2-1.6 fold variation in hospital case fatality between districts depending on age and sex. Hospital case fatality rates were highest in the North West in the majority of age groups. For the oldest age group (85+ years) hospital case fatality rates were highest in the South West for both men and women. They were also high in the South West for women age 45-54 years, but results in women aged 45-54 years are likely to be unstable as there are very few AMI deaths in this group. This is reflected in the very flat posterior probability map in this group with all values being close to 0.5 (Figure 9.9a-j at end of chapter, left-hand panels). Within London there appeared to be an East-West divide with higher hospital case fatality generally being seen in the East.
9.3.3 Influence of proportion of all events resulting in out-of-hospital death and hospital case fatality on total case fatality

Out-of-hospital deaths as a proportion of all events and hospital case fatality were somewhat correlated with each other, correlation coefficient 0.44 (CI 0.35-0.52) in men and 0.56 (CI 0.48-0.62) in women (Figure 9.6a and 9.6b). Both variables had a significant effect on total case fatality in univariate regression analysis, but proportion of all events which resulted in out-of-hospital death reduced over 90% of the residual deviance when considered alone (Table 9.1). Hospital case fatality appeared to have more influence overall in women than men. For men, hospital case fatality had more effect in middle ages than in the youngest and oldest age groups. For women larger proportions of the variability in total case fatality was accounted for by the variation in hospital case fatality at younger and older ages than in the 65-74 year age group.
Figure 9.6a. Relationship between out-of-hospital deaths as a proportion of all events and hospital case fatality across English districts in men coloured by district case fatality decile.
Figure 9.6b. Relationship between out-of-hospital deaths as a proportion of all events and hospital case fatality across English districts in women coloured by district case fatality decile.
<table>
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<th>Univariate analysis 1</th>
<th>Univariate analysis 2</th>
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<td></td>
<td>Variation explained by out-of-hospital deaths as a proportion of all events (%)</td>
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Table 9.1. Results of univariate regression analysis with case fatality as outcome variable. Analysis 1 logit case fatality adjusted for logit out-of-hospital deaths as a proportion of all events. Analysis 2 logit case fatality adjusted for logit hospital case fatality.³

9.3.4 Sensitivity analysis

9.3.4.1 True out-of-hospital deaths

When only true out-of-hospital deaths were counted in group C, and admissions without a primary diagnosis of AMI which resulted in AMI death within 28 days were shifted into group B (Figure 9.1b), the number of events in group B increased by 40% and hospital case fatality rose to 21.5% in men and 22% in women. The variability in hospital case fatality between the first and 99th percentile of districts also increased 1.3-1.9 fold depending on age and sex, and hospital

³ model1<-lm(logitCaseFatality~logitOut-of-hospital-deaths-as-a-proportion-of-all-events)
model2<-lm(logitCaseFatality~logitHospitalCaseFatality)
case fatality became more strongly correlated with total case fatality. The correlation between proportion of all events resulting in out-of-hospital death and total case fatality remained strong (there were large numbers of events in group C to start with and shifting some of these to group B had little effect on group C). Thus hospital case fatality and proportion of all events resulting in out-of-hospital death became more closely aligned across districts (correlation coefficient 0.68 (CI 0.62-0.73) in men and 0.72 (CI 0.66-0.77) in women) and as a result hospital case fatality exerted a more equal influence on total case fatality than in the primary analysis. This is demonstrated visually in the cross plots in Figure 9.7a and 9.7b and confirmed in the linear regressions (Table 9.2). Interestingly both hospital case fatality and the proportion of all events resulting in out-of-hospital deaths correlated even less well with area deprivation when the proportion of out-of-hospital deaths was restricted to those which were true out-of-hospital deaths.
Figure 9.7a. Relationship between out-of-hospital deaths as a proportion of all events and hospital case fatality across English districts in men coloured by district case fatality decile (sensitivity analysis).
Figure 9.7b. Relationship between out-of-hospital deaths as a proportion of all events and hospital case fatality across English districts in women coloured by district case fatality decile (sensitivity analysis).
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Table 9.2. Linear regression (univariate) with AMI case fatality as outcome variable (sensitivity analysis). Analysis 1 logit case fatality adjusted for logit out-of-hospital deaths as a proportion of all events. Analysis 2 logit case fatality adjusted for logit hospital case fatality.4

9.3.4.2 ACS

Non-AMI ACS make up about 40-50% of all ACS admissions but only 1-2% of ACS deaths (see Chapter 7.4). Non-AMI ACS also makes up a larger proportion of all ACS events in women than in men (Chapter 8.4). The sensitivity analysis for all ACS (which includes non-AMI ACS) in Chapter 8.4, demonstrated that case fatality for ACS was 25% lower than that for AMI in men and 30% lower in women. The concomitant reductions in proportion of all events resulting in out-of-hospital death and hospital case fatality were 28% and 26.5% respectively in men and 33.3% and 31.5% respectively in women. For ACS, unlike for AMI, women had both lower age

4 model1<-lm(logitCaseFatality~logitOut-of-hospital-deaths-as-a-proportion-of-all-events)
model2<-lm(logitCaseFatality~logitHopsitalCaseFatality)
standardised hospital case fatality and age standardised proportions of events resulting in out-of-hospital deaths than men; this was driven by lower rates in younger age groups – rates in the oldest age groups were the same in both genders. As expected, the association between hospital case fatality and total case fatality as well as between proportion of all events resulting in out-of-hospital death and total case fatality remained almost the same as for AMI events.

9.4 Discussion

Districts with a high proportion of events which result in out-of-hospital AMI death also have high hospital case fatality rates for AMI. The correlation increases when out-of-hospital deaths are restricted to true out-of-hospital deaths and AMI deaths within 28 days of a non-AMI admission are counted with hospital case fatality. Hospital case fatality tends to be slightly higher in women than men and the proportion of all events resulting in out-of-hospital deaths slightly lower in women than in men except in the very elderly (85 years and over). Neither out-of-hospital AMI deaths nor hospital case fatality show strong correlation with district level deprivation scores. The implications of these findings in terms of health service performance are discussed below.

Restricting hospital case fatality to fatality in admissions with a well-defined primary diagnosis of AMI results in very low hospital case fatality rates with relatively little variability. This practice has been adopted from studies which attempted to replicate the mortality benefits seen in randomised controlled trials of AMI treatment, in hospitalised patients. Such an approach does not make sense from a health systems perspective as it excludes 40% of all admissions which result in an AMI death within 28 days. The analysis in Chapter 7 demonstrated that such admissions, whilst they do not have a primary diagnosis of AMI, frequently have another
cardiovascular diagnosis which marks the patient as being at high risk of AMI, or have symptoms which may herald the fatal AMI event. As such there may be opportunities to intervene and reduce mortality in these patients which are missed by excluding them from analysis. Grouping these persons with out-of-hospital deaths blurs the distinction between hospital associated and out-of-hospital deaths and dilutes the relationship between hospital case fatality and total case fatality. Thus many previous studies report that the variation in case fatality is driven largely by the variation in out-of-hospital deaths and has little to do with hospitalised events. I found hospital case fatality for well-defined AMI events to be 14% in this national study. This result is very close to the rates reported in other population based studies from England and Europe.(68,175) However, it is considerably higher than the 5% value reported by registries such as GRACE in which inclusion criteria for hospitalised AMI events are even more narrow.(170)

Secondly, it is interesting to note that hospital case fatality and proportion of all events which result in out-of-hospital death are positively correlated in both the baseline and the sensitivity analysis, although one might expect that as the proportion of all events which are out-of-hospital deaths rises, hospital case fatality would fall. Although this analysis has not looked into the drivers of hospital case fatality and out-of-hospital deaths, it may be that common factors drive both in the same direction. These may range from higher levels of risk factors such as blood pressure or smoking prevalence in some areas leading to more severe events, higher levels of comorbidity in some populations making events more difficult to treat, through to health system problems or variations in local NHS practice which affect both pre-hospital care and response times as well as hospital management of AMI. The time period of the analysis 2006-2010, was one during which primary angioplasty was being rolled out across the country as a more
effective treatment for STEMI than thrombolysis. Some areas of the country (London, the Black Country and West Yorkshire) had well established primary angioplasty even before this, however roll out was slow and still incomplete in the North West, in East Yorkshire and in the South West by 2010.(51) South Western areas of the country where population density is sparser and travel times longer appeared to experience both higher hospital case fatality and higher proportions of out-of-hospital deaths, especially in older ages where the majority of events occur, and high hospital case fatality rates were seen in the North West and East Yorkshire for younger age groups. Area level deprivation did not account for the patterns seen.

Thirdly, as reported in previous studies,(151,152,271,272) I found higher levels of hospital case fatality and lower proportions of events which resulted in out-of-hospital AMI death in women than men at ages below 75 years. There is some evidence that AMI in women present with different symptoms to those in men and that clinicians have a different prior index of suspicion for women than men leading to fewer and more delayed diagnosis in women.(273) Studies have also noted differential treatment of women and men in terms of numbers of angioplasties performed and other treatments,(274) these may partly explain the higher hospital case fatality seen in women. From this analysis this seems to be more the case for women in younger and older age groups than for the 65-74 year age group. It is possible that AMI are more frequently suspected and therefore more rapidly diagnosed and treated in 65-74 year old women than in very young or very old women – less of the variation in total case fatality was explained by variations in hospital case fatality in this age group than in others. In Chapter 7 I showed that women also experience proportionately more non-AMI admissions which result in AMI death within 28 days.
9.4.1 Strengths

This is a nationwide study which allows the full spectrum of hospital and out-of-hospital case fatality to be examined at the same time. This allows events such as AMI deaths within 28 days of a non-AMI admission, which might otherwise be missed by a hospital based or out-of-hospital approach, to be identified. These events point to patients who represent a high risk group. It is possible to study the characteristics of this group as was done in Chapter 7 with a view to modifying their risk of death. Additional strengths of the data and modelling strategy have been described in Chapter 8.5.1.

9.4.2 Limitations

Routine data do not contain information on individual risk factors. It was thus not possible to adjust variations in case fatality for the risk profiles or case-mix of the populations studied in this analysis. Case-mix adjustment has commonly been used in studies looking at variation between facilities such as hospitals, to adjust for, for example, the more complex cases seen by teaching hospitals vs. general hospitals. In such studies case-mix adjustment does not appear to change the rankings for true outliers in terms of performance. (74,275,276) Case-mix adjustment may be less helpful for area based studies; over-adjustment for factors which may be amenable to public health intervention is problematic as it masks variations which should be highlighted and addressed.

The availability of sensitive troponin based diagnosis for AMI was widespread in England by 2006 and thus differences in hospital case fatality are unlikely to represent differences in diagnostic ability. However, it may be the case that less serious AMI events are more systematically coded in some areas than others. This would lead to lower case fatality and higher
event rates in these areas. There was no clear relationship between case fatality and event rates to suggest this in my data, but correlation with clinical data would be needed for confirmation.

Hospital case fatality and the proportion of all events resulting in out-of-hospital AMI death were correlated and their relative contributions to total case fatality could not readily be decomposed.

Additional limitations of analyses based on routine data have been discussed in Chapter 7.5.2 and 8.5.2.

9.5 Conclusion

The largest source of error in estimates of hospital case fatality may not be case mix but rather the way in which events are assigned to hospital vs. out-of-hospital deaths. This analysis shows that the potential contribution of variations in secondary care to the variation in total case fatality may be comparable to that of pre-hospital care, and larger than has been previously reported.
Figure 9.8a. Hospital case fatality, out-of-hospital deaths as a proportion of all events and total case fatality (top left to right) and corresponding posterior probabilities (bottom) for men aged 45-54 years. Boxed area = London.
Figure 9.8b. Hospital case fatality, out-of-hospital deaths as a proportion of all events and total case fatality (top left to right) and corresponding posterior probabilities (bottom) for men aged 55-64 years. Boxed area = London.
Figure 9.8c. Hospital case fatality, out-of-hospital deaths as a proportion of all events and total case fatality (top left to right) and corresponding posterior probabilities (bottom) for men aged 65-74 years. Boxed area = London.
Figure 9.8d. Hospital case fatality, out-of-hospital deaths as a proportion of all events and total case fatality (top left to right) and corresponding posterior probabilities (bottom) for men aged 75-84 years. Boxed area = London.
Figure 9.8e. Hospital case fatality, out-of-hospital deaths as a proportion of all events and total case fatality (top left to right) and corresponding posterior probabilities (bottom) for men aged 85 years and over. Boxed area = London.
Figure 9.8f. Hospital case fatality, out-of-hospital deaths as a proportion of all events and total case fatality (top left to right) and corresponding posterior probabilities (bottom) for women aged 45-54 years. Boxed area = London.
Figure 9.8g. Hospital case fatality, out-of-hospital deaths as a proportion of all events and total case fatality (top left to right) and corresponding posterior probabilities (bottom) for women aged 55-64 years. Boxed area = London.
Figure 9.8h. Hospital case fatality, out-of-hospital deaths as a proportion of all events and total case fatality (top left to right) and corresponding posterior probabilities (bottom) for women aged 65-74 years. Boxed area = London.
Figure 9.8i. Hospital case fatality, out-of-hospital deaths as a proportion of all events and total case fatality (top left to right) and corresponding posterior probabilities (bottom) for women aged 75-84 years. Boxed area = London.
Figure 9.8j. Hospital case fatality, out-of-hospital deaths as a proportion of all events and total case fatality (top left to right) and corresponding posterior probabilities (bottom) for women aged 85 years and over. Boxed area = London.
Chapter 10: Discussion

10.1 Main findings

- There was a 66% decline in CVD mortality in England over the 30 years between 1982 and 2012.
- AMI mortality varies by 2.4 fold between the 1st (best) and 99th (worst) percentile of districts.
- Event rates explain between 60-80% of the between district variation in AMI mortality and case fatality accounts for 15-30%.
- Variations in event rates, case fatality and mortality within a decile of IMD deprivation are larger than variation between deciles.
- Event rates and mortality show some correlation with area deprivation. Once event rates are accounted for case fatality shows little correlation with district IMD.
- Districts with a high proportion of events which result in out-of-hospital AMI death also have high hospital case fatality rates for AMI. The correlation increases when out-of-hospital deaths are restricted to true out-of-hospital deaths and AMI deaths within 28 days of a non-AMI admission are counted with hospital case fatality.
- The largest source of error in estimates of hospital case fatality may not be case mix but the way in which events are assigned to hospital vs. out-of-hospital deaths.
- The potential contribution of variations in secondary care to the variation in total case fatality may be comparable to that of pre-hospital care and larger than has been previously reported.
I have created a database of ACS events in England incorporating both fatal and non-fatal AMI and non-AMI ACS. Such an approach has not been undertaken previously, although various aspects of the health system for the prevention and management of AMI have been studied in isolation. A broad spectrum, whole system approach is essential if the costs, opportunity costs and benefits of different policy approaches to the ACS burden and its regional inequalities are to be assessed. Entry points along the pathway of an event from risk reduction, to impacting patient delay to first call for help, to transport times, access to specialist services and rapid diagnosis and intervention can be used to target specific drivers of the burden such as event rates or proportion of all events that result in out-of-hospital deaths. The contribution of these drivers to the overall mortality burden gives an indication of the maximum potential impact the intervention may have. For example if hospital associated deaths constitute 10% of the mortality burden, then even if they are reduced to zero, 90% of ACS mortality would still remain. Furthermore a whole system approach allows events in patients that no-one in the system wants to take responsibility for – such as those who are admitted with a non-ACS event but go on to die of ACS within 28 days - to be identified. Approaches which look solely at hospital quality of care for ACS as well as those which focus solely on out-of-hospital death would ignore these persons and miss opportunities for intervention.

The question of whether public health measures to reduce population risk are more beneficial than medical intervention, first posed by the cohort studies of the 1970’s is now outdated. There has been a dramatic change in the management of ACS which includes the use of treatment that reduces the risk of recurrent events as well as death. Furthermore, primary prevention and public health strategies now incorporate the prescription of risk-modifying medication. Thus medical
intervention and population measures to reduce risk can no longer be disentangled from each other. However, the utility of knowing which aspects of the sequence - event rates, proportion of events resulting in out-of-hospital death and hospital case fatality – contribute most to the overall variation in mortality between districts remains pertinent for research. This could allow research questions to be focused on the aspects of the ACS sequence most likely to be affected, lessening the dilution of effect size by outcomes which are unaffected.

Documenting variation within a system can be useful for benchmarking what is possible at the best extreme and for highlighting poor performance. There has been much debate over ‘warranted’ vs. ‘unwarranted’ variation, most of it stemming from the USA where there are multiple private providers in the health care system.(277) It has been argued that variations in clinical practice between physicians and institutions might be deemed to be unwarranted and may in fact be driven by supplier induced demand. Variations which reflect disease risk or severity in the underlying patient population on the other hand are deemed to be ‘warranted’ and not due to health system performance; various approaches have been developed to control for this in comparative studies. The majority of previous comparative literature in this field focuses on institutional rather than area based comparisons. However, in the case of regional comparisons even ‘warranted variation’ e.g. due to case mix should prompt the question of why the case mix is ‘bad’ in a particular area.

The health system geography of England is continually changing. Neither hospital nor GP catchment areas are clearly geographically defined. Regional ambulance networks have different boundaries to other healthcare providers, and social and community based care is indexed to local authority boundaries. At the time of this study 2006-2010, the health system structure was organised at the level of the Primary Care Trust (PCT) which constituted groups of GP practices
with boundaries almost coterminous with Local Authority Districts.(278) Resource allocation was through the PCTs which held 80% of the NHS budget and commissioned services from NHS primary and secondary care providers. The PCT was accountable to a Strategic Health Authority which in turn was accountable to the Department of Health. The ultimate responsibility for the Nation’s health lay with the Secretary of State for Health.

Since the Health and Social Care Act 2012, which came into force on 31st March 2013, the Secretary of State for Health no longer has a legal responsibility for the nation’s health. The PCT’s public health functions (ensuring population health) have been co-located with other local authority services such as education, refuse collection etc. Furthermore the healthcare market has been opened up to ‘any willing provider’. PCTs have been abolished and replaced by clinical commissioning groups (CCGs) – conglomerations of GP practices which do not necessarily have to have geographical contiguity,(279) although they are contained within Local Authority Boundaries. CCGs may contract services from fully private providers and may restrict access to certain services for their populations. Whilst the government speaks the rhetoric of reducing regional inequality and had even published an Atlas of Variation in Healthcare since 2010, the multiplicity of geographies for different aspects of the healthcare system and the constant reconfigurations make it difficult to compare burdens and outcomes in reality. Thus the Atlas of Variation appears largely to track process measures, such as number of operations performed or intermediate indicators, but does not relate these to health outcomes or mortality.(280) Along with the devolution of healthcare to multiple private providers, the lack of ability to track outcomes consistently limits accountability.

If each willing provider is allowed only to report their own measures, reporting will inevitably be biased by the exclusion of more difficult or intractable cases that the provider does not in fact,
provide for. In such an environment geographical comparison of outcomes becomes even more important to ensure accountability to all sections of the population. Area based rates are able to offer this advantage over institution based ones. Administrative boundaries are well defined and relatively constant, with excellent resources to be able to map boundary changes to a consistent geography. The utility of quality improvement initiatives such as the Atlas of Variation would be greatly improved if there was a mapping capability allowing rates of service provision to be aligned with administrative boundaries so that variations in process could be readily compared to variations in outcome.

The phenomenal rise and decline in IHD over the twentieth century remains one in which currently recognised risk factors and interventions are late entrants (Chapter 2). There is no clear indication in the medical literature of what precipitated the turning point and the start of the dramatic declines seen since the 1970’s, although later medical interventions may have prolonged or accelerated the trajectory. The temporal tale of IHD mirrors the wider transformation of Britain from an agrarian to an industrialised and then a post industrial nation with all the enormous societal reforms that accompany this. The massive decline in CVD mortality has resulted in a reduction in absolute inequality between most deprived and least deprived areas especially in younger age groups but relative inequalities have remained the same or worsened. The burden of ACS has shifted to older ages. The overall spatial pattern of high and low mortality areas in the under 65s reflects the patterns of industrialisation and the fall of industry – with post-industrial towns of the North bearing the brunt of high mortality. This pattern is not very different to that presented by Gardner in his Atlas of Mortality from 1968-1978.(22) It has been suggested that these areas have suffered the worst during serial economic depressions and are the slowest to recover, leading to serial disadvantage over generations. The
pattern of case fatality for ACS however is very different, with rural areas of the South West having high case fatality especially for elderly people. Both the proportion of events leading to out-of-hospital deaths and hospital case fatality tend to be high in the same areas. ACS event rates however, which account for the majority of the ACS mortality burden, follow the North-South pattern of mortality. A previous study suggested that classical risk factors, such as smoking, hypertension and social class can account for 42% of regional variation in ACS,(30) but the remainder is unexplained. The key to the drivers of the regional inequalities in event rate and therefore mortality may lie in the wider social context, outside of the healthcare system. From this perspective public health bodies co-located with local authorities may provide opportunities for broader social interventions to disrupt spatial patterns of disadvantage which have become entrenched.(281,282) The manner in which we structure our societies is not inevitable and regional inequalities in ACS are the end production of this construction. This work moves the ACS burden from a narrowly focused medical intervention perspective to a somewhat broader health systems perspective, but there is still some way to go to place ACS in the context of the social factors that drive it.

10.2 Further work

There are a number of further studies which are needed; first, verification of events in routine data against medical records of ACS is needed for English ICD-10 coding and particularly for the coding of non-AMI ACS events. Second, studies are needed to assess the completeness of capture of ACS events in hospitalisation data, and to assess what events are being missed and what their outcomes are. Third, there needs to be an analysis of the variability in coding practices and recording of mild vs. severe events between areas, as well as in the consistency of capture of comorbid diagnoses. It would be of particular interest to assess how much variability there is in
the recording of non-ACS admissions which nevertheless result in an ACS death within 28 days. Fourth, work is needed to align the geography of process indicators such as ambulance response times, to that of outcomes so that the effects of differences in process and policy can be measured. Such measurement may then be used to generate hypotheses for interventional studies – for example for community based studies where a policy is implemented in one area but not another. Fifth, as computational power increases and more data become available the limitations in modelling will lessen and it may be possible to estimate spatio-temporal changes in ACS outcomes for all age sex groups within a single model. Finally, broader studies are needed on the effects of social and economic change on the patterns of ACS event rates and case fatality.

10.3 Conclusion

IHD mortality has long been used as a barometer of the function of the healthcare system itself. There is a 2.4 fold variation in AMI mortality between districts in England (2.6 fold for ACS). This is the first analysis to decompose that variation into the portion driven by event rates vs. that driven by case fatality. Event rates account for the majority of the mortality variation and may be a barometer not just of the health system but of the wider social inequalities existing in England in the twenty-first century.
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Appendix A

Map of English Geography