

Prognosis of angina and myocardial infarction in
South Asian and White populations in the United
Kingdom

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I, Justin Zaman, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Background

Coronary mortality rates amongst South Asian populations are higher than in White populations in the UK. The contribution of incidence and prognosis of coronary disease to the higher coronary mortality rates amongst South Asian populations is unknown. Incident coronary disease commonly presents as angina and non-fatal myocardial infarction rather than as fatal events.

Aim

This thesis sought to investigate the incidence and prognosis of differing clinical presentations of coronary disease such as angina and myocardial infarction in South Asian compared to White populations in the UK.

Methods

Four new prospective studies, one aetiologic (South Asian N=580 initially healthy) and three prognostic (N=2189 with suspected new-onset stable angina, N=502 undergoing coronary angiography and N=3037 with acute coronary syndromes) were examined, using multi-variate regression analyses. A systematic review and meta-analysis of these and previously published studies was performed.

Results

- Incidence of angina was higher in South Asian than in White people in a healthy population, and angina was similarly valid in predicting a poor prognosis in both ethnic groups compared to those with no chest pain.
- In those with chronic angina, South Asian patients did not have a higher future risk of myocardial infarction and death than White patients, but had a worse symptomatic prognosis following coronary revascularisation when compared to White patients.
- South Asian patients had no worse a prognosis for mortality than White patients after myocardial infarction
- On meta-analysis, incidence of fatal and non-fatal coronary disease was higher in South Asian populations compared to White populations whilst prognosis of coronary disease in South Asian populations was not worse than in White populations.

Conclusions

Increased coronary mortality rates in South Asian populations compared to the White populations are due to the higher incidence of fatal and non-fatal coronary disease in South Asian people, as the prognosis of manifest coronary disease in South Asian people is not worse than in White people.

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iii. Statement of contribution to the research

I formulated the research aims and objectives jointly with Professor Harry Hemingway from 2002-2004 and co-wrote the PhD grant proposal with him. After having completed a Masters in Epidemiology in 2005, I was responsible for all analyses on this PhD from 2005-2008. I selected the variables used in the analyses, performed all the statistical analyses, interpreted the results and wrote the thesis. I produced all figures and tables and was solely responsible for the design of posters and presentation of them, as well as for delivering talks, at regional, national and international meetings. I led authorship of all papers resulting from these analyses.

I was responsible for ethics approval of use of clinical data for research purposes in part of the chest pain clinic study to the Central Office for Research Ethics Committees, as well as site-specific approval at Newham. I was responsible for obtaining Patient Information Advisory Group permission to link anonymised data sets without obtaining individual patient consent. I recruited patient and user organisations/representatives from my practice as a cardiologist at Newham to advice on the purpose and ethics of the study.

I led on a successful grant application to further the work of this PhD thesis. With support from the £67934 grant awarded by the Clinical Research and Development Committee of University College London Hospitals, a statistician will be recruited to design and conduct multi-level analyses to assess further the impact of ethnicity and social deprivation on outcomes from acute coronary syndromes in MINAP.

iv. Acknowledgements

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The use of four studies entails the co-operation of many, so firstly I thank all the participants who gave up their time to take part in the studies. I thank the Whitehall-II group for access to and assistance with the database (especially Martin Shipley), and to the Clinical Epidemiology group at UCL for all their individual inputs into my work over the last three years (Natalie Fitzpatrick, Connie Junghans, Angela Crook, Ruoling Chen, Jackie Damant, Kate McAllister, Charlotte Ashton, Gene Feder and Jessica Sheringham).

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Finally, none of this would have been possible without the relentless and untiring support of my amazing wife, who - aside from her instant and total comprehension of my goals in life and of my reasons for undertaking this research, and thus providing unfaltering support - has ensured I neither went hungry nor without sleep whilst completing this thesis. Thank you, Aisha.

v. Abbreviations

ACRE	Appropriateness of Coronary Revascularisation
ACS	acute coronary syndrome
BMI	body mass index
CABG	coronary artery bypass surgery
CCS	Canadian Cardiovascular Society
CK/CK-MB	Creatine phosphokinase/-MB isoenzyme
ECG	electrocardiogram
GP	general practitioner
GTN	glyceryl trinitrate (nitroglycerin)
HES	Hospital Episode Statistics
HDL	high density lipoprotein
ICD	International Classification of Diseases
IMD	Indices of Multiple Deprivation
IQR	inter-quartile range
LDL	low density lipoprotein
MI	Myocardial Infarction
MINAP	Myocardial Infarction National Audit Project
NFMI	Non-fatal myocardial infarction
NHS	National Health Service
NSTEMI	non-ST-segment elevation myocardial infarction
PCI	percutaneous coronary intervention
PTCA	percutaneous trans-luminal coronary angioplasty
RQ	Rose angina questionnaire
STEMI	ST-segment elevation myocardial infarction

1 Introduction

1.1 The higher coronary mortality in South Asian compared to White populations

Of all the estimated 57 million deaths in the world in 2002, cardiovascular disease was the largest single cause, resulting in 17 million deaths. Societies across the world experience different rates of different cardiovascular diseases, and within those societies, there exists differences between social class, gender and ethnicity. In the 1950s, studies began to report differences in coronary disease rates between ethnic groups, and in particular the South Asian group (predominately people from India, Bangladesh, Pakistan and Sri Lanka).¹⁻⁴ Shaper and Jones in 1959 stated that "in the African population of Uganda coronary heart disease is almost non-existent. In the Asian community on the other hand coronary heart disease is a major problem".¹ Adelstein in 1963 pointed out that among the South African ethnic types, 'Asians' (almost entirely of Indian descent) showed the most unfavourable mortality rates from cardiovascular disease and that these rates were among the highest of the national rates on record.³ Walker presented similar findings from South Africa 17 years later, having examined death certificates of members of different ethnic populations in Johannesburg who had died of ischaemic heart disease, and used them to calculate age-specific mortality rates. As well as an extremely high mortality rate among White populations (especially among the Jewish sector), an equally high or higher rate was found among Indians, in the context of a lower rate among 'Coloureds' and an extremely low rate among blacks.⁵

Coronary heart disease remains the most common cause of premature death in the UK, although mortality has been falling continuously since its peak in the early 1970s.^{6 7} However, UK studies of mortality in the 1970s and 1980s highlighted differences in cause of death between different immigrant groups. Balarajan presented data based on the 1981 census showing that mortality from ischaemic heart disease was highest in men and women born in the Indian subcontinent with standardised mortality ratios of 136 and 146 respectively,⁸

adding value to the data he had presented seven years earlier showing higher proportional mortality due to ischaemic heart disease in immigrants to England and Wales from the Indian subcontinent.⁹

A study based on 1991 census data revealed higher standardised mortality ratios for those born in South Asia, of 151 (141 to 162) for women and 146 (141 to 151) for men.¹⁰ This study further demonstrated that from 1971 to 1991, standardised mortality ratios for ischaemic heart disease in the general UK population fell by 29% for men and by 17% for women, whilst South Asian immigrants experienced a shallower decline (20% for men and 7% for women). Latest data from the 2001 UK census noted that though coronary mortality fell among migrants, rate ratios for coronary mortality remained higher than for men and women from South Asia.¹¹⁻¹³

Similar disparities in mortality continue to be reported internationally. Sheth et al reported on cardiovascular mortality among Canadians of European, South Asian and Chinese origin from 1979 to 1993.¹⁴ In their analysis of 1.2 million deaths, rates of death from ischaemic heart disease were highest among Canadians of South Asian origin whereas those of Chinese origin had a substantially lower rate. In Palaniappan et al's study of coronary heart disease mortality for six ethnic groups in California between 1990 and 2000, proportional mortality rates were highest in Asian Indian men (161) and women (144).¹⁵

1.2 Explaining ethnic differences in coronary mortality

This thesis seeks to explain why there is a higher coronary mortality rate in South Asian compared to White populations. Epidemiologically, the explanation for this may be either as a consequence of higher **incidence** of coronary disease in South Asian populations or a worse **prognosis** of already-manifested coronary disease – or a combination of both. Evidence for the contributions of disease incidence and prognosis requires, respectively, incident events in 'healthy' cohort studies and examination of outcomes in clinical cohorts with coronary disease.

1.3 Ethnicity

The Department of Health's definition of an ethnic group is 'a group of people who share characteristics such as language, history, culture, upbringing, religion, nationality, geographical and ancestral origins and place'. In contrast, the use of 'race' in epidemiological research is based on biological features principally centred around physical factors, and ignores the wider societal context.¹⁶ Ethnicity depends on a wider socio-environmental and behavioural context and thus makes its identification and hence use as a variable in research – of vital importance in epidemiology – more difficult than race. Whereas biological differences between ethnic groups (e.g. in cholesterol levels) can be measured by a blood test, sociological and behavioural differences between ethnic groups (e.g. deprivation, cultural preferences for medical treatments) are more difficult to measure. Advantageously, by considering the influence of such components that make up ethnicity, ethnicity allows the incorporation of socio-environmental and behavioural factors associated with differing ethnic groups beyond just the genetic and biological factors that race is limited to when considering the origins of diseases.

Ultimately, such labelling is only of importance if differences between ethnic groups exist in the population. Clearly, if there were no ethnic differences in disease patterns, epidemiological investigation in the field would be pointless. As long as ethnic disparities in health are suggested however, then careful and critical analyses of them are merited. As the aetiology of disease is not just biological but socio-environmental and behavioural, ethnicity as an exposure has clear advantages to race as an epidemiological variable, aside from any moral arguments for its use.

The recording of ethnicity is thus of importance. The 1991 Census of Population was the first to collect information on the ethnic group of every individual in the population of Great Britain. The Office for National Statistics April 2001 census question was similar to the one asked in 1991, but with changes in some categories - in particular, people could tick "mixed" for the first time. They were asked "What is your ethnic group?" According to this census, South Asian people

made up just over 3.5% of the total UK population, about 2,084,000 out of nearly 58,800,000. Of these nearly 1,054,000 (1.8%) were Indian, 747,000 (1.25%) were Pakistani and just under 283,000 (0.5%) were Bangladeshi. In comparison, there were 247,403 (0.4%) Chinese people, 565,876 (1.0%) Black Caribbean people and 485,277 (0.8%) Black African people. The average ages of minority ethnic communities were younger than the White European population.¹⁷ The Office for National Statistics 2001 census types were:

- A. White: British; Irish or Any other White background
- B. Mixed: White and Black Caribbean; White and Black African; White and Asian or any other mixed background
- C. Asian or Asian British: Indian; Pakistani; Bangladeshi; Any other Asian background
- D. Black or Black British: Caribbean; African; Any other Black background
- E. Chinese or other ethnic group: Chinese; Any other

(more detailed data from The Office for National Statistics 2001 in Appendix 13.1)

1.3.1 South Asian populations

South Asian people are part of a heterogeneous group composed of different nationalities and religions (e.g. Indians and Bangladeshis, Muslims and Hindus). Ideally, all analyses comparing the health of this population with white majority populations should take this into account. However, the vast majority of studies that have presented results on ethnic differences between these two populations have used the aggregated 'South Asian' category, and those that collect data on the constituent peoples often do not have the power required for statistical analyses between South Asian peoples.

Hence, the acceptability of the broader 'South Asian' group as a means of description of this population needs to be examined. Despite its heterogeneity, the term South Asian is growing in acceptance culturally among the people it seeks to classify because it acknowledges common interests while it allows for

difference.¹⁸ This also parallels the gradual acceptance of the term "Asian American" by peoples primarily of East and Southeast Asian ancestry, who found reason to claim a shared identity in dealing with bureaucratic matters and racism. Despite doubts as to the inclusiveness of such terms and their wider applicability, especially with respect to health and disease,¹⁹ there exist similarities in behaviour within the South Asian peoples. Poverty and smoking are more prevalent among Pakistanis and Bangladeshis whilst obesity and a lack of exercise are associated with all South Asian peoples, though Pakistanis and Bangladeshis are more likely to have higher levels of inactivity.^{20 21}

Furthermore, though differences between the differing peoples of the South Asian category may result in different patterns of incident disease, it is unlikely that such differences would result in differential prognoses when presenting with coronary disease. For example, the vast majority of studies have reported that South Asian patients of any origin (from Bangladeshis in London to Indians in the USA) present with coronary disease at younger ages than White patients and this younger age. Thus, age – rather than the nationality – will exert a stronger effect on prognosis.

1.3.2 White populations

Much of the work in ethnic differences has used relatively homogenous White populations as the comparison group. However, the heterogeneity of the 'White' group should be appreciated, for example the increased socioeconomic disadvantage and mortality of Irish people living in England and Wales.²² Any conclusions from analyses on ethnic comparisons should be applied to those specific White populations being studied, and not extrapolated to other 'White' populations outside the inclusion criteria of that study. It is of further interest that work from Scotland did not reveal worse coronary mortality in those born in South Asia compared to those Scottish-born, but that the use of England and Wales as a comparison group showed a substantial excess of coronary risk among South Asians in Scotland, comparable to that reported in England and Wales.¹³ Comparisons with England and Wales showed high all-cause, coronary heart disease and stroke mortality among Scottish residents born in Scotland,

Northern Ireland, the Republic of Ireland. Thus, inferences from analyses between White populations in England and South Asian populations in England cannot then be assumed to apply to White populations in Scotland and Ireland. The increasing migration from Southern and Eastern Europe of 'Whites' adds further heterogeneity to the category.

Within England itself, evidence reporting worse coronary health within deprived neighbourhoods can be explained away once individual measures of socio-demographic status are adjusted for.²³ Thus, conclusions applied to White populations within smaller geographical areas such as England (or even within cities) require consideration of such factors. However, Scotland's relative mortality disadvantage compared to the rest of Great Britain is not explained away fully even after allowing for deprivation.²⁴

1.3.3 Assessment of ethnicity

The current preference for practical reasons is for self-assessment of ethnicity²⁵ In a USA study, there was reasonable concordance between self-assessment of ethnicity and ethnicity recorded by an outside observer for some ethnic groups (such as blacks, White populations and 'Asians'^a, whilst other groups were less concordant (e.g. Hispanic and American Indian).²⁶

1.4 The migration history of South Asian people to the United Kingdom

1.4.1 Moving to the United Kingdom

Migration into the UK began in significant numbers after the 1962 Commonwealth Immigrants Act. The Moving Here website and partnership (<http://www.movinghere.org.uk>), led by the National Archives, reports that before 1960 such immigration had been small and migrants generally had a significant knowledge of the English language or Britain, or both. This group comprised seamen, ex-Indian army personnel, university graduates, teachers, doctors and other professionals. The entry of South Asian people to England was controlled at source by the Indian and Pakistani governments.

^a 'Asian' in the USA refers to East Asians e.g. Chinese, Filipinos, Japanese

The majority of those who entered the UK after 1960 came to fill jobs in industry, and were unskilled in comparison. Most were literate in Urdu, Punjabi and Gujarati but few had much in the way of formal educational qualifications. South Asian immigrants tended to now come from a rural background and were generally unfamiliar with the language and culture of Britain. They were more often political or economic migrants - such as the Bangladeshis who immigrated to the UK during the violent birth of their country in 1971 - rather than professional or educational. Notable exceptions were in the considerable number of Indian doctors who arrived to fill shortages in the National Health Service, and South Asian people expelled from East Africa in the 1960s and 1970s of higher socio-economic status, heralding from professional and mercantile backgrounds.

1.4.2 Geographical origins of migrants

The majority of South Asian migrants in the UK originate from only a few of the many communities in the sub-continent. These communities are linked to pre-war geographical patterns of settlement that persist today within the UK. Demobbed soldiers came mostly from Punjab and Gujarat, and deserters from the merchant navy from Mirpur and Sylhet. Up to 90% of Pakistanis in Bradford and Birmingham come from the area of Mirpur. Indians who are Sikh in religion tend to originate from mainly the Punjab region (Southall in West London is now home to a large Punjabi Sikh community) whilst Hindus originate mostly from the Gujarat, Punjab and West Bengal regions. British Bangladeshis largely originate from the north-eastern Sylhet region of their country - they were often employed as ship's cooks at the beginning of the century and many of them went on to work in the 'Indian' restaurants, which they still dominate today. In 2001 Bangladeshis made up 33.4% of the population of Tower Hamlets in London whilst 95% of those Bangladeshis came from the rural north-eastern district of Sylhet. Many East African Asian people have settled in London in areas such as Wembley and Harrow. Thus, these pockets of relative social homogeneity exist within the heterogeneous category of the 'South Asian'.

1.5 The pathology of the stages of coronary disease underlying its differing clinical presentations

Atherosclerosis can be staged into a complex series of molecular and cellular processes in the circulatory system leading ultimately to arterial thrombosis. These stages correlate with differing clinical presentations relevant to this thesis. Many presentations of coronary disease exist, but atheroma within the coronary artery itself results in specific clinical presentations such as angina and myocardial ischaemia.

1.5.1 Asymptomatic coronary atheroma

The first stage in atherogenesis is the formation of the fatty streak. Firstly, there is infiltration and entrapment of low density lipoprotein (LDL) in the blood vessel wall. Once entrapped in the vessel wall, LDL undergoes modification which results in the secretion of a chemotactic substance that attracts monocytes. These cells then migrate through the vessel wall, transform into macrophages which then digest the LDL particles. The cytoplasm of the cell is increasingly packed with lipid forming the fatty streak. Fatty streaks are smooth raised plaques located beneath the endothelium and have been observed in the coronary arteries of asymptomatic young adults.²⁷ This stage of atheroma is 'sub-clinical' as it is not associated with symptoms of angina, i.e., the symptom of chest discomfort or pain associated with reduced myocardial arterial blood supply as a result of increasing arterial luminal stenosis.

1.5.2 Exertional angina and the fibrous plaque

The fibrous plaque represents the next phase. With progression of the fatty streak, smooth muscle cells (not normally present in the sub-endothelial space) migrate from the media to the sub-endothelial space where they proliferate and produce connective tissue to form a fibrous cap. Increasing diameter of the plaque increasingly obstructs the blood flow through the lumen of the coronary artery, progressively restricting blood supply to the myocardium, causing clinically apparent exertional angina, or 'chronic stable angina pectoris', in the

patient.^b Non-invasive tests such as exercise electrocardiography may reveal electrical changes indicative of ischaemia.

1.5.3 The acute coronary syndrome and the ruptured plaque

The next stage is the development of a lesion which can calcify, haemorrhage, ulcerate and thrombose. It is the progression of the stable atherosclerotic fibrous plaque (that results in exertional angina) into this vulnerable and unstable lesion (the rupture of which results in thrombosis) that leads to the clinical presentation of unstable angina (recurrent episodes of angina on minimal effort or at rest). If coronary blood supply is sufficiently reduced, infarction of the myocardium can then result as a result of a total or a sub-total occlusion of the coronary artery.

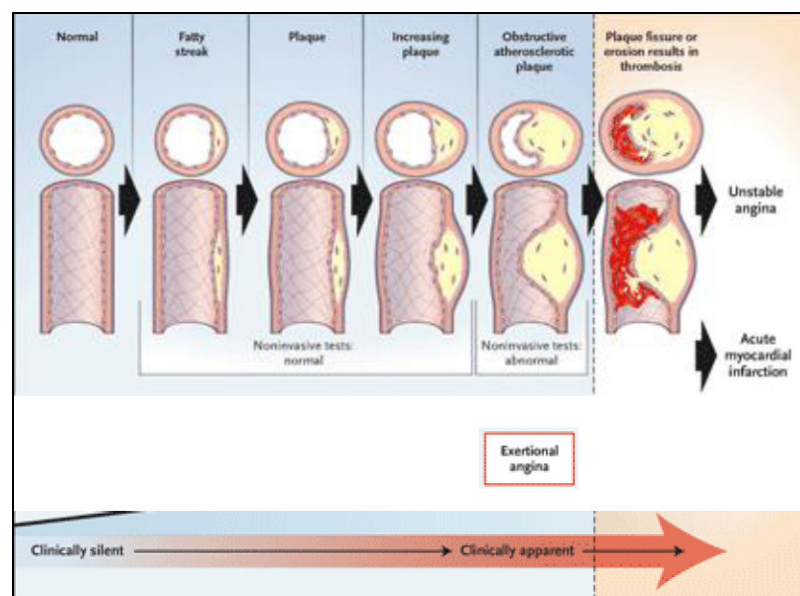


Figure 1 Stages of atherosclerosis and correlation with clinical presentations

(adapted from Abrams 2005²⁸)

^b The term angina in this thesis will henceforth imply chronic stable angina pectoris rather than unstable angina (described on next page)

1.5.4 Prediction of outcomes at differing clinical presentations of coronary disease

To understand the relative contributions of incidence and prognosis that underlie the epidemiology of coronary death, stages within coronary disease need to be considered. Though incidence itself implies first event, this can be non-fatal or fatal, correlating with different stages of coronary disease. The sub-clinical coronary plaque can cause both the gradual encroachment of coronary blood flow causing angina as an incident clinical event, and can also present directly as thrombosis leading to unstable angina or myocardial infarction or death. Incident angina can itself progress to myocardial infarction or death. Hence, knowledge of non-fatal and fatal incidence is of importance to overall coronary disease epidemiology. Most incident coronary disease is non-fatal rather than fatal,^{29 30} and of these non-fatal presentations, the prognosis of presentations such as angina and myocardial infarction are different. Factors that affect prognosis will also be different in angina compared to myocardial infarction.

1.5.5 Other presentations of ischaemic heart disease

Many presentations of ischaemic heart disease exist, and have been measured both in epidemiological studies and by clinical means. The International Classification of Diseases (ICD 10th Revision, Version for 2007, appendix 13.2) lists angina pectoris (I20) and myocardial infarction (I21, I22) as three of the five categories making up the ischaemic heart diseases category (I20-I25). Further clinical presentations of ischaemic heart disease exist within the ICD classification – such as coronary failure (within I24) and ischaemic cardiomyopathy (within I25), end-results of the infarcted myocardium or extensive atherosclerosis. Furthermore, the complications listed within I23 often result in sudden cardiac death, another clinical presentation of ischaemic heart disease. Other categories within I25 include those that do not present clinically but are often found fortuitously, such as silent ischaemia and ECG changes such as q waves (I25.2) and arrhythmic sudden cardiac death, which previous clinical and epidemiological studies have used as measures to assess the incidence and prevalence of ischaemic heart disease.

Coronary failure, cardiomyopathy and arrhythmias strictly refer to pathological processes arising from the myocardium (as a result of coronary insufficiency) rather than the coronary artery, whilst ECG changes may not be associated with symptomatic disease. This thesis seeks to examine symptomatic clinical syndromes that require the patient where possible to have presented themselves to the healthcare service, and focuses on events within the lumen of the coronary artery and are hence the primary clinical presentations of the pathological process of coronary atherosclerosis. This thesis hence will focus on angina and myocardial infarction in its study of incidence and prognosis, whilst appreciating that coronary disease may also present as silent ischemia, coronary failure and arrhythmias.

1.6 Angina

Angina is a common initial manifestation of coronary heart disease,²⁹ a significant burden in primary care³¹ and has considerable economic implications. A UK study conservatively estimated that angina accounted for 1.3% of the annual health expenditure.³²

1.6.1 Definition of angina

Angina is diagnosed from a clinical constellation of symptoms from the patient history. Descriptions of symptoms, articulated by patients to their doctors, remain a cornerstone of diagnosis in clinical medicine. The clinical history is the first step in assessing chest pain or discomfort in order to ascertain whether or not it represents angina. The history also allows the doctor to identify patients in whom additional investigation is necessary and in whom it may be spared,^{33 34} and whether additional therapy including coronary revascularisation through percutaneous coronary intervention (PCI, using balloon angioplasty and stenting) or coronary artery bypass surgery (CABG) is needed.

1.6.1.1 Diamond and Forrester definition

One of the most widely used definitions of chronic stable angina pectoris was presented in 1979 by Diamond and Forrester who analysed 4952 patients with chest discomfort. They showed that typicality of symptoms correlated with

angiographic coronary disease.³⁴ The authors described three types of chest pain: nonanginal, atypical, and typical.

The pain was assessed with these questions:

- 1) Is the pain retrosternal?
- 2) Is the pain precipitated by stress?
- 3) Is the pain relieved by rest or nitroglycerin?

Patients who answer yes to all three questions were determined to have typical chest pain, those who answered yes to two of the questions to have atypical chest pain and those who answered yes to only one question were deemed to have nonanginal chest pain.

1.6.1.2 European Task Force definition

The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology defined angina as follows in its 2006 consensus document:³⁵

Stable angina is a clinical syndrome characterized by discomfort in the chest, jaw, shoulder, back, or arms, typically elicited by exertion or emotional stress and relieved by rest or nitroglycerin.

It continued:

The characteristics of discomfort related to myocardial ischaemia (angina pectoris) have been extensively described and may be divided into four types: location, character, duration and relation to exertion, and other exacerbating or relieving factors. The discomfort caused by myocardial ischaemia is usually located in the chest, near the sternum, but may be felt anywhere from the epigastrium to the lower jaw or teeth, between the shoulder blades or in either arm to the wrist and fingers. The discomfort is usually described as pressure, tightness, or heaviness, sometimes strangling, constricting, or burning. The severity of the discomfort varies greatly and is not related to the severity of the underlying coronary disease. Shortness of breath may accompany angina, and chest discomfort may also be accompanied by less specific symptoms such as fatigue or faintness, nausea, burping, restlessness, or a sense of impending doom.

The duration of the discomfort is brief, not more than 10 minutes in the majority of cases, and more commonly even less. An important characteristic is the relation to exercise, specific activities, or

emotional stress. Symptoms classically deteriorate with increased levels of exertion, such as walking up an incline or against a breeze, and rapidly disappear within a few minutes, when these causal factors abate. Exacerbations of symptoms after a heavy meal or first thing in the morning are classical features of angina. Buccal or sublingual nitrates rapidly relieve angina, and a similar rapid response may be observed with chewing nifedipine capsules.

Finally, to classify, it presented the following classification:

Typical angina (definite) - **Meets three of the following characteristics**

- Substernal chest discomfort of characteristic quality and duration
- Provoked by exertion or emotional stress
- Relieved by rest and/or GTN (glyceryl trinitrate)

Atypical angina (probable) - **Meets two of the above characteristics**

Non-cardiac chest pain - **Meets one or none of the above**

This definition outlined what constitutes typical characteristics of angina pectoris, and framed it into the categories of location, character, duration and relation to exertion, and other exacerbating or relieving factors. What constitutes typical characteristics of angina was not specified in the Diamond and Forrester definition.

1.6.1.3 The Rose angina questionnaire

The Rose angina questionnaire (RQ) is a widely-used survey tool for the measuring of angina in populations (see appendix 13.3).³⁶ The questionnaire was introduced in 1962 and defines angina as chest pain that limits exertion, is situated over the sternum or in the left chest and left arm, and is relieved within 10 minutes by rest. It is highly specific when compared against a medical record of doctor-diagnosed angina,³⁷ and is strongly associated with subsequent risk of coronary events in European populations.³⁸ This definition outlines typical characteristics of angina pectoris within the categories of location, duration and relation to exertion.

1.6.2 *Measuring angina*

The early and appropriate identification of angina will result in early and appropriate investigation and treatment.^{33 34}

1.6.2.1 Typicality of angina

While laboratories standardise assays for biomarkers in the measurement of a myocardial infarction, angina is a clinical constellation of symptom descriptors, rendering quantitative measurement difficult. There are no large studies comparing the diagnostic and prognostic value of chest pain descriptors between ethnic groups, as symptoms have been predominately investigated in White male populations. Furthermore, there is a perception that all South Asian populations³⁹⁻⁴¹ and other ethnic minorities^{42 43} with suspected ischaemia are more likely to report atypical symptom descriptors of pain. This has been attributed to cultural differences in the experience, interpretation and understanding of pain,³⁹ whilst biologically, there is evidence to suggest that there are ethnic differences in the interpretation of cutaneous pain (to a series of thermal stimuli in a study of 27 White participants and 24 African Americans participants),⁴⁴ implying that similar differences may occur in the interpretation of visceral pain such as angina although this is far from proven.

Most studies have been performed in those presenting with the acute chest pain of a suspected myocardial infarction.^{40 45} Teoh et al studied symptom distribution between Asian and Caucasian patients at presentation with acute coronary syndromes at a London hospital. They concluded that 'Asian patients were younger, more likely to be diabetic and tended to report a higher intensity of pain and over a higher area of their body, and more frequent discomfort over the rear of their upper thorax than Caucasian patients'. In a study examining first myocardial infarctions in South Asian and White patients who had presented to the coronary care unit of a district general hospital,⁴⁶ chest pain was deemed atypical in 26 (51%) of the Asian and 30 (39%) of the White patients.

Fewer studies have examined the typicality of chronic angina symptoms. The reliability of the Rose angina questionnaire was reported in a 2001 cross-sectional study to be inconsistent in South Asian populations when compared to

self-reported doctor-diagnosed angina and independently coded electrocardiogram (ECG) abnormalities.³⁹ The capacity of RQ 'definite angina' to identify doctor-diagnosed angina was lower in South Asian populations compared to European populations.

Beyond these cross-sectional studies, the prospective validity of angina measures in comparing prognosis between ethnic groups is also unknown. Thus, ethnic differences in angina prognosis may not be apparent if ethnic differences in the description of symptoms are not taken into account.

1.6.2.2 Severity of angina

Ambulatory patients reporting a significant deterioration in their angina over the preceding month have been found to have a higher one-year mortality rate than those with more stable symptoms.⁴⁷ Furthermore, a higher burden of symptoms is associated with higher physical and role functioning.⁴⁸ As angina has potentially adverse prognoses both in terms of mortality and morbidity if not adequately managed, accurate measurement of its severity is of clinical importance.

The Canadian Cardiovascular Society (CCS) classification system has been used as an epidemiological tool to measure the severity of angina.⁴⁹ Worse severity of angina on the CCS score is associated with a more adverse prognosis as measured by rates of myocardial infarction and death.⁵⁰ This measure is a scale ranging from I, when angina is mild and does not limit physical activity, through to IV, when angina severely restricts activities (box below).

Canadian Cardiovascular Society Functional Classification of Angina		
Class	Activity Evoking Angina	Limits to Physical Activity
I	Prolonged exertion	None
II	Walking > 2 blocks or > 1 flight of stairs	Slight
III	Walking < 2 blocks or < 1 flight of stairs	Marked
IV	Minimal or at rest	Severe

1.6.3 Prevalence of angina

Around 2 million women and men in the UK have angina and about 1% of the population visit their general practitioner at least once yearly with symptoms of angina.³⁰ National surveys have produced data on the prevalence of angina in the UK, as tabulated below (Table 1). In a meta-analysis on the international prevalence of angina, angina varied from 0.73% to 14.4% in women (population weighted mean, 6.7%) and 0.76% to 15.1% in men (population weighted mean, 5.7%).²⁹

Study, year	Study population	Definition of angina	Prevalence of angina (%)			
			Ages 55-64		Ages 65-74	
			Women	Men	Women	Men
Health survey for England, 2006*	Random sample of addresses - 14,142 adults interviewed	Rose Angina Questionnaire/Self-reported doctor-diagnosed angina	3.3/3.2	3.6/8.0	5.0/8.3	4.9/14.2
The Scottish Health Survey, 2003**	Random sample of addresses - 8,148 adults interviewed	Rose Angina Questionnaire/Self-reported doctor-diagnosed angina	4.0/7.4	5.1/11.2	16.8/14.2	6.7/20.8

* <http://www.ic.nhs.uk/statistics-and-data-collections/health-and-lifestyles-related-surveys/health-survey-for-england/health-survey-for-england-2006:-cvd-and-risk-factors-adults-obesity-and-risk-factors-children>

** <http://www.scotland.gov.uk/Publications/2005/11/25145024/50253>

Table 1 Prevalence of angina in UK adults from survey data

The incidence of diagnosed angina appears to be increasing when examining secular trends from 1978 to 2000. This is in contrast to a decline in rates of all other types of major coronary events among British men.⁵¹ General practice morbidity survey data from England and Wales also indicates that angina may be increasing,³¹ with the rate of consultation for angina among men and women in the 1990s higher than in the 1980s, the comparable statistic for myocardial infarction having fallen during this time. Contrasting evidence from the British Regional Heart Study reported that the prevalence of angina symptoms fell from 1978-1996, among men with and without a diagnosis of coronary heart disease.⁵²

This was a study in which angina was defined in a standardised way throughout follow-up. However, this reported finding is limited by the authors' technique of determining overall population prevalence of angina through the use of a series of cross sectional studies nested within what is a prospective cohort study. Though analyses were age-adjusted, the presented 'trend' in prevalence of angina should be interpreted cautiously. Their findings of a decline in age-specific angina prevalence are more robust among the men aged between 55 and 64 years, who contributed to at least three of the cross sectional studies. Data from successive Health Surveys for England can provide information on such trends and overall show no evidence of any significant change in the prevalence of self reported symptoms as assessed by the Rose Questionnaire between 1991 and 1994 and only a small, non-significant decline in men between 1994 and 1998.⁵³ Thus, a valid measurement of chest pain is important for the true assessment of prevalence.

1.6.3.1 Prevalence of angina by minority ethnic group

Clinical trials of angina have largely recruited male, White patients from secondary and tertiary centres,⁵⁴⁻⁵⁷ rendering conclusions on the prevalence of angina in ethnic groups difficult. Furthermore, the definitions and measures of angina have been largely derived and validated in White male populations. The prevalence of angina was reported to be higher in some South Asian peoples compared to the majority White population (self-reported 'ever diagnosed by the participant's doctor') in the Health Survey for England in 2004 (Table 2).⁵⁸

	Caribbean	Indian	Pakistani	Bangladeshi	Chinese	Irish	General population
Men							
Observed %	3.4	4.9	6.9	3.1	1.6	4.0	4.8
Standardised risk ratio	0.73	1.26	2.85	1.24	0.60	0.73	1
Women							
Observed %	1.5	3.2	2.5	2.0	1.2	2.5	3.4
Standardised risk ratio	0.61	1.79	2.19	2.22	1.00	0.87	1

Table 2 Prevalence of angina in minority ethnic groups, Health Survey for England in 2004

However, when angina was assessed in this survey by the Rose questionnaire, the differences between minority ethnic groups and the general population were

smaller than those assessed by the self-reported diagnosis. Hence, the finding that the Rose questionnaire seemed to produce different responses to the self-reported diagnoses thus questions the validity of methods used to measure angina in South Asian populations. If the accurate measurement of angina is of importance in determining prevalence and prognosis, this assumes a higher importance if ethnic differences are apparent as a result of usage of these measures.

1.6.4 *Treatment of angina*

The management of angina comprises two main strategies:

- Anti-anginal medication - β -blockers, calcium-channel antagonists, nitrates and potassium-channel activators like nicorandil
- Coronary revascularisation (following investigation by invasive coronary angiography) – percutaneously by balloon angioplasty/stenting, or surgically through bypass grafting.

Many patients with angina are not investigated through coronary angiography, as symptoms may settle on medication alone. As the risk of death from coronary angiography is around 1 in 1000,⁵⁹ the purpose of coronary angiography is to plan a management strategy beyond medication alone that will improve the patient's quality of life or prognosis. American College of Cardiology/American Heart Association Guidelines for Coronary Angiography⁶⁰ recommend invasive investigation in patients with CCS class III and IV angina despite being on anti-anginal medication.

In patients with angina, those of South Asian origin have been reported to be less likely to undergo coronary revascularisation than those of White origin.⁶¹ This may not be solely explained by access to specialist services, as general practices with a higher proportion of South Asian patients have been reported as having higher rates of coronary angiography.⁵⁷ South Asian populations have also been shown to have higher rates of angiography than White populations in studies of healthy individuals.⁶² Furthermore, South Asian people were more likely to seek immediate care for (hypothetical) anginal symptoms than White people⁴¹ in a

survey on attitudes to health seeking behaviour and have been reported to have had more consultations with a general practitioner in the year before coronary angiography than White people.⁶¹ It has been proposed that differences in the description of symptoms might contribute to inequalities in medical care,^{40 63} as the diagnostic validity of symptoms plays an important role in deciding appropriate further clinical investigation and hence management.⁴⁷ This may explain ethnic differences in the loss of patients between getting a coronary angiogram and ultimately receiving the treatment, coronary revascularisation, after it.

1.6.5 Prognosis of angina

In patients with a diagnosis of angina, it has been reported that 17% will have died from coronary heart disease or been admitted with a non-fatal myocardial infarction or unstable angina within three years.²⁹

Prognosis of angina can be investigated both in terms of:

- the future risk of serious manifestations of coronary disease such as unstable angina, myocardial infarction and coronary death;
- as an outcome itself, as those who suffer angina and undergo treatment to allay their symptoms may have their symptoms return (symptomatic prognosis).

1.6.5.1 Risk of future myocardial infarction and coronary death

In those patients with exertional angina, prognosis for myocardial infarction and death is not improved by coronary revascularisation:

- A meta-analysis of randomised controlled trials in 2000 comparing PTCA (percutaneous trans-luminal coronary angioplasty, balloon angioplasty alone without stenting) with medical treatment alone in chronic coronary heart disease concluded that PTCA led to a reduction in angina (relative risk (RR) 0.70 (95% confidence interval (CI) 0.50-0.98)) but conferred no beneficial effects on risk of myocardial infarction or death.⁶⁴

- In the Second Randomized Intervention Treatment of Angina (RITA-2),⁶⁵ death or myocardial infarction occurred in 73 (14.5%) PTCA patients and 63 (12.3%) medical patients (p=0.21).
- A 1994 meta-analysis compared CABG with medical treatment and found that surgery conferred a survival advantage only in those patients with severe left main stem coronary disease, three-vessel disease, or two-vessel disease with a severely stenosed proximal left anterior descending artery.⁶⁶ However, only 10% of trial patients received an internal mammary artery graft in addition to their vein grafts, routine practice in current surgery now. Only 25% received anti-platelet drugs whilst use of statins was similarly low compared to current standards.

Secondary prevention medical therapy (aspirin, statins) on the other hand plays a role in the stabilisation of the atherosclerotic process, as shown in studies such as the REVERSAL study, where intensive lipid-lowering treatment with statins reduced the progression of coronary atherosclerosis as measured by intravascular ultrasound.⁶⁷ The effect of cholesterol lowering with statins on mortality and morbidity in patients with coronary heart disease is well-known, first muted on a large scale by the 4S study,⁶⁸ and subsequently shown on meta-analysis of 4S and four subsequent trials.⁵⁴

1.6.5.2 Risk of future recurrent angina

The importance of revascularisation in improving symptomatic outcomes has been shown in both meta-analyses⁶⁴ and large clinical trials.⁴⁷ However, studies have documented that many patients undergoing revascularisation still have angina after 1 year^{69 70} and ethnic disparities in clinical outcomes have been reported in African-American patients who reported higher rates of angina than White patients at six months following coronary angiography.⁷¹ A study on outcomes following coronary bypass surgery revealed that medical management, length of stay and hospital morbidity in Indo-Asian patients was no different from that of their White Caucasian counterparts, though numbers were small (n=194 in both arms) and follow-up short, limited to in-patient stay post-operatively.⁷² If South Asian patients do have higher long-term symptomatic

outcomes however, this would increase the size of the prevalent pool of angina in South Asian populations. This is of importance to public health as angina places a significant burden on both morbidity and health service usage, with angina patients constituting up to two thirds of the patients that undergo PCI in Western countries.^{64 73}

1.7 Myocardial infarction

The arrival of sensitive and specific serologic biomarkers has led to a change in the definitions of myocardial infarction. The World Health Organisation had defined myocardial infarction as a combination of two of three characteristics: typical symptoms (i.e., chest pain/discomfort), enzyme rise and a typical electrocardiogram pattern involving the development of Q waves.⁷⁴ The arrival of biomarkers has led to the introduction of the term 'acute coronary syndrome' which now includes all those with ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina.^c

1.7.1 Definition of myocardial infarction

The ability to detect very small infarcts that would not previously have been considered a myocardial infarction has resulted in many individuals, who were formerly diagnosed as having unstable angina, being diagnosed today as having had a myocardial infarction. This has resulted in a change of definition of myocardial infarction as presented in the consensus document of the Joint European Society of Cardiology/American College of Cardiology committee in 2000.⁷⁵ Creatine phosphokinase-MB isoenzyme (CK-MB), a previously widely-used biomarker for myocardial infarction, has now been shown to be unsuitable as a diagnostic gold standard for the diagnosis of myocardial infarction⁷⁶ and the use of cardiac troponins are now widespread. Troponins are integrally involved in the process of myofibril contraction and relaxation within the cardiac myocyte and troponin T and troponin I are highly sensitive and specific markers of myocardial injury.

^c The term acute coronary syndrome in this thesis will henceforth imply the inclusion of myocardial infarction within it

The new definition of a myocardial infarction now requires a raised troponin level, after which electrocardiogram changes indicative of ischaemia allow further classification into clinically-relevant types which determine appropriate clinical management. These types include STEMI with ST segment elevation on ECG representing total occlusion of a coronary artery and NSTEMI with ST segment depression representing sub-total occlusion of a coronary artery. The term 'unstable angina' still represents the initial presenting clinical syndrome of recurrent episodes of angina on minimal effort or at rest, and a raised troponin consequently redefines it as a NSTEMI.

A troponin value of 0.05 µg/l has been proposed as the most appropriate to define an acute coronary syndrome,⁷⁶ though what constitutes a myocardial infarction remains unclear, the most recent consensus document (Joint Task Force for the Redefinition of Myocardial Infarction) simply stating that 'an increased value for cardiac troponin is defined as a measurement exceeding the 99th percentile of a normal reference population'.⁷⁷ Many hospitals define a NSTEMI as a troponin above a certain level, such as 0.05 µg/l or above, and thus use the term 'troponin-positive acute coronary syndrome' for those with a raised troponin, but which is less than 0.05 µg/l. There is no consensus however for this, and the troponin cut-point is often used simply to allocate those who would have cardiac rehabilitation. In practice, the treatment of NSTEMI and 'troponin-positive acute coronary syndrome' are broadly similar.

1.7.2 Prevalence of myocardial infarction

National surveys^d report a prevalence of myocardial infarction in the UK of around 14% in men and 3-7% in women aged 65-74. The prevalence of myocardial infarction in men aged 55-64 is between 6-9%, whilst for women the figures are 2-4%. However, the situation is complicated by the heterogeneous

^dHealth Survey for England 2006 <http://www.ic.nhs.uk/statistics-and-data-collections/health-and-lifestyles-related-surveys/health-survey-for-england/health-survey-for-england-2006:-cvd-and-risk-factors-adults-obesity-and-risk-factors-children>

The Scottish Health Survey 2003 <http://www.scotland.gov.uk/Publications/2005/11/25145024/50253>

nature of myocardial infarction as described above. Furthermore, from a predominance of STEMI in the past, STEMIs are declining in prevalence,⁷⁸ with the overall proportion of NSTEMI increasing.⁷⁹

The multinational Global Registry of Acute Coronary Events (GRACE) project reported data from its first 11543 patients in 2002.⁸⁰ Of these patients included, 38% had a final diagnosis of unstable angina, 30% had STEMI, and 25% had NSTEMI. The ENACT study in 1999 on patients hospitalised with acute coronary syndromes in 390 hospitals in 29 European countries reported that unstable angina was the most frequent cause of hospitalisation (46%), followed by acute myocardial infarction (39%).⁸¹ In a prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe, the Euro Heart Survey of Acute Coronary Syndromes reported an initial diagnosis of STEMI in 42.3%, NSTEMI in 51.2%, and 'undetermined electrocardiogram acute coronary syndrome' in 6.5%.⁸²

1.7.2.1 Prevalence of myocardial infarction by minority ethnic group

With regard to ethnicity, the age-standardised risk ratios of myocardial infarction for South Asian men and women did not differ significantly from men and women in the general population in the Health Survey for England in 2004 in all aged above 16 years.⁵⁸ There is a trend towards a younger age of presentation in South Asian patients.^{8 83}

1.7.3 *Treatment of myocardial infarction*

Treatment of patients with an acute coronary syndrome who present with ST-segment elevation on the ECG (STEMIs) is principally aimed at restoration of myocardial perfusion (reperfusion) using fibrinolysis (thrombolytic drugs) or increasingly primary percutaneous coronary intervention (PCI, angioplasty/stenting). However, NSTEMIs and unstable angina are more heterogeneous in their presentation and are associated with a higher variation in diagnosis and treatment.⁸⁴ Variations in receipt of medical treatment such as statins as well as access to angiography and subsequent receipt of coronary revascularisation are widely present in such patients.⁸⁵ The wide range of clinical

manifestations and hence treatments will result in variable prognoses. Reasons behind these variations may include:

- the use of different definitions for 'unstable angina' and 'NSTEMI'⁸⁴
- differences in the characteristics of presenting patients
- geographical practice variation,⁸¹ which is influenced by the incidence of coronary heart disease in the local population, the type of resources available, and doctors' perceptions of existing therapies.

It is conceivable that ethnic differences will exist in treatment and hence prognosis and explaining reasons behind such differences will entail consideration of not only biological differences but also socio-demographic and clinical management variables.

1.7.4 Prognosis of acute coronary syndromes

The hospital death rate for patients with STEMI in the GRACE study was 7%,⁸⁵ whilst those patients with NSTEMI and unstable angina had a rate of death at seven days of 6% and 3% respectively. Longer-term follow-up has shown that within five years of first admission with an acute myocardial infarction, around 40% of patients will have died, principally of a repeat myocardial infarction or other coronary cause.⁸⁶

However, it has been reported that 70% of those with 'unstable angina' can have detectable elevated troponin levels.⁷⁶ These patient would have had CK-MB's reported as within the normal range. The importance of this is more than just to categorise. These patients with elevated troponin levels are subject to a significant risk of adverse cardiac events. 50% of these patients will experience recurrent ischaemia and 10% will die or re-infarct within 30 days despite optimum medical management. This has prompted investigation into better pharmacological therapy and the role of invasive procedures.⁸⁷ Patients with the highest risk of adverse complications are most likely to derive the greatest benefit from invasive therapy and the release of troponin identifies high-risk patients where early coronary intervention significantly reduces adverse coronary outcomes, as those without a troponin release have similar outcomes

with either a pharmacological therapy approach or an invasive revascularisation approach.⁸⁸

Using troponin testing as a means of improved discrimination of those at risk, inequalities in the clinical management of acute coronary syndromes may be reduced. Prior to the widespread introduction of troponin testing, a considerable difficulty in clinical practice was in identifying those at risk within the wide spectrum of patients that presented with acute chest pain.

1.8 Factors determining prognosis of angina and myocardial infarction

Aetiological factors that predict incidence, both biological and social, may also influence prognosis. Prognosis will also be affected by strategies of clinical management and level of disease severity at time of presentation of coronary disease. Furthermore, prognostic outcomes should include not only the risk of future death and other serious clinical presentations but also those that measure morbidity, i.e., in patients with angina, the study of symptomatic outcomes (improvement of angina).

1.8.1 Risk factors

In White populations, aetiologic risk factors for myocardial infarction such as hypertension, diabetes and smoking are in addition prognostic factors.^{89 90} In patients diagnosed with coronary heart disease who smoked, a systematic review of cohort studies showed a 36% reduction in crude relative risk of mortality for patients who quit compared with those who continued smoking.⁹¹ However, such patterns may not be as simple in South Asian populations. In a prospective cohort study conducted of 828 South Asian and 27,962 non South Asian patients in the UK with insulin-treated diabetes diagnosed at ages under 50 years, standardised mortality ratios for South Asian patients (mainly of Indian or Pakistani descent) diagnosed with diabetes under age 30 years were 3.9 (95% CI 2.0-6.9) in men and 10.1 (5.6-16.6) in women, and in the corresponding non South Asian patients were 2.7 (2.6-2.9) and 4.0 (3.6-4.3), respectively.⁹² That diabetes mellitus may have a worse prognosis in South Asian patients for future adverse coronary outcomes and diabetes-related complications has been

proposed by others,⁹³ and the finding that South Asian patients have poorer knowledge and understanding of diabetes⁹⁴ may play a role in this.

The prevalence of risk factors also differs by ethnic groups, and prevalence is not necessarily higher in South Asian populations, with lower levels of total cholesterol and smoking prevalence than the White majority population.⁹⁵ Furthermore, South Asian patients, from Bangladeshis in London to Indians in the USA, present with coronary disease at younger ages than White patients,^{96 97} age being the most important non-modifiable risk factor in the aetiology and prognosis of coronary disease from large population studies such as Framingham⁹⁸ and the World Health Organisation MONICA Project (multinational monitoring of trends and determinants in cardiovascular disease).⁹⁹

1.8.2 Disease severity

Within the coronary disease phenotypes of angina and myocardial infarction, the severity of disease at presentation will affect prognosis. Severity of disease can be classed as anatomical, functional and symptomatic.

1.8.2.1 Anatomical severity

The degree of coronary disease at coronary angiography predicts future risk of adverse outcomes in those presenting with myocardial infarction.¹⁰⁰ Previously reported ethnic differences in degree of coronary disease between South Asian and White populations may therefore be a factor in prognosis, as South Asian patients have been reported to have more severe coronary disease at angiography than White patients when presenting with coronary disease.¹⁰¹

The breakdown of acute coronary syndrome by degree of coronary occlusion (e.g. STEMI/NSTEMI) and whether an effect modification of this on the relationship between ethnicity and prognosis exists is not known. Furthermore, it is not known whether South Asian patients present with differing severity of myocardial infarction (levels of troponin, left ventricular function) to White patients and whether this in turns affects prognosis.

1.8.2.2 Functional severity

The degree of myocardial ischaemia associated with coronary artery disease can be measured by exercise ECG testing, which remains the most widely accessible and relatively inexpensive method. Prediction of future coronary events and mortality is also an important use of the exercise ECG.¹⁰²

1.8.2.3 Symptomatic severity

That the South Asian population is more likely to report atypical features of pain require prognostic analyses to take this into account. Typical pain is suggestive of more severe coronary disease than atypical pain.¹⁰³ Comparing the prognostic validity of typical against atypical chest pain descriptors for severe adverse outcomes such as myocardial infarction and coronary death is therefore of importance. Furthermore, severity of angina predicts higher physical and role functioning and hence prognosis in terms of symptomatic outcomes (improvement in angina) needs studying.

1.8.3 *Social environment*

The comparative prognosis of acute coronary syndromes in South Asian and White patients may be affected by a range of factors that are not only biological but social. Previous research has shown the association between individual-level socioeconomic characteristics and coronary heart disease, a higher socioeconomic status associated with a lower coronary mortality,¹⁰⁴ and that the social deprivation of areas influences the aetiology and prognosis of coronary disease.¹⁰⁵

1.8.3.1 Deprivation

South Asian populations are more likely to live in areas with relative social and economic deprivation.¹⁰⁶ Studies that report that South Asian patients receive worse clinical management suggest this may be associated with the deprived areas they live in.²⁹

1.8.3.2 Access to care

The relationship between social environment and minority ethnic group health need not necessarily be a negative one. Distance from hospital is a prognostic factor – in a study examining ambulance journeys to hospital of patient with potentially life-threatening conditions, increased distance from hospital was

associated with increased risk of death (odds ratio 1.02 per kilometre; 95% CI 1.01 to 1.03; $p < 0.001$). This association was not changed by adjustment for confounding by age, sex, clinical category or illness severity.¹⁰⁷ This is of relevance to prognostic analyses in acute coronary syndromes considering minority ethnic groups in the UK tend to live close to acute hospitals.¹⁰⁸ It has long been recognised that access to coronary revascularisation services may, paradoxically, be increased in deprived areas in the UK, probably as a result of their proximity to specialist cardiac centres such as teaching hospitals.¹⁰⁹

1.8.4 Clinical management

1.8.4.1 Secondary prevention drugs

Cross-sectional studies have reported in ecological-type analyses that general practitioner prescribing rates of statin prescription were lower in primary care trusts with a higher percentage of South Asian people.¹¹⁰ However, more recent studies using data from the 2001 Census and Quality and Outcomes Framework data suggest that such medical therapy, which plays an important role in improving prognosis,^{68 111} is on the contrary more highly prescribed in South Asian and more deprived communities.¹¹² Hence, taking into account such differences in clinical management is of importance in prognostic analyses.

1.8.4.2 Specialist investigation and treatment

Some studies report an underuse of coronary revascularisation amongst South Asian patients deemed appropriate to receive it.⁶¹ In acute coronary syndromes, an elevated troponin level subjects that patient to a significant risk of adverse cardiac events such as death, and hence access to early coronary revascularisation that reduces the risk of premature death is of higher importance. Thus, any underuse in a particular ethnic group will potentially worsen their prognosis.

In those patients with exertional angina, access to clinical management strategies which provide symptomatic relief for the patient will be of higher importance.

1.9 Relationship between healthy individuals and those with coronary disease, and factors affecting incidence and prognosis

Understanding the relationship between healthy individuals and those with coronary disease, and of how factors affecting incidence also affect prognosis requires the disaggregation of the coronary disease entity. The figure below (Figure 2) highlights the complexity of these relationships, and serves as a model for the prospective analyses of my thesis. It outlines the relationships within the umbrella of coronary disease of the primary clinical presentations of the pathological process of coronary atherosclerosis, angina and myocardial infarction. It demonstrates the possible pathways a healthy individual may present themselves to healthcare services with coronary disease, and the relationships of these coronary phenotypes with ensuing death.

This thesis seeks to compare if these relationships vary between South Asian and White populations, to investigate ethnic differences in incidence and prognosis of angina and myocardial infarction, and factors determining prognosis of these differing clinical presentations of coronary disease.

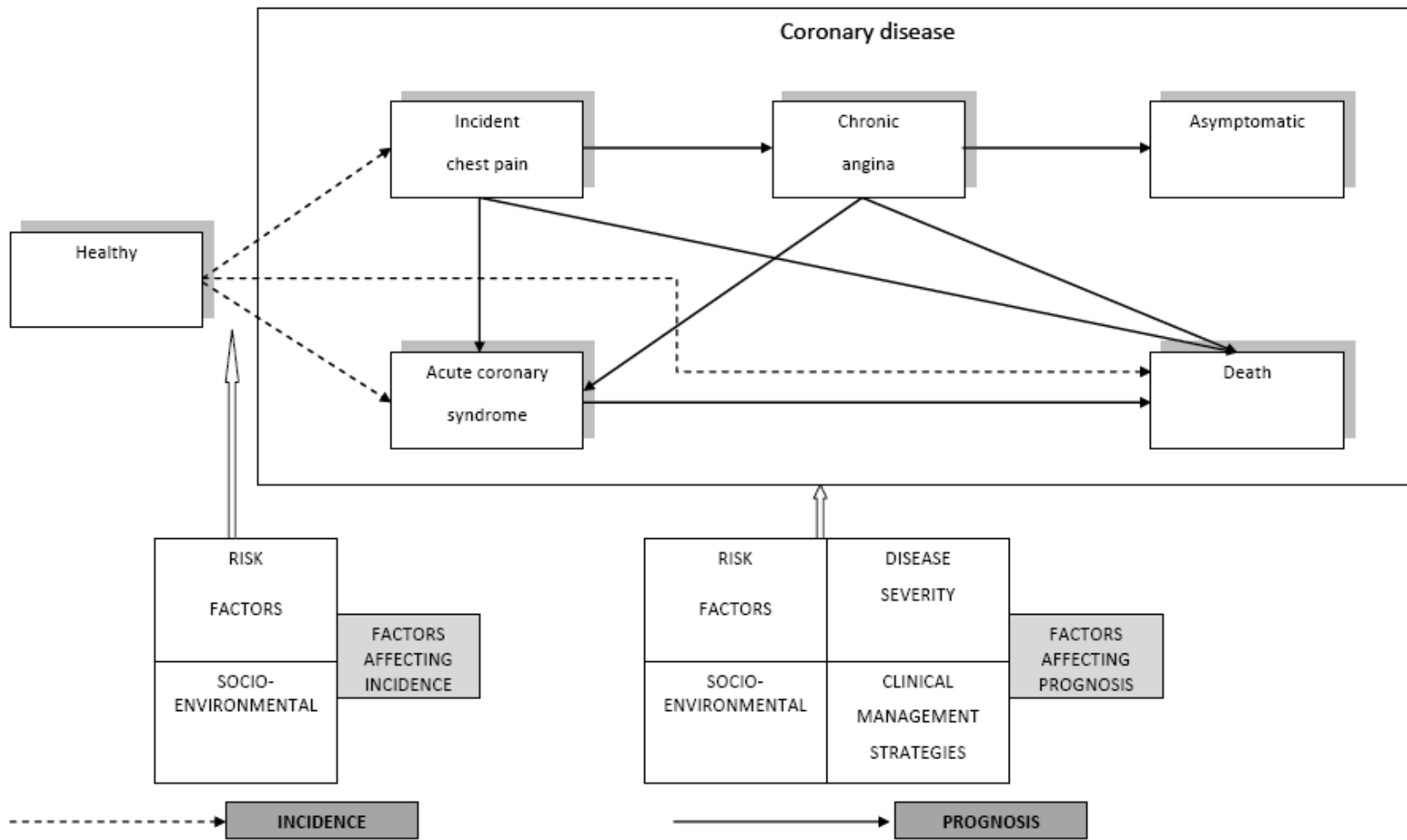


Figure 2 Relationship between healthy individuals and those with coronary disease, and factors affecting incidence and prognosis

2 Aims and objectives

2.1 Aim

This thesis seeks to investigate the contribution of incidence and prognosis of differing clinical presentations of coronary disease such as angina and myocardial infarction to the higher coronary mortality rates observed in South Asian compared to White populations in the UK.

2.2 Specific research objectives

1. To determine the incidence and prognosis of angina in healthy South Asian and White populations.
2. To determine in those presenting with incident chest pain whether differences exist in the description of symptoms between South Asian and White populations, and the association of symptom descriptors with prognosis and receipt of management strategies for chronic coronary disease.
3. To determine impact on symptomatic prognostic outcomes (change in angina severity) in South Asian and White populations from different management strategies for chronic angina.
4. To compare fatal prognostic outcomes of acute coronary syndromes in South Asian and White populations and assess factors underlying prognosis.
5. To assess the contribution of incidence and prognosis to the higher coronary death rates in South Asian compared to White populations through meta-analysis of the four cohorts and previously reported studies.

3 Systematic literature review

3.1 Summary of chapter

Background The higher coronary mortality in South Asian compared to White populations may be either due to a higher incidence of coronary disease in South Asian populations or a worse prognosis in them. A review in 2000 reported no evidence for a higher incidence of coronary disease in South Asian populations and the overall prognosis of coronary disease in South Asian compared to White populations was not known.

Methods A systematic review was conducted on MEDLINE and Embase from January 1966 to November 2008 to identify eligible prospective studies that compared incidence and prognosis of coronary artery disease in South Asian and White populations. Backward citation tracking through hand-searching of reference lists of eligible studies and forward citation tracking of subsequent articles that cited eligible studies were conducted.

Results Of six studies on incidence, five reported that South Asian populations have a higher incidence of coronary disease. There were few data on non-fatal incidence. When considering the seven studies on prognosis, event numbers were low in South Asian participants (221 recorded in total, they were heterogeneous in their methods and adjustment for confounders was lacking. Studies focussed more on fatal rather than non-fatal outcomes, and on presentation with myocardial infarction rather than angina.

Conclusions The literature on incidence of coronary disease in South Asian populations suggests a higher incidence of fatal coronary disease in them compared to White populations, but the literature on non-fatal incidence is sparse. When considering prognosis, the literature is unable to definitively answer whether prognosis is worse in South Asian compared to White populations.

3.2 Introduction

A higher coronary mortality in South Asian compared to White populations has been reported from census data in the UK. Whether this is a consequence of higher incidence of coronary disease or a worse prognosis of already-manifested coronary disease in South Asian compared to White populations is not known. Furthermore, incidence itself can be non-fatal or fatal and the prognoses of differing clinical presentations such as angina and myocardial infarction are different. Prognostic outcomes should also examine not only the risk of future death but also non-fatal outcomes for the overall assessment of prognosis.

A systematic review published in 2000 examining the evidence of coronary disease in South Asian compared to White populations reported that of the 19 studies retrieved, none reported incidence, and highlighted the higher number of cross-sectional studies measuring prevalence of coronary disease phenotypes such as self-reported angina.¹¹³ No prospective studies were reported. There was also wide heterogeneity in case definitions of ethnic grouping, and in the measurement of differing clinical presentations of coronary disease such as angina and myocardial infarction. The overall picture of incidence and prognosis of coronary disease in South Asian compared to White populations is thus not known.

3.3 Research objective to be investigated

This chapter sought to systematically identify and critically evaluate published literature relating to all five specific research objectives of this thesis.

3.4 Specific research questions

- i. What is the current knowledge from peer-reviewed published literature on the incidence of coronary disease (fatal and non-fatal) in healthy South Asian and White populations?
- ii. What is the current knowledge from peer-reviewed published literature on the comparative prognosis of the coronary disease presentations of

angina and myocardial infarction in South Asian and White populations?

3.5 Methods

3.5.1 Search strategy

MEDLINE 1966-2008 was searched without any language restriction and using the following Medical Subject Heading terms:

(India or Pakistan or Bangladesh or Sri Lanka or Ethnic Groups or ethnology or Asian Continental Ancestry Group or Asia) AND (coronary or myocardial infarction or myocardial ischaemia or cardiovascular disease)

Studies were identified for incidence or prognosis by adding these as text word search terms. To focus further on longitudinal studies and incidence, the search was expanded using a combination of all the Medline Clinical Queries filters for incidence,¹¹⁴ and including 'follow-up studies' and 'treatment/disease-outcome' as terms as well. The search was repeated in Embase. Hand-searching of the reference list of eligible studies was conducted to identify further relevant work (backward citation tracking). Science Citation Index was used to identify all the subsequent papers that cited any of the eligible studies (forward citation tracking) using ISI Web of Science.

This search was undertaken prior to commencement of this PhD and updated in November 2008.

3.5.2 Inclusion criteria

The titles and abstracts and, where not clear, full manuscripts of all identified studies were examined and eligibility for inclusion was defined if:

- The study compared South Asian and White ethnic groups.
- For incidence:
 - The study was prospective in populations without clinically manifested coronary disease, or presented data on relative risk of coronary mortality from cross-sectional analysis.

- Outcomes were defined as death and incident non-fatal myocardial infarction or angina.
- For prognosis:
 - The study was prospective in a population with the coronary disease phenotypes of angina (stable or unstable) or myocardial infarction/acute coronary syndrome.
 - Outcomes were defined as mortality from coronary disease or non-fatal angina/myocardial infarction.

3.5.3 *Data extracted*

The full manuscripts of the papers remaining were obtained and the following data extracted from each paper

- setting of study
- number of participants by ethnic group
- the terminology used for the ethnic groups (retained in describing eligible studies in this chapter)
- age (mean or median)
- numbers of women/men and diabetics
- outcome and duration of follow-up
- risk factors that were adjusted for in prospective analyses.

3.5.4 *Incidence of coronary disease*

The MEDLINE search strategy for incidence is outlined in appendix 13.4. 137 relevant publications were found.

3.5.4.1 *Papers excluded after reviewing titles and abstracts*

Of the 137 results obtained, after scanning the titles and abstracts, 46 were excluded on the basis that the study focussed on an ethnic group other than

South Asian (such as Black, Far Eastern), or used a comparison group other than White.^{115 e}

Four studies within these 46 presented mortality data by splitting the South Asian population into their constituent peoples. As this thesis aims to study the South Asian population as a whole group, these studies were not comparable to the planned analyses for this thesis.^{11 13 116 12} As outlined earlier, many similarities exist between South Asian peoples, and differences between South Asian peoples are less likely to affect prognosis than incidence.

However, these studies are of broader relevance and are outlined in the table below. The study by Harding et al¹¹ examined trends for coronary heart disease mortality among migrants in England and Wales from 1979–2003. Most South Asian populations remained at higher risk of death in all three time periods. Wild's study of 2001 census data¹² utilised the ability of this latest census to code the South Asian population by their constituent peoples. Mortality rates remained higher in all South Asian peoples. The group were unable to provide a standardised mortality ratio for the South Asian population as a whole (personal communication, Sarah Wild). Hippisley-Cox et al¹¹⁶ examined incidence of cardiovascular disease and found a higher incidence of combined non-fatal events in all South Asian peoples. Fischbacher et al's¹³ comparisons within the Scottish population did not report excess coronary mortality in all South Asian peoples. However, the authors commented that when using England and Wales as a comparison group, the excess of coronary mortality risk among the South Asian population in Scotland was comparable to that reported in England and Wales.

^e An example of the latter showed that Asian Indian male migrants were more prone to suffer from a myocardial infarction or coronary death than the majority populations of Chinese and Malays in Singapore.

Study (year of publication)	Methods	Outcomes	Results
Harding (2008)	From Office for National Statistics anonymised death records 1979-83, 1989-93 and 1999-2003.	Cross-sectional age-standardised and sex-specific death rates and rate ratios	In all three time periods, compared with men born in England and Wales, men born in East Africa, India, Pakistan, Bangladesh, Scotland, Northern Ireland, Republic of Ireland or Poland had higher mortality. Among women, consistently higher mortality was seen for those born in India, Scotland, Northern Ireland or Republic of Ireland in all time periods compared to women born in England and Wales. Rate ratios in Pakistan-born women in 1999–2003 were more than twice that of England and Wales born women.
Hippisley-Cox (2008)	Prospective open cohort study with routinely collected data from general practice and linked Office for National Statistics death certificates, 1 January 1993 to 31 March 2008	Incident diagnosis of cardiovascular disease (coronary heart disease, stroke, and transient ischaemic attack)	Adjusted risk is 45% higher (29% to 63%) among Indian men, 67% higher (40% to 101%) among Bangladeshi men, and 97% higher (70% to 129%) among Pakistani men
Fischbacher (2007)	Census data for Scottish residents aged 25 years and over between January 1997 and March 2003.	Standardised mortality ratios by country of birth	High all-cause, coronary heart disease (CHD) and stroke mortality among Scottish residents born in Scotland, Northern Ireland, the Republic of Ireland, India and Hong Kong.
Wild (2007)	Population data from the 2001 Census and mortality data for 2001-2003.	All-cause and circulatory disease sex-specific standardised mortality ratios (SMRs) and 95% confidence intervals (CI) people aged 20 years and over in England and Wales by country of birth	SMRs for circulatory disease were as follows: people born in Bangladesh 167 (136–204); India 149 (142–157); Pakistan 174 (159–192).

Table 3 Studies examining mortality and incidence of coronary disease within South Asian peoples compared to White majority populations

Two studies within these 46 were North American studies which used proportional mortality ratios and did not present direct comparisons between South Asian and White populations and hence were not included.^{14 15}

77 were excluded as the study was not on coronary disease and 11 on the basis that the study examined cross-sectional associations of cardiovascular risk factors rather than coronary disease. The systematic review on the subject by Bhopal was in itself not an original study.¹¹³

Expanding the search traced a further six studies to add to the two from the initial search leaving eight in total for which manuscripts of the papers were obtained for full inspection.

3.5.4.2 Papers excluded after review of full text

The following were excluded:

A study which had originally recruited participants with hypertension from a time period between 1979 to 1993 used a combined outcome that made comparison with other studies' outcomes impossible.¹¹⁷ Khattar et al published a longitudinal comparison of morbidity and mortality among White, South Asian and Afro-Caribbean participants with hypertension, originally recruited between 1979 to 1993 at a North-West London district general hospital, and followed-up at five years for the risk of non-cardiovascular death, coronary events, cerebrovascular events, and peripheral vascular death. Coronary events consisted of a combined coronary death (myocardial infarction or ischaemia, ventricular fibrillation, and cardiac failure), nonfatal myocardial infarction, coronary artery bypass graft surgery, and percutaneous transluminal coronary angioplasty. South Asian participants had the highest all-cause event rate of the ethnic groups, the high event rate because of an excess of coronary events (2.86 in South Asian participants compared to 1.32 events/100 participant-years in White participants, $p < 0.01$). Cox proportional hazards regression analysis (adjusting for age, sex, diabetes, previous cardiovascular disease and 24 hour systolic blood pressure) revealed that South Asian origin was an independent predictor of time to a first event (South Asian v White participants: $p = 0.008$).

Patel et al's study followed up participants with hypertension¹¹⁸ to compare rates of myocardial infarction amongst South Asian participants compared to White European Caucasian participants. On comparison of baseline risk factors, Caucasian participants with hypertension were older, more likely to smoke, more obese and more hyperlipidaemic than South Asian participants, who had more diabetes. The use of antihypertensive therapies was more common amongst the Caucasian participants compared to South Asian participants. During the 5-year follow-up period the rate of myocardial infarction was double in South Asian

participants to that observed in European Caucasian participants. This increased incidence of myocardial infarction was fully accounted for by diabetes, and the group could not provide a multivariate-adjusted incidence rate ratio (personal communication, Jeetesh Patel).

This left six eligible studies comparing the incidence of coronary disease in South Asian alongside White populations, of which two were cross-sectional studies on mortality.

3.5.4.3 Flow diagram of search

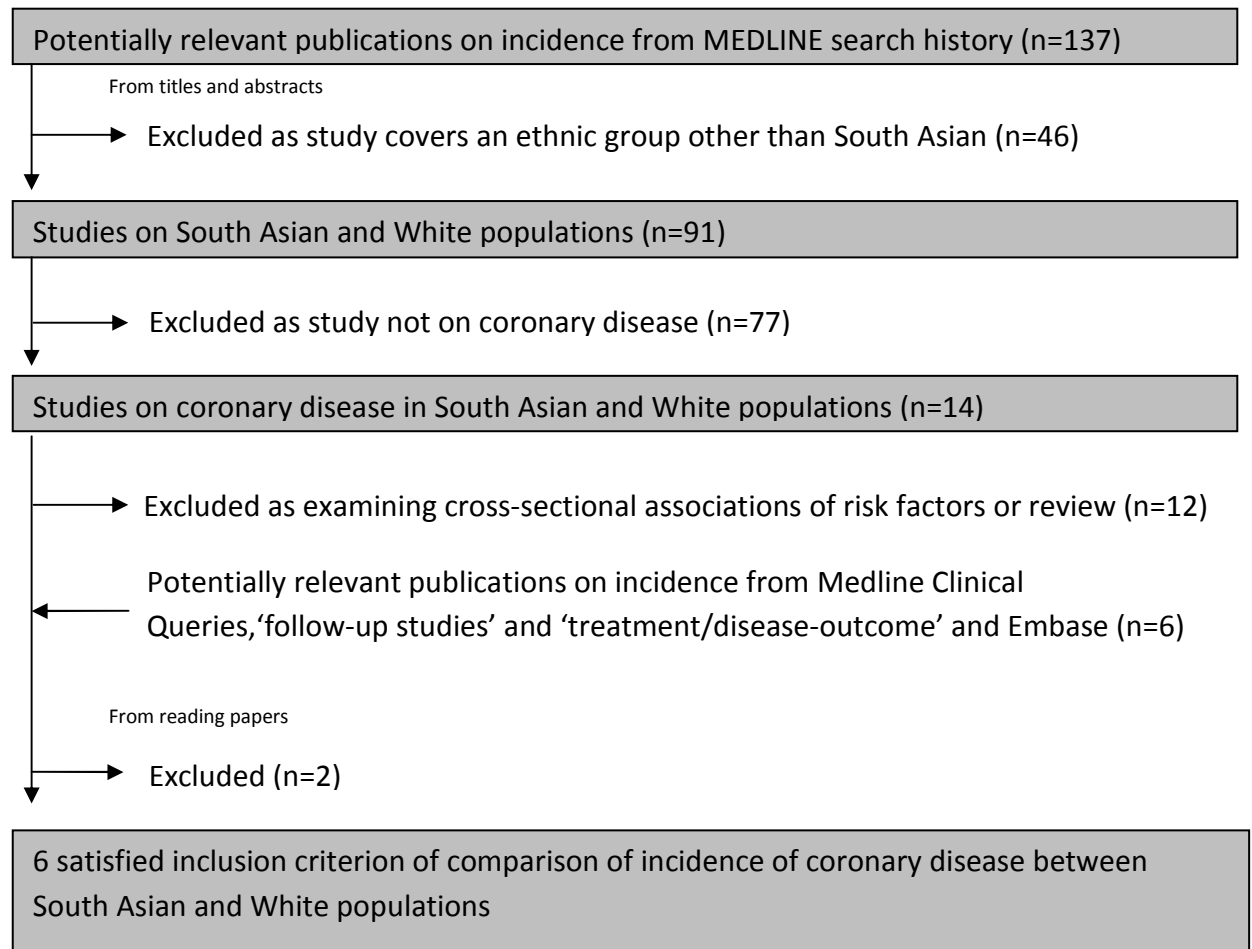


Figure 3 Literature search flow diagram for the comparison of incidence of coronary disease between South Asian and White populations

3.5.5 Prognosis of coronary disease

The MEDLINE search strategy is outlined in appendix 13.5. Using the clip-board facility on Search 2.0 to collate the articles found from searches numbered 28, 29, 30, 37, 43, there were 426 relevant publications.

3.5.5.1 Papers excluded after reviewing titles and abstracts

Of the 426 results obtained, after scanning the titles and abstracts, 100 were excluded on the basis that the study focussed on an ethnic group other than South Asian (such as Black, Far Eastern), or used a comparison group other than

White.¹¹⁹ ^f 246 were excluded as the study was not on coronary disease and 72 on the basis that the study examined cross-sectional associations of cardiovascular risk factors rather than coronary disease or was a review (Bhopal).¹¹³ This left eight studies.

Expanding the search traced a further study (appendix 13.6) to add to the eight from the initial search leaving nine in total for which manuscripts of the papers were obtained for full inspection.

3.5.5.2 Papers excluded after review of full text
The following were excluded:

Lane et al compared cardiovascular and all-cause mortality among White European, African-Caribbean and South Asian populations through an observational follow-up study in Birmingham. However, the dataset had serious limitations, given that significantly fewer South Asian men could be traced by the Office for National Statistics, and there were no data on follow-up for the South Asian women in the study at all.¹²⁰

Shaukat et al had in 1997 presented results in the BMJ that patients of Indian subcontinent origin were at substantially higher risk of mortality and of further coronary events than patients of European origin after first myocardial infarction. However, this work was subsequently retracted due to research fraud.¹²¹

This left seven eligible studies comparing the prognosis of coronary disease in South Asian and White populations.

^f An example of the latter is of Mak et al, who reported on myocardial infarction mortality event rates and mortality among Chinese, Malay and Indian residents of Singapore. In comparison with the Chinese population, the Malay population had the highest case-fatality.

3.5.5.3 Flow diagram of search

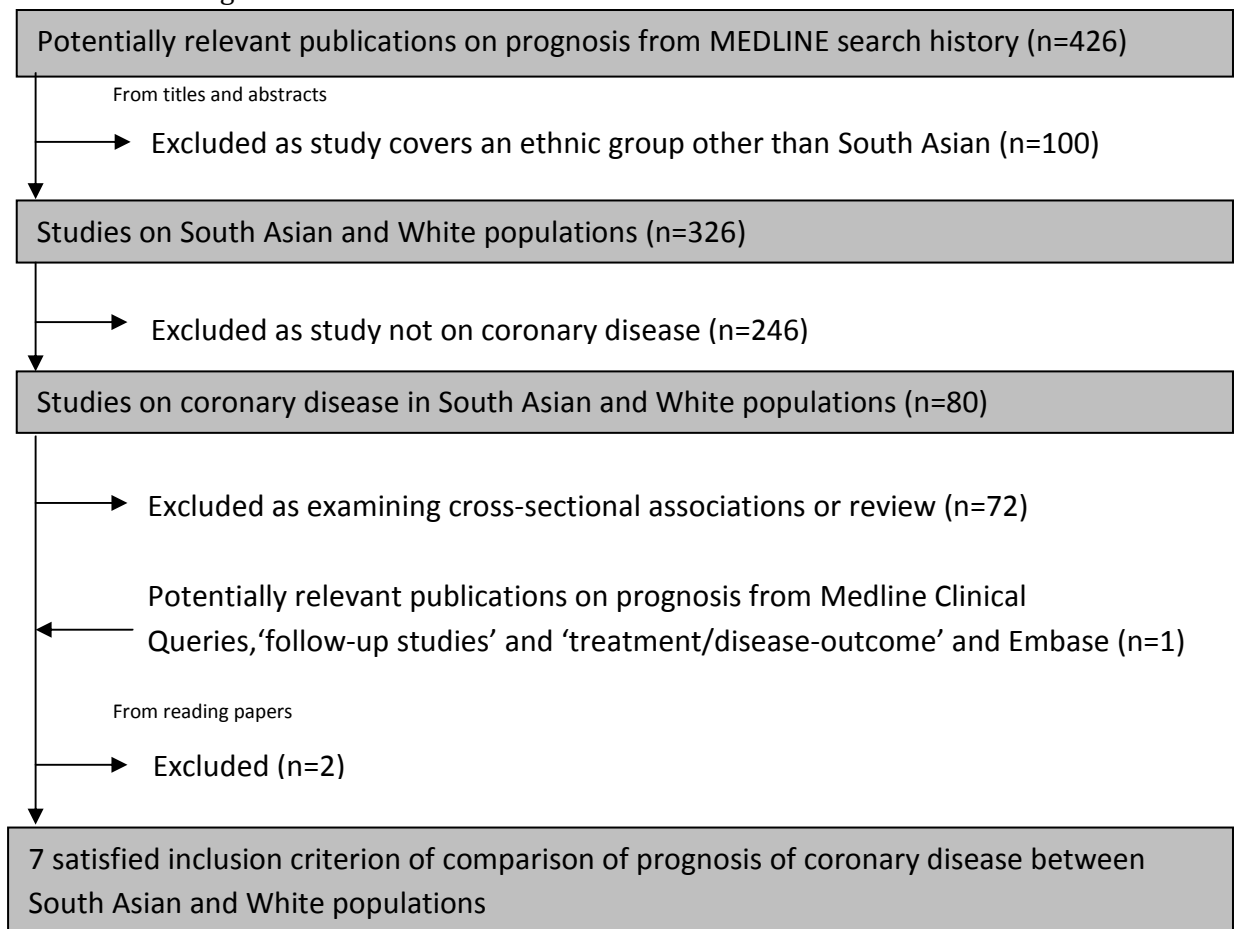


Figure 4 Literature search flow diagram for the comparison of prognosis of coronary disease between South Asian and White populations

3.6 Results

3.6.1 Studies included on incidence of coronary disease

These are described below, and further details tabulated after (Table 4).

3.6.1.1 Fatal outcomes

Two studies presented census data on the increased coronary mortality in South Asian compared with White populations. Balarajan's study based on the 1981 census,⁸ and Wild and McKeigue's study based on 1991 census data¹⁰ have already both been discussed in chapter 1.

One prospective cohort study that examined coronary death as a longitudinal outcome in healthy individuals comparing South Asian and White populations was found. Forouhi et al (2006)¹²² was designed to prospectively assess the survival of 1787 European and 1420 South Asian men recruited in West London in 1988. Ethnicity was identified on the basis of name, country of birth and appearance, supplemented by direct enquiry in cases of doubt. Follow-up, flagged for death notification from the Office for National Statistics, was 99.4%. Multi-variate Cox regression models were developed, and analyses adjusted for age and coronary risk factors. The results showed that South Asian men in this study had higher coronary mortality than European men, and this remained significantly higher in multi-variate models.

3.6.1.2 Non-fatal outcomes

3.6.1.2.1 *Healthy individuals*

Fischbacher et al's¹²³ 2007 paper examined incidence of fatal and non-fatal myocardial infarction. It was a record-linked retrospective cohort study of 4.6 million people. It linked information on individual ethnic group from the 2001 census to Scottish hospital discharge and mortality data. 94% of the census records were matched to a unique national health identifier, the Community Health Index record. Myocardial infarction was as recorded by a clinician at hospital discharge or recorded as the underlying cause of death on a death certificate. The South Asian population comprised people who were designated as the head of household at the 2001 census as Pakistani, Indian, Bangladeshi and other South Asian. The paper reported that the incidence rate ratio for acute myocardial infarction, fatal combined with non-fatal, was 1.45 (95% CI 1.17-1.78) for South Asian compared to non-South Asian men and 1.80 (95% CI 1.31-2.48) for South Asian women compared to non-South Asian women. Age, sex and previous admission for diabetes were adjusted for in the analyses. Out of the 126 incident myocardial infarctions in South Asian people, 21(17%) were fatal; in non-South Asian people, 9672(31%) of the 30978 events were fatal.

3.6.1.2.2 *Individuals with coronary disease risk factors but no coronary disease*

The UK Prospective Diabetes Study 32¹²⁴ sought to estimate the incidence of myocardial infarction (fatal and non-fatal combined) by ethnicity in participants

with diabetes (4974 patients, aged 25-65 years, 82% White, 10% South Asian). General practitioners referred 7,108 newly diagnosed participants with diabetes, aged 25–65 years, to 23 clinical centres throughout the UK between 1977 and 1991. The participant defined his or her own ethnicity. The median follow-up was 8.7 years. This study reported that the hazard ratio for the South Asian compared to the White population of myocardial infarction was 1.2 (95% CI 0.9-1.7), after adjusting for age, sex, year of study entry, systolic blood pressure, smoking, social class, total cholesterol, and high density lipoprotein (HDL) cholesterol.

The 11-year follow-up on the Southall Diabetes Survey¹²⁵ was undertaken in 1984. All subjects who could be traced for follow-up were sent a questionnaire which enquired about a history of heart attack requiring hospital admission. A 100% concordance was noted between self-reporting of morbid events and hospital case-notes. The study used the term European for the reference population. Completed questionnaires were obtained from 89% of the South Asian participants and 93% of European participants still alive. The method of ascertainment of ethnicity was not specified in the paper. A history of myocardial infarction requiring hospital admission (hence allowing ascertainment of incidence for solely non-fatal events) was 2.5 times more common in South Asian participants as in European participants and adjustment for the younger age of South Asian participants further increased the odds ratio for a history of myocardial infarction to 3.8 (95% CI 1.8–8.0, $p=0.001$). The study did also examine the coronary mortality rate ratio for the South Asian population versus the European population, though due to the age difference between ethnic groups, age-stratified analyses rather than an age-adjusted mortality was presented in the paper. This made it difficult to compare incidence of fatal events with other studies retrieved earlier with fatal outcomes. In those aged 30-64, risk of death from circulatory disease for ischaemic heart disease was twice as high in South Asian participants than in European participants, whereas coronary death rates in more elderly (age above 75) South Asian participants with diabetes appeared better than elderly European participants with diabetes.

Table 4 Literature search for the comparison of incidence of coronary disease between South Asian and White populations

Study (year of publication)	Design, setting and recruitment time	N (men/women)	Percentage diabetic (S. Asian/White)	Age	Length of follow-up in years/outcome	Number of events (S. Asian/White)	Results	Variables adjusted for in analyses
CROSS-SECTIONAL								
Wild (1997)	Cross-sectional census data, England and Wales, 1989-92	SA: 318,805/ 315,382 W: 15,634,589/ 16,070,270	-	-	-/coronary death	4230/177327	SMRs for those born in South Asia of 151 for women and 146 for men	Age
Balarajan (1991)	Cross-sectional census data, England and Wales, 1979-83	SA: 3410/798 W: 207,936/6248	-	-	-/coronary death	4208/277184	SMRs for those born in South Asia of 146 for women and 136 for men	Age
COHORT								
Forouhi (2006)	Cohort study of healthy men aged 40-69 from general practice lists in West London, 1988	SA: 1420/- W: 1787/-	35.4/ 19.6	South Asian 51.2 (7.0) White 52.9 (7.1) Mean (SD)	16.2/Coronary death	108/95	Adjusted coronary mortality higher in South Asian men (HR 1.68 (1.21,1.94))	Age, smoking, blood pressure, diabetes, lipids
Fischbacher (2007)	Census data, Scotland, 2001-2003	SA: 9706/9285 W: 1,464,458/ 1,709,148	-	-	2/fatal or first nonfatal MI	126 (38 women)/ 30978 (13276 women)	Incidence rate ratios in South Asian compared to non-South Asian 1.45 (1.17, 1.78) in men, 1.80 (1.31, 2.48) in women	Age, sex, previous admission for diabetes
U.K. Prospective Diabetes Study 32 (1998)	Prospective cohort study of patients with new type 2 diabetes, aged 25–65 years, from 23 UK clinics, 1977-91	SA: 336/154 W: 2367/1734	All	South Asian 47.0 White 52.2 Mean	8.7/ fatal or first nonfatal MI	490/4101	Adjusted hazard ratio for MI in South Asian compared to White participants 1.2 (0.9-1.7).	Age, sex, systolic blood pressure, smoking history, lipids, HbA1c
Mather (1998)	Prospective cohort study of patients with diabetes, aged 30 years and over, from community survey, 1984	SA: 730 (m+w) W: 304 (m+w)	All	South Asian 55.0 White 67.0 Mean	11/nonfatal MI	82/9	myocardial infarction requiring hospital admission 2.5 times more common in South Asian as in White participants	Age

HbA1c - haemoglobin A1C (glycosylated haemoglobin); MI – myocardial infarction

3.6.2 *Studies included on prognosis of coronary disease*

These are described below, and further details tabulated after (Table 5).

3.6.2.1 Outcomes from myocardial infarction

Six studies that compared prognosis between South Asian and White populations following presentation with myocardial infarction were found. All of these studies examined fatal outcomes, with none of them examining non-fatal outcomes.

The most recent paper was Fischbacher et al's study,¹²³ described above within the incidence search, which had also examined prognosis following myocardial infarction. After adjustment for age, sex and any previous admission for diabetes, the hazard ratio for death following myocardial infarction reflected better survival among the South Asian population.

Liew et al¹²⁶ reported on case fatality rates for acute myocardial infarction in South Asian and White patients admitted to a single centre coronary care unit. This study examined short-term (in-hospital) outcomes of patients over a period of 15 years. Hence the design of the study was to examine cross-sectional outcomes of patients with acute myocardial infarction treated in an inner city coronary care unit over a specific time period rather than specifically the outcomes of one cohort. Analysis of the records of all coronary care unit admissions of patients with acute coronary syndromes during 2002 at the unit was used to record ethnicity and this showed that 38% (196 of 521) were South Asian, which approximated well to the proportion of South Asian people (33%) living in the catchment area of the hospital at the time. Myocardial infarction was defined as any two of typical chest pain, 0.1 mV ST elevation on ECG and a rise in serum CK. The study concluded that the rate of in-hospital mortality was in progressive decline and that these improvements were observed in both South Asian and White patients. No difference in case fatality rates between South Asian and White patients was observed. Analyses were not designed to adjust for potential confounders.

Gupta et al published¹²⁷ a follow-up study of Canadian South Asian patients with myocardial infarction, albeit based on a retrospective review of charts from two

hospital sites, and only looking at in-hospital outcomes. Participants were matched for age, sex, hospital and discharge date. A list of all patients with a discharge diagnosis of myocardial infarction between January 1994 and April 1999 was obtained from the two hospitals in the study (n=4180). They identified South Asian patients by their surnames and first names, and by using self-reported ethnicity and country of birth when available. Of the 734 patients identified as probably from the South Asian population, 553 were matched to non-South Asian patients by age within five years, sex, hospital and discharge date within six months. Most of the remaining 181 South Asian patients were excluded because of inability to find a matched control subject or missing charts. Anterior infarctions occurred more frequently among the South Asian patients than among the control subjects but infarct size as measured by creatine phosphokinase did not differ significantly between the two groups. They reported similar in-hospital outcomes between the South Asian patients and matched control groups (in a logistic regression model using age, smoking status and diabetes, the risk-adjusted death rate was similar for the two ethnic groups (9.1% and 7.7% respectively, p=0.20).

Wilkinson et al compared mortality in South Asian and White patients in the six months after hospital admission for acute myocardial infarction in the east London borough of Newham.⁹⁶ They recorded ethnic group in all patients from their response to a direct question. South Asian patients were younger, a higher proportion of them did not smoke and a substantially higher proportion had diabetes (38.3% v 10.9%). After adjustment for age, sex, previous myocardial infarction, and treatment with thrombolysis or aspirin, or both, South Asian patients had a poorer survival over the six months from myocardial infarction (HR (95%CI) 2.02 (1.14-3.56)). Additional adjustments for diabetes, and also clinical symptoms and signs of left ventricular failure were performed, and this resulted in the excess risk disappearing (HR (95%CI) 1.44 (0.79-2.61)).

Mukhtar and Littler compared outcomes after myocardial infarction in South Asian patients with those of White patients in a prospective case-control study undertaken in Birmingham, UK.¹²⁸ All patients of South Asian ethnic origin aged

69 or less who were admitted with chest pain to the coronary care units of five hospitals in Birmingham between 1 July 1986 and 30 June 1987 were documented. Details of ethnic origin were recorded on the original admission and confirmed before discharge. All South Asian patients were matched for age and sex with White patients who were admitted to the same hospital during the same period of time and discharged alive with a confirmed diagnosis of acute myocardial infarction. There was no significant difference between the two groups with regard to the main risk factors for coronary artery disease. There was also no difference in the range of cardiac medication taken by the South Asian and White patients in the follow-up period. Information as to whether patients were alive or dead was obtained from their general practitioners. Patients with a confirmed myocardial infarction were invited for a follow-up interview 18 months after the original infarct. Four South Asian patients could not be traced. The paper reported no significant difference in survival or complications during the four years after an acute myocardial infarction in South Asian and White patients.

Hughes et al⁴⁶ compared the natural course of first myocardial infarction in Asian and White patients who had presented to the coronary care unit of a district general hospital in north-west London. The primary aim of the paper was to present data on the prevalence and characteristics of myocardial infarction between the two ethnic groups. Over two years from June 1985 to June 1987, 128 men (77 White, 54 Asian) presenting consecutively with a first myocardial infarction were recruited into the study. Myocardial infarction was diagnosed in the presence of any two of a clinical history compatible with infarction, a serial rise and fall in creatine phosphokinase activity and typical electrocardiographic changes persisting for a minimum of 24 hours. All patients were followed up for one year. Patients lost to follow up (seven White, eight Asian) were assumed to have followed a similar clinical course to the remainder of their ethnic group. Data on one-year follow-up for all-cause death showed that 14% of Asian patients had died compared to 10% of White patients (numbers of deaths being respectively six and seven in Asian and White groups). No account was taken for confounders such as diabetes and age.

3.6.2.2 Outcomes from angina

One study compared prognosis between South Asian and White patients of any other presentation of coronary disease bar myocardial infarction. This was an earlier report from one of the cohorts for this thesis. It examined South Asian and White patients with chronic angina undergoing coronary angiography and found no differences in mortality between South Asian and White patients (age-adjusted HR 1.05 (95% CI 0.68 to 1.63)) nor in rates of combined death and non-fatal myocardial infarction (HR 1.07, 95% CI 0.78 to 1.47) at median follow-up for 30 months.⁶¹ The paper's remit was not a focus on outcomes but more on appropriateness of care, and further adjustments for confounding variables were not performed.

3.6.2.3 Non-fatal outcomes

There were no studies retrieved that examined non-fatal outcomes such as angina.

Study (year of publication)	Design, setting and recruitment time	N (men/women)	Percentage diabetic (South Asian/White)	Age	Length of follow-up /outcome	Number of events (South Asian/White)	Results	Variables adjusted for in analyses
Fischbacher et al (2007)	Retrospective myocardial infarction cohort from census data (Scotland) 2001-2003	SA: 88/38 W: 17,696/13,276	-	-	2 years/all-cause death	40/17,075	Risk of death 0.59 (95% CI 0.43-0.81), reflecting better survival among South Asian patients.	Age, sex and any previous admission for diabetes
Liew et al (2003)	Myocardial infarction cohort (London, UK) 1998-2002	SA: 303 W: 469	-	-	days/all-cause death	19/56	No ethnic difference in in case fatality rates	Nil
Feder et al (2002)	Coronary angiography cohort (London, UK) 1996-1997	SA: 391/111 W: 2112/862	33/9	South Asian patients older (presented as age categories)	30 months/death or non-fatal MI	50/386	No ethnic differences in outcomes	Age
Gupta et al (2002)	Matched myocardial infarction cohort (Canada) 1994-1999	SA: 381/172 W: 381/172	43.4/28.2	South Asian 62.6 White 63.0 Mean age	6 days/Coronary death	45/39	Similar in-hospital mortality (9.6% and 7.8%, p = 0.27)	Age, sex, smoking, diabetes
Wilkinson et al (1996)	Myocardial infarction cohort (London, UK) 1988-1992	SA:129/20 W:259/54	38.3/10.9	South Asian 54 (49-59) White 57 (50-60) Median (inter-quartile range)	0.5 years/ all-cause death	49/78	South Asian population had poorer survival accounted for by diabetes	Age, sex, previous admission for diabetes, impaired left ventricle
Mukhtar et al (1995)	Matched myocardial infarction cohort (Birmingham, UK) 1986-1987	SA:102 W:102	23.5/14.7	South Asian 54.0(8.6) White 53.9 (68.5) Mean age (SD)	8.7 years/ fatal or first non-fatal MI	12/10	No significant difference in survival	Age, sex
Hughes et al (1989)	Myocardial infarction cohort (London, UK) 1985-1987	SA:23/20 W:50/20	-	South Asian 50.2 (9.0) White 55.5 (6.7) Mean age (SD)	1 year/all-cause death	6/7	14% of South Asian compared to 10% of the White population had died	Nil

Table 5 Literature search for the comparison of prognosis of coronary disease between South Asian and White populations

3.7 Discussion

From the systematic review of this chapter, there were some prospective studies on incidence of coronary disease, whilst still few in numbers, whilst the literature on prognosis in South Asian compared to White populations was heterogeneous and focussed mostly on fatal outcomes following myocardial infarction. The review of Bhopal in 2000 had concentrated on incidence and prevalence. It found no evidence was available on incidence of coronary disease in South Asian compared to White populations, and did not report any prognostic studies.

3.7.1 Incident disease

There were few studies examining incidence of solely non-fatal events and no studies on the incidence of angina in South Asian and White populations. There were only two prospective studies in healthy individuals, Forouhi et al¹²² and Fischbacher et al¹²³ both showing that South Asian populations had a higher incidence of coronary disease compared to White populations. Of the other studies in individuals with risk factors but no manifest coronary disease, all but one reported a higher incidence of coronary disease in South Asian compared to White populations. Hence, though few studies exist on incidence, there are at least some and this represents an improvement on Bhopal's review in 2000 which retrieved none.

3.7.2 Prognosis of disease

When considering prognosis, the literature was heterogeneous in terms of length of follow-up, with three of the studies on participants with myocardial infarction focussing solely on short-term, in-hospital events. Participant numbers were small, resulting in small numbers of outcomes. In total, across seven studies spanning recruitment from 1989-2003, there were only 221 events recorded in South Asian populations. Over half of these, 114 in total, were within one month of the index event. Adjustment for confounders was lacking – though all studies that recorded diabetes prevalence reported a higher prevalence in South Asian compared to White populations, multi-variate regression analyses were not consistently performed to account for this. None of the studies fully took into account ethnic differences in clinical management, social environment and

disease severity. Studies tended to focus mostly on fatal outcomes following presentation with myocardial infarction, and there was only one study examining prognosis of angina, and none on non-fatal outcomes. Finally, throughout all these studies, the method of recording of ethnic group was not consistent.

3.7.3 Implications

3.7.3.1 Incidence of coronary disease

The lack of studies examining incidence of solely non-fatal events such as angina between South Asian and White populations is significant. If incidence of non-fatal events such as angina is higher among South Asian populations than White populations, then the appropriate identification and management at this initial presentation may prevent progression to more serious later-phase manifestations of coronary disease such as myocardial infarction and ultimately coronary death. Therefore, knowledge of the incidence of angina is important to the overall picture of coronary disease epidemiology between South Asian and White populations.

3.7.3.2 Prognosis of coronary disease

Studies retrieved were heterogeneous in their methods and thus makes it difficult to render a conclusion on the prognosis between South Asian and White populations. No contemporary studies have examined prognosis between South Asian and White populations using the newer definitions of myocardial infarction taking into account troponin level. Furthermore, few studies exist that have compared prognosis between South Asian and White populations of any other presentation of coronary disease bar myocardial infarction such as angina.

3.8 Conclusion

The literature on incidence of coronary disease in the South Asian population is sparse but suggests overall a higher incidence of fatal coronary disease in South Asian compared to White populations. There are few studies on non-fatal incidence. When considering prognosis, the literature is heterogeneous and focussed mostly on myocardial infarction and thus is unable to answer whether prognosis is worse in South Asian compared to White populations.

4 Data in four cohorts used for this PhD

4.1 Summary of chapter

The purpose of this chapter is to present the four studies chosen to span the natural history of coronary disease and prognostic risk. The methodology of the datasets is compared and contrasted, and in particular the quality and validity of the data examined for those variables essential for the analyses of this thesis such as ethnicity and chest pain. This is of greatest importance in the acute coronary syndrome registry (MINAP), as the other three cohort studies were designed for research.

4.2 The cohorts

To answer the specific objectives of the thesis, four cohort studies were chosen to span the natural history of coronary disease.

4.2.1 *Healthy population cohort*

The Whitehall-II study was set up to examine reasons behind the social gradient in health and disease found in the original Whitehall study of the 1960s.¹²⁹ The target population for the Whitehall-II study was all civil servants aged 35–55 years working in the London offices of 20 Whitehall departments in 1985–88. 10308 people were recruited, 3413 women and 6895 men. The participants included all grades, from clerical and office support grades through middle-ranking executive grades up to senior administrative grades, differing widely in salary. The whole cohort was surveyed at the research clinic at 5-year intervals, and a postal questionnaire was sent out to them between clinic phases.^{130 131}

Ethical approval for the study was obtained from the University College London Medical School Committee on the ethics of human research.

4.2.2 *Chest pain clinic cohort*

The Chest Pain Clinic study recruited participants, all with suspected new-onset stable angina, in six rapid access chest pain clinics in the United Kingdom from 2 January 1996 to 31 December 2002. The participating centres were:

- ❖ Newham General Hospital
- ❖ Oldchurch Hospital
- ❖ Manchester Royal Infirmary
- ❖ Blackburn Royal Infirmary
- ❖ Burnley General Hospital
- ❖ Kingston General Hospital

The rapid access chest pain clinic at Newham General Hospital (now University Hospital) in east London was the first of these to be established in January 1996. It was one of the first nationally and four years later became the service model for the National Service Framework.¹³² § The National Service Framework for coronary artery disease recommended rapid access chest pain clinics for cardiological assessment of recent onset chest pain within two weeks of referral from primary care. This compressed timeframe from generalist to specialist could not be achieved in the conventional outpatient cardiology clinic with its referrals for a wide range of other cardiac conditions. Rapid access chest pain clinics concentrate cases of chest pain and thus can model revascularisation requirements by measuring the population frequency of the indications for which revascularisation confers benefit. Such an "incidence of indications" approach has been applied in other conditions (for example, the need for total hip replacement¹³³).

At the time the rapid access chest pain clinic was established, an electronic database was developed in which registry baseline data on consecutive patients attendances were recorded. The success of the database led to its utilisation in five other rapid access chest pain clinics around the country, all of which recorded data in identical fields to those used at Newham.

Ethical approval for the multi-centre study was obtained from a multiregional ethics committee (Multi-centre Research Ethics Committee /02/04/095). The National Patient Information Advisory Group gave permission to link anonymised data sets without obtaining individual patient consent.

4.2.3 Coronary angiography cohort

The Appropriateness of Coronary Revascularisation (ACRE) Study was a prospective study investigating clinical outcomes in patients undergoing coronary angiography at two hospitals within one NHS Trust – The London Chest

§ Policies set by the National Health Service in the United Kingdom to define standards of care for major medical issues and long term strategies for improving specific areas of care. They set national standards, identify key interventions and put in place agreed time scales for implementation

and St Bartholomew's Hospitals. It was set up in 1995 to assess the appropriate use of coronary angiography, as wide variations in practice existed. The resident population of the combined catchment area was 2,833,000 with 89% of the angiography procedures performed in this population being performed at this NHS Trust. Patients were referred from five different health authorities (East London and the City, Barking and Havering, Redbridge and Waltham Forest, North or South Essex) and 13 hospitals as well as approximately 700 GP practices.

Coronary angiography is defined by the American Heart Association as the 'radiographic visualization of the coronary vessels after injection of radio-opaque contrast media'.⁶⁰ A sheath is inserted percutaneously into a peripheral artery (most commonly the femoral artery in the groin) under local anaesthesia through which a fine hollow coronary catheter is manipulated, under x-ray guidance, into the origin of the coronary arteries. It is a relatively safe procedure, the risk of major complications being ~1 in 1000.⁵⁹ Complications include death, myocardial infarction, stroke, aortic or coronary dissection, cardiac rupture, air embolus, cardiac arrhythmia and peripheral arterial injury.

In ACRE, all consecutive patients undergoing elective (more than 90%) and emergency coronary angiography admitted between April 15th 1996 and April 14th 1997 were recruited at the time of their coronary angiogram. 4120 patients were identified from ward admission and catheter laboratory log books. There were no exclusion criteria. 54% of the ACRE cohort went on to revascularisation at 2.5 years. Ethical approval for the study came from the five local research ethics committees.

4.2.4 Acute coronary syndrome cohort

The Myocardial Infarction National Audit Project (MINAP) is a registry which contains data from patients with an acute coronary syndrome who have been admitted to all 230 hospitals in England and Wales.¹³⁴ The use of medical registries to audit clinical practice has sharply increased due to progress in information technology and increasing demands for accountability. A medical registry has been defined as 'a systematic collection of a clearly defined set of

health and demographic data for patients with specific health characteristics, held in a central database for a predefined purpose'.¹³⁵ Beyond their role as tools to monitor and improve quality of care, registries can also be a resource for epidemiological research. An advantage of such databases is that they include all-comers, and therefore have no exclusion criteria as in the case of clinical trials. Thus, conclusions from research from them are potentially applicable to all with the condition under study. Exclusion criteria within trials often exclude for example high-risk patients.

The degree of the population coverage within MINAP cannot be matched by the national register in the USA (which selects 20% of hospitals)¹³⁶ or elsewhere in Europe.¹³⁷ Each month, MINAP accrues over 7000 acute coronary syndrome events. MINAP records 108 data fields, covering acute coronary syndrome type and severity (such as ECG changes and markers of myocardial necrosis) risk factors, drugs and invasive management. Such data are not available in routinely collected Hospital Episode Statistics data, the national statistical data warehouse for England of the care provided by NHS hospitals and for NHS hospital patients treated elsewhere.^h Large-scale data on admission rates with ACS with respect to ethnicity, or by specific sub-types of ACS cannot be provided by Hospital Episode Statistics because there is no coding of ethnicity or of STEMI, ACS (troponin positive or negative) or NSTEMI. The database thus has the potential, through its large numbers of participants, to examine in detail hypotheses pertaining to the differing types of the acute coronary syndromes. Furthermore, it has the ability to take into account the multitude of confounding factors that operate when considering the prognosis of acute coronary syndromes. The MINAP dataset is a collection of terms and definitions which allows national consistency when comparing or describing any aspect of care of acute coronary syndromes. Not every data item is relevant for every patient, as those with STEMI will for example have a different clinical management strategy to those with NSTEMI. However, the value of such clinical registration datasets to research depends on

^h <http://www.hesonline.nhs.uk>

the quality of the data as the validity of registry data is most threatened by incomplete and incorrect data entry.

Between 1 January 2004 to 31 December 2004, 91684 patients were entered onto the database of which 27573 had an ST-elevation myocardial infarction (STEMI), 42281 had a non ST-elevation myocardial infarction (NSTEMI) and 7318 had a troponin-negative acute coronary syndrome. 2003 was the first year in which a full dataset was available using all 230 hospitals, as prior to this, hospitals were being increasingly recruited into the registry. The patients in MINAP have been followed up for their vital status, linked to the Office of National Statistics. MINAP has National Patient Information Advisory Group and Central Office for Research Ethics Committees approval for individual patient anonymous linkage for mortality. No patient identifiers are given out to researchers. MINAP is funded by the Healthcare Commission.

4.3 Assessment of data quality in each cohort

4.3.1 Data checking

The cohorts for study in this thesis were selected on account of the coverage they provide across the different stages of the natural history of coronary disease. The populations and methodology of the studies varied.

The following checks were performed on the data (definitions from Last's Dictionary of Epidemiology¹³⁸):

- Selection bias – “Error due to systematic differences in characteristics between those who take part in a study and those who do not.”
 - At the start-point of data collection within a research study is the recruitment process at which point such a bias can exist
- Information bias – “A flaw in measuring exposure or outcome data that results in different quality (accuracy) of information between comparison groups.” Within this category are:

- Recall bias – “Systematic error due to differences in accuracy or completeness of recall to memory of past event or experiences.”
- Observer bias – “Systematic difference between a true value and that actually observed, due to observer variation.”
- Cohort studies rarely suffer from recall bias due to their prospective nature, and observer bias was minimised in all these studies as classification of exposure status (e.g. ethnicity) was done prior to onset of disease.
- Measurement bias – “Systematic error arising from inaccurate measurements of subjects on study variable(s).”
 - This can result from missing data and also is the extent to which an instrument (such as a questionnaire) actually measures the characteristic that is of interest, its validity.

The table below outlines the data sources and methodology of the four datasets used, and potential areas where biases and errors may result.

Page 1/2	Aetiologic study	Prognostic studies (patients with coronary disease)		
Cohort	Whitehall-II	Chest pain clinic	ACRE	MINAP
Population	Healthy population, as yet having no diagnosis of coronary disease	People with chest pain of recent onset referred from primary care	Patients undergoing coronary angiography for chronic angina who have been reviewed by a cardiologist	Patients presenting as emergencies with acute, severe chest pain at rest
Location	London offices of 20 civil service departments	Six rapid access chest pain clinics across England	Two hospitals within one NHS Trust, London	230 hospitals across England and Wales
Dates of baseline data collection	1985–8	2 January 1996 to 31 December 2002.	15 April 1996 to 14 April 1997.	Full national recruitment from 2003 onwards. Continuous registry and data accrue year on year.
Recruitment method	Epidemiological research study, consented participants, with clinical examinations and questionnaires administered at baseline by designated research staff.	Clinical database within an NHS clinic. Data recorded by a cardiologist using identical databases.	Clinical research study, consented participants, with baseline questionnaire administered and review of case notes by designated research staff.	Clinical database, with data recorded by coders at individual hospitals and sent to a collating centre.
Total numbers/response rate at baseline	10308 recruited/73%	11185/100% consecutive patients	4020/100% consecutive patients	91687/100% consecutive patients (in 2004)
Baseline data completeness	99.9%	92.5%	98.0%	Variable
Collection of ethnicity variable	Ethnicity was defined according to the Office for National Statistics 1991 census types. Participants self-reported their ethnicity at	Cardiologist ascribed ethnicity as Asian, White, Black or other during the consultation.	Self-assigned ethnicity was based on the 1991 census classification by questionnaire	The patient's ethnic group was determined by the clinician/health care worker. Ethnicity was coded as Asian, Caucasian, Black, Oriental or

Page 2/2	phase 5 (1997–1999), observer-assigned ethnicity at baseline.			other.
Completeness of data for ethnicity	99.9%	81.2%	89.7%	80.2% (in 2004)
Number of South Asians	580	2900	502	3236
Main exposures used for analyses of thesis	Rose questionnaire angina	Chest pain descriptors (typical/atypical)	Canadian Cardiovascular Society classification of angina severity	Diabetes, disease severity (troponin) and acute coronary syndrome type
Follow-up	Seven follow-up phases over 18 years by post and by interview/examination. Office for National Statistics	Office for National Statistics, Hospital Episode Statistics	Six-year follow-up by post. Office for National Statistics, Hospital Episode Statistics. Case notes and Patient Administration Systems	Office for National Statistics
Outcomes	Chest pain Non-fatal MI Death	Angiography/Revascularisation Non-fatal MI Death	Change in angina Non-fatal MI Death	one-year all-cause mortality
Completeness of follow-up	99% of participants were flagged for mortality. Follow- up for the whole cohort by questionnaire was 67%.	99.5% of participants were flagged for mortality, hospital admissions, coronary angiography and revascularisation.	99% of participants were flagged for mortality, all-cause hospital inpatient admissions, and on hospital admission for revascularisation and non-fatal myocardial infarction	85.6% of South Asian and 91.2% of White populations were followed up for all-cause mortality.
Thesis objectives to be answered (thesis chapter)	1,5 (5)	2,5 (6)	3,5 (7)	4,5 (8)
Cohort	Whitehall-II	Chest pain clinic	ACRE	MINAP

Table 6 The four cohorts used for the thesis – data sources and methodology

4.3.2 *Recruitment at baseline*

Of the four studies, MINAP differed in being a database where individual consent is not sought at baseline admission and data entry is undertaken by the individual different hospitals, rather than dedicated members of a research team - hence checking the quality of baseline data variables was of particular importance.

Selection bias within cohort studies can occur if the exposed and unexposed groups differ in a fixed way. In an occupational cohort for example, the unexposed control group may be healthier than an exposed group of workers simply because they are healthy enough to stay in work. In the four studies chosen for this thesis, the exposed (South Asian population) and the unexposed (White population) groups were chosen from within the same study populations, prior to the development of the outcome (e.g., myocardial infarction, death) of interest. Thus, selection bias is reduced, and the checks undertaken for baseline recruitment and data collection revolved predominantly around data completeness.

4.3.2.1 Whitehall-II

This study initially recruited by inviting all non-industrial civil servants aged 35-55 working in the London offices of 20 departments. The overall original response rate at recruitment (Phase 1) was 73%, high for such a study,¹³⁹ reducing the possibility of selection bias. A further 4% of the civil servants on the lists provided by the civil service had moved before the study and were therefore not eligible for inclusion.¹⁴⁰ Completeness of data in those recruited was high at baseline in Whitehall-II as all participants were interviewed in person by research staff.

4.3.2.2 Chest pain clinic

As a prospectively recruited clinical cohort, all patients who consecutively attended to the clinics over the recruitment phase were included. The nature of the chest pain clinic is such that recent-onset chest pain is keenly sought, and referral guidelines to the clinic were agreed following discussions between general practitioners and the department of cardiology. The clinic is relatively easy to access in terms of logistics (appointments given within days rather than

months) and there are few hurdles to assessment in clinic presented to the general practitioner. Among patients fulfilling eligibility criteria, the cohort has previously reported that the chest pain clinic substituted for conventional cardiology out-patients clinic in all but 3% of cases.²⁹ Thus, significant differential referral by ethnicity to chest pain clinic is unlikely thus reducing the chance of selection bias. Consent was not sought at baseline due to the nature of the database as an on-going clinical database and completeness of baseline data in chest pain clinic was high at 92.5%.

Though data entry for smoking status, history of hypertension and diabetes and medication were 100% complete, history of hypercholesterolemia was unknown in 68.49% of the cohort and 78.4% did not have a cholesterol level. Data were available on the whole cohort for statin therapy - 1.9% of those with no data on hypercholesterolemia were on a statin, compared to 5.9% defined as not having hypercholesterolemia and 40.6% of those defined as having hypercholesterolemia. Thus, it is likely that among those in whom cholesterol was not known, a high cholesterol level was unlikely judging by their low statin prescription rates.

A previously published sensitivity analysis showed that the rates of coronary deaths and non-fatal events for patients with missing baseline data were not significantly different from those complete baseline data.²⁹

4.3.2.3 ACRE

As a prospectively recruited clinical cohort, all patients who consecutively attended for angiography over the recruitment phase were included – this eliminates selection bias in following up those selected for angiography, though it can not take into account selection bias in the actual selection process for angiography. On the day of coronary angiography, eligible patients were identified by examination of ward admission and catheter books. Trained nurses extracted data (e.g. on smoking, history of hypertension, diabetes, results of exercise electrocardiography, blood pressure) from all 4020 case notes using standardised forms. Furthermore, patients completed a questionnaire about their general health, coronary heart disease risk factors and angina symptoms

(data available for 3301/4020, 82% response rate). Within those case notes searched and questionnaires completed, completeness of data was high at 98%.

4.3.2.4 MINAP

MINAP is a continuous registry and data accrue year on year. Longitudinal patterns were investigated in a number of important fields to test the year-on-year consistency of data field entry and thus the quality of its measurements. Disease patterns in one year are likely to be comparable to the next if definitions of that disease have not changed.

Secular data entry patterns in percentages of electrocardiogram findings and diagnosis of acute coronary syndrome type were examined. MINAP has available, from 2003, four years of full data from all 230 hospitals in England and Wales. These years were also compared to pre-2003 data, during which time hospitals were being progressively recruited and hence data would be incomplete.

The results are shown in the table below.

Year	<i>Pre-03</i>	2003	2004	2005	2006
N	2769	92,252	93,469	89,635	77,255
ECG					
ST segment elevation	27.99	32.15	31.86	31.50	29.58
LBBB	7.87	4.98	5.29	5.53	4.90
ST segment depression	14.12	11.92	13.28	15.11	14.95
T wave changes	13.69	12.33	13.08	14.59	14.09
Other abnormality	24.63	13.44	14.52	14.98	14.08
Normal	6.36	8.88	8.97	9.11	8.16
Unknown	5.34	11.25	13.0	9.18	14.24
ACS type					
STEMI	28.17	29.65	29.50	29.58	27.59
NSTEMI	27.01	41.85	45.24	47.48	50.29
Troponin negative	0.22	4.45	7.83	8.25	7.0
Unknown	44.60	24.04	17.44	14.69	15.12

Figures are percentages apart from N

Table 7 MINAP - Proportions of ECG abnormalities and ACS type in successive yearly datasets

The data showed a consistency from 2004-2006. STEMI's constituted around 28-29% of acute coronary syndromes, and percentages for the breakdown of the other types of acute coronary syndrome and within ECG were also consistent

across the years. The percentage of ST segment depression remained consistently around 13-15 across 2004-1006.

These results were suggestive that, year on year, a degree of consistency was found, and a pattern of changing data entry over the years was not seen.

4.3.3 Ethnicity

As the main exposure of interest to this thesis was ethnicity, the validity of measures of ethnicity within the four cohorts was checked.

4.3.3.1 Whitehall-II

Ethnicity was defined in Whitehall-II according to the Office for National Statistics 1991 census types. Though ethnicity was observer-assigned at phase 1, at phase 5, participants self-reported their ethnicity. This was then used to validate the ethnicity data collected at phase 1. There was strong agreement between data on observer-assigned ethnicity from phase 1 and self-reported ethnicity at phase 5 - 93% of ascribed South Asian participants described themselves South Asian, 99.3% of self-ascribed White participants described themselves as White. Hence, Whitehall-II had a high degree of completeness of data for ethnicity, and the data appeared valid.

4.3.3.2 Chest pain clinic

In the chest pain clinic study, the cardiologist ascribed ethnicity as “Asian”, “White”, “black” or “other” during the consultation. In a validation study within the Newham chest pain clinic, I found that of 34 consecutive patients (25 South Asians), 88% self-assigned their ethnicity using the 2001 census classification in line with the assessment of the cardiologist (kappa statistic 0.766). Those patients who self-assigned their ethnicity as Bangladeshi, Indian, Pakistani or Sri Lankan I refer to as ‘South Asian’. Hence, data on ethnicity in this study appeared valid.

4.3.3.3 ACRE

Self-assigned ethnicity was based on the 1991 census classification by questionnaire on the day of index coronary angiography and identified 424 South Asian patients. For patients with missing data, given and family names were cross matched on a database of 15 000 names used to identify South Asian

patients in routine data from east London.¹⁴¹ This database identified a further 78 South Asian patients. This system was considered valid because the name database is highly specific (99%); the name assigned and self assigned methods identified similar proportions of South Asian people (15.6% and 12.8%, respectively) and confining the analyses to those with self-assigned ethnicity did not affect the results. Overall, 3607/4020 (89.7%) patients on the database had data available for ethnicity, with 57 being coded black, 74 other.

Baseline ethnic profiles of this cohort have been previously reported in the literature.⁶¹ The risk factor profile between White and South Asian patients revealed patterns consistent with previous literature in South Asian populations^{58 142} such as their younger age (6% of South Asian patients aged 70 or over compared to 20% in White patients), the high percentage of diabetics (33% in South Asian compared to 9% in White patients) and the lower percentage of smokers (8% in South Asian compared to 13% in White patients).

Hence, ACRE had a high degree of completeness of data for ethnicity, and the data appeared valid.

4.3.3.4 MINAP

In MINAP, the patient's ethnic group was determined by the coder assessing the case notes and patient computer records. Ethnicity within case notes or on the hospital computer system can be entered in a number of ways. The patient can themselves complete an administration form asking for personal details which can include other items such as address and next of kin details, or can verbally offer their ethnicity when asked. The ethnic group may also have been determined by the healthcare professional entering administrative data on the patient, and this information may come from self-assessed ethnicity from another source such as letter from the general practitioner, or be assigned by the healthcare professional. Ethnicity was coded Caucasian, Black, Asian, Oriental, Other and Unknown in the database.

I sought to:

- investigate the degree to which coding ethnic group was missing, and to examine admission characteristics between those with an ethnic code present and those without to assess the possibility of selection bias.
- examine whether the coronary risk profile of the Asian patients in the database was consistent with coronary risk profiles previously reported in the South Asian population, such as their high prevalence of diabetes.

19.8% of the entries for 2004 did not have a coding of ethnic group entered. When analysing admission characteristics between those with an ethnic code present and those without, there were similar patterns in characteristics between the groups (Table 8), although many were rendered statistically significant as a consequence of the large numbers involved. Importantly, percentages of diabetics were similar between those with an ethnic code present and those without, as a bigger percentage in the missing group may have suggested that the South Asian patients, who would be expected to have more diabetes, had more missing data for ethnic code than the White patients.

Data	Ethnic code		P
	Present	Missing	
N	79906	19666	
Age (mean, years)	68.86	68.32	<0.001
Men	63.64	63.08	<0.001
Infarct pattern			
STEMI	31.97	31.56	<0.001
NSTEMI/troponin positive	59.30	55.51	
troponin negative	8.73	12.93	
Smoking ex/current	70.67	72.41	<0.001
Hypertensive	45.21	43.01	<0.001
Diabetes	19.09	18.33	0.022
Hyperlipidaemia treatment	30.03	27.94	<0.001
Previous heart failure	7.19	6.41	<0.001
Previous chronic renal failure	3.56	3.85	0.082
Previous peripheral vascular disease	5.07	5.28	0.271
Previous revascularisation			
PCI	6.80	8.07	<0.001
CABG	6.23	6.98	<0.001

Figures are percentages apart from N and age

Table 8 MINAP - Admission characteristics, comparing availability of ethnic group data, in 2004

Analyses on risk factor profile between White and Asian patients revealed patterns consistent with previous literature in South Asian populations⁵⁸ - the high percentage of diabetics, the lower percentage of smokers (especially in Asian women) and similar percentages of hypertensives (Table 9).¹⁴³ The MINAP study is primarily focussed on outcomes as opposed to expected patterns of health when presenting with acute coronary syndromes. Hence, it is of reassurance that the patterns of risk factors at baseline by ethnicity conform to previously reported patterns.

	Men		Women	
	Asian	White	Asian	White
N	2374	46829	849	27387
Current smokers	28.7	28.3	3.7	20.2
Hypertensive	44.3	38.1	58.8	46.9
Hyperlipidaemia treatment	35.9	26.3	35.2	25.0
Diabetes				
Oral medication	19.4	6.9	22.9	7.0
Insulin	11.8	4.7	7.2	5.3

Figures are percentages apart from N

Table 9 MINAP - Risk factor profile, comparing White and Asian patients, by sex, in 2004

Hence, data on the 'Asian' patients in this study appeared to be valid in measuring the true South Asian population.

4.3.4 Follow-up

The most important source of selection bias in cohort studies is when completeness of follow-up data differs between exposure categories. This loss can reduce the statistical power of the study (through a reduction in sample size) and, if selective, can cause bias as the remaining sample may not represent the population it was originally selected from.

4.3.4.1 Whitehall-II

The study maintained good follow-up through its procedures. The methodology of interviewing participants in person at alternate stages (invited to the research clinic at 5-year intervals, and a postal questionnaire between clinic phases) ensured a low attrition rate. Furthermore, home visits by nurses were offered for the first time to participants unwilling or unable to travel to the Phase 7 clinic and a brief telephone questionnaire was administered to those who decline clinic and full questionnaire participation at each phase.

Follow-up for death and myocardial infarction was 99.9% complete. In particular, this thesis sought prospective data on chest pain as measured on the Rose questionnaire. I found that that loss to follow-up for South Asian participants in answering questions on chest pain was higher than in White participants. However, there were no differences in baseline risk factor profile (smoking, hypertension and total cholesterol) between those South Asian participants with follow-up for chest pain and those without at phase 7. 9% of non-response in South Asian participants and 11% in White participants were accounted for by death. Subjects in both ethnic groups with missing follow-up were more likely to be in a lower grade of work. Those that are more likely to drop out completely are also more likely to have more health problems and be of lower socio-economic status¹⁴⁴ which may result in an underestimate of angina in a South Asian population, as significantly more South Asian participants were in a lower grade of work in Whitehall-II. With 18-year phase 7 follow-up for the whole cohort being a reasonable 67%, the biggest cause of loss to follow-up for chest pain data was loss of overall questionnaire follow-up rather than chest pain non-response.

4.3.4.2 Chest pain clinic

The study was able to monitor mortality among patients by use of data from the Office for National Statistics and monitor hospital admissions, coronary angiography and revascularisation by use of the national Hospital Episode Statistics, supplied by the National Health Service Wide Clearing System, using unique National Health Service numbers. Successful matching was achieved for 99.5% of the cohort.

4.3.4.3 ACRE

The major variable of study within ACRE was angina, and its change from baseline to follow-up. Analyses on whether significant differences existed between ethnic groups in those with data on angina and those without are presented in section 4.3.5.2. Follow-up for death and myocardial infarction was 99% complete.

4.3.4.4 MINAP

Follow-up in MINAP was in the form of all-cause mortality, at one year. Using 2004 data, follow-up for all-cause mortality was 85.6% complete in South Asian patients, 91.2% in White patients. Examining admission characteristics stratified by availability of follow-up data, both South Asian and White patients without data for follow-up were younger and more likely to have had a troponin-negative ACS, but there were no significant differences in the other categories (Table 10).

	South Asian		p	White		p
	Yes	No		Yes	No	
Data available for one-year follow-up						
N	2769	467		57109	13016	
Age (mean, years)	61.87	60.32	0.027	69.66	66.02	<0.001
Men	73.37	73.45	0.904	62.99	63.68	<0.001
Infarct pattern						
STEMI	32.20	40.26	0.004	31.37	36.22	<0.001
NSTEMI/trop +ve	52.11	43.64		60.78	49.30	
troponin -ve	15.69	16.10		7.85	14.48	
Smoking ex/current	46.33	51.30	0.072	71.72	72.19	0.449
Hypertensive	45.23	41.44	<0.001	53.64	46.32	0.005
Diabetes	42.48	37.59	0.067	29.36	30.13	0.214
Hyperlipidaemia treatment	39.46	31.00	0.001	14.38	12.25	<0.001
Previous heart failure	6.96	4.67	0.086	7.55	5.02	<0.001
Previous chronic renal failure	4.76	3.47	0.250	3.65	2.42	<0.001
Previous peripheral vascular disease	3.03	2.45	0.519	5.23	4.90	0.267
Previous revascularisation						
PCI	12.51	11.03	0.400	6.47	7.53	0.002
CABG	9.31	7.04	0.136	5.95	8.47	<0.001

Figures are percentages apart from N and age

Table 10 MINAP - Admission characteristics, comparing status (dead/alive) at 1 year, in South Asian and White patients, in 2004

I performed further checks on the data. Among those lost to follow up (i.e., unknown vital status from the Office for National Statistics), a number were retrieved from information on in-hospital death that was present in the database. 233 of the 5462 with missing one year follow-up had died in hospital from the 2004 cohort and hence were recorded as death. Overall figures for follow-up at one year were now 87.7% complete in South Asian patients, 95.6% in White patients.

4.3.5 Cohort-specific data field checks

4.3.5.1 Chest pain in Whitehall-II

Chest pain as recorded by the Rose questionnaire was an important variable for planned analyses. Of the 9775, 577 (99.5%) South Asian participants and 9184 (99.9%) White participants had data available on chest pain at phase 1. By 18 year follow-up at phase 7, 41 South Asian participants and 525 White participants had died, and data on chest pain were available on 317 South Asian and 6268 White participants. No differences in baseline risk factor profile were found between those South Asian participants with follow-up for chest pain at phase 7 and those without, and the rate of chest pain non-response on those who filled in the questionnaire was low.

4.3.5.2 Angina in ACRE

The major variable of study within ACRE was angina and its improvement from baseline to follow-up. There were a greater proportion of South Asian patients with missing data for angina, and I examined whether significant differences existed in baseline characteristics in risk factors, past coronary history and management, socio-economic characteristics, the CCS as defined by the doctor on admission and angiographic findings within ethnic groups between those with data on angina (at both baseline and follow-up) and those without. This analysis revealed that no significant differences existed (Table 11).

Table 11 ACRE - Comparison of baseline factors between those with data and those missing data for angina at baseline and follow-up, in South Asian and White patients

Ethnic group	SOUTH ASIAN		p	WHITE		p
	Missing	Not missing		Missing	Not missing	
Data for angina						
N	306 (60.96)	196		1466 (49.29)	1508	
Age (mean, (SD) in years)	56.33 (9.98)	54.19 (9.10)	0.016	61.38 (10.74)	60.46 (9.34)	0.013
Men	244 (79.74)	147 (75.00)	0.212	1061 (72.37)	1051 (69.69)	0.107
Ever smoked	90 (47.87)	88 (46.56)	0.799	889 (76.77)	1048 (70.86)	0.001
Hypertensive	117 (38.24)	74 (37.76)	0.914	445 (30.35)	444 (29.44)	0.587
Total cholesterol (mean, (SD, range)) in mmol/l	5.56 (1.17)	5.61 (1.17)	0.673	5.59 (1.12)	5.61 (1.13)	0.708
Diabetes	108 (35.29)	48 (24.49)	0.011	149 (10.16)	139 (9.22)	0.383
Body Mass Index (mean (SD))	26.01 (4.08)	25.89 (3.94)	0.767	27.24 (4.45)	27.56 (4.50)	0.077
Family history of coronary heart disease	54 (31.03)	73 (40.11)	0.074	503 (45.48)	654 (45.54)	0.974
Lower social class	70 (32.41)	68 (35.42)	0.521	557 (39.76)	669 (45.17)	0.003
Left school < 16 yrs	75 (42.37)	74 (44.85)	0.645	1104 (85.85)	1242 (86.37)	0.694
Heart failure	40 (13.07)	18 (9.18)	0.184	237 (16.17)	157 (10.41)	<0.001
Previous myocardial infarction	129 (42.16)	71 (36.22)	0.185	651 (44.41)	599 (39.72)	0.010
Doctor-defined angina status CCS III-IV	129 (47.78)	72 (41.38)	0.186	534 (40.45)	542 (39.50)	0.615
Previous PCI	21 (6.86)	19 (9.69)	0.253	112 (7.64)	133 (8.82)	0.242
Previous CABG	22 (7.19)	15 (7.65)	0.846	151 (10.30)	146 (9.68)	0.574
>1 diseased coronary vessel	229 (75.58)	138 (70.77)	0.234	1128 (77.74)	1189 (79.27)	0.313
Impaired left ventricular function	67 (22.11)	31 (15.90)	0.089	347 (23.91)	216 (14.40)	<0.001

Data are (n, (%)) unless specified

4.3.5.3 Diagnosis of acute coronary syndrome type in MINAP

A major variable for analysis within MINAP was the final (discharge) diagnosis. This coded types of acute coronary syndrome, beyond the previously narrow category of myocardial infarction, which now exist as a result of troponin measurement. Only 3.5% of entries for 2004 had missing data. I then sought to check the data validity within this field - the extent to which the category final diagnosis measured the specific ACS types within it. The data collection form, available on the website of MINAP,ⁱ stipulated that all hospitals use the following types:

Discharge diagnosis	<ol style="list-style-type: none">1. Myocardial Infarction (ST elevation)2. Myocardial Infarction (non ST elevation)3. Threatened MI4. Acute Coronary Syndrome (troponin positive)5. Acute Coronary Syndrome (troponin negative)6. Chest pain of uncertain cause7. Myocardial Infarction (unconfirmed)8. Other diagnosis10 Acute Coronary Syndrome (troponin unspecified)
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The definitions of the most relevant types of acute coronary syndrome to this thesis were defined in MINAP thus:

- ST elevation myocardial infarction required the presence of electrocardiographic changes of ST elevation consistent with infarction of =>2mm in contiguous chest leads and/or ST elevation of =>1 mm ST elevation in 2 or more standard leads.

ⁱ <http://www.rcplondon.ac.uk/CLINICAL-STANDARDS/ORGANISATION/PARTNERSHIP/Pages/MINAP-.aspx>

- Non-ST elevation myocardial infarction required electrocardiographic changes including new ST or T wave changes (except ST elevation) and/or cardiac enzyme or troponin elevation (CK twice the upper limit of the reference range; locally accepted cut off value for troponin).
- Acute coronary syndrome (troponin positive) was defined when there were symptoms consistent with cardiac ischaemia with troponin release with dynamic ECG changes consistent with fluctuating ischaemia.
- Acute coronary syndrome (troponin negative) was defined when there were symptoms consistent with cardiac ischaemia without troponin release with dynamic ECG changes consistent with fluctuating ischaemia.

I sought to check whether data in these types had been collected as stipulated within the whole MINAP database.

I sought to do this by:

- cross-tabulation of the diagnoses with ensuing treatment strategy, which are specific to each type of acute coronary syndrome;
- cross-tabulation with data on biochemical markers of myocardial infarction, such as troponin, on which the definitions partly rely on.

Thus, the validity of types of acute coronary syndrome within the category of final diagnosis could be achieved by comparison to other clinical assessments.

4.3.5.3.1 Final diagnosis and reperfusion strategy

I compared final diagnoses to final reperfusion strategy, as the vast majority of STEMIs would have had thrombolytic treatment with a fibrinolytic drug to reperfuse a completely occluded artery.

The table below (Table 12) shows that the majority of STEMIs received thrombolytic therapy. Of those without a diagnosis of STEMI or NSTEMI, both those with positive and negative troponins appropriately had very low numbers of thrombolytics administered. An appropriately low percentage of NSTEMI had reperfusion, though numbers were higher than in acute coronary syndrome

(troponin positive), probably as a result of inadvertent reperfusion, which is more common in this group as their ECG changes may resemble STEMIs.

Final diagnosis	Reperfusion
STEMI	21275 (86.4)
NSTEMI	2853 (11.6)
Acute Coronary Syndrome (trop+ve)	200 (0.81)
Acute Coronary Syndrome (trop-ve)	311 (1.3)

Percentages in brackets

Table 12 MINAP - Final diagnosis against reperfusion treatment, in 2004

4.3.5.3.2 Final diagnosis and biochemical markers

I then examined troponin levels with the final diagnosis. I expected that STEMIs would have the highest levels of troponin, followed by NSTEMIs, Troponin positives and then troponin negative diagnoses to have a level near to zero. This was confirmed in the following table:

Final diagnosis	Mean troponin (SD) in ng/ml
STEMI	24.36 (22.8-26.0)
NSTEMI	10.50 (9.48-11.52)
Acute Coronary Syndrome (trop+ve)	2.91 (2.58-3.24)
Acute Coronary Syndrome (trop-ve)	0.11 (0.05-0.17)

Table 13 MINAP - Final diagnosis against troponin levels, in 2004

Thus, overall I found no significant measurement errors in the coding of ACS type under the variable 'final diagnosis'.

4.3.5.4 Cardiac biomarkers in MINAP

I sought to investigate the quality and validity of data on troponin, vital to the types of ACS diagnosis, and which also allows quantification of severity of disease, allowing further disaggregation of the heterogeneous entity that is ACS. Data on biomarkers were collected as 'elevated cardiac markers' as well as actual troponin level in the MINAP database.

I sought to:

- examine the degree of missingness for entry of the troponin field;
- test validity by tabulating peak troponin against the ECG findings recorded on arrival.

Analyses showed that prior to 2003, there was a low rate of entry for troponin which then improved 2004 onwards (Table 14) - this is most likely attributable to the increasing use of troponin in hospitals. The field 'elevated markers' had only 11.71% missing data, as pre-2003 entries would have included elevated CK. The usage of CK started to diminish post-2003 to be replaced increasingly by troponin. There was consistency observed in the levels of data entry in the fields on troponin and also in the field elevated markers across years 2003-2006 (table below).

	Pre-03	2003	2004	2005	2006
N	2769	92,252	93,469	89,635	77,255
Troponin	39.11	18.69	18.52	19.71	16.18
Elevated markers	11.71	14.18	11.73	11.11	13.82

Figures are percentages apart from N

Table 14 MINAP - Proportions of data fields for cardiac marker with missing entries in successive yearly datasets

I then tabulated peak troponin against the ECG findings recorded on arrival, as higher troponin levels would be seen in those with ischaemic ECGs, and this was confirmed in the table below:

ECG findings on arrival	Peak troponin (mean, SD) in ng/ml
ST/T changes	17.8 (227)
normal/other	6.7 (229)

Table 15 MINAP - ECG findings on arrival against troponin levels, in 2004

4.4 Statistical power

The primary outcome for prognosis in this thesis was the comparative risk of risk of death and non-fatal myocardial infarction between ethnic groups. Examination for other outcomes (receipt of investigations, improvement in symptoms) was exploratory and there is a lack of prior data in these outcomes from other studies. Hence, as the magnitude and direction of difference (if any) between the two ethnic groups were unknown for such outcomes, power calculations using estimated relative risks were not possible.

On the combined endpoint of death and non-fatal myocardial infarction, there is 80% power at the P=0.05% level to detect a relative risk of at least 1.30 between South Asian and White participants (chest pain clinic study), and 1.26 (ACRE

study) and 1.59 (Whitehall II) between South Asians and White participants, assuming the annual event rates shown in Table 16. In MINAP, there is 90% power at the P=0.05% level to detect a relative risk of at least 1.3 between between South Asian and White participants for death. Statistical power is largely determined by the number of events occurring in South Asian participants and this exceeds 100 for each study.

	Aetiologic study		Prognostic studies		
	Whitehall I	Chest pain clinic	ACRE	MINAP	
Follow up until	2002 (14 yrs)	2004 (3 yrs)	2003 (7 yrs)	1 year	
Estimated N events in South Asians	121	174	181	300	
Estimated annual risk death / MI in South Asians	1.5%	2%	6%	3% (risk of death only)	

Table 16 Estimated risk of outcomes in South Asian participants in the studies of this thesis

4.5 Conclusions

The four studies chosen to span the natural history of coronary disease and prognostic risk, though different in their methodologies, stood up to scrutiny in terms of data quality in order to examine the specific objectives of this thesis.

5 Incidence and prognosis of suspected angina in a healthy population

5.1 Summary of chapter

Background The incidence of symptoms of stable angina in South Asian populations is not known and the consistency of measurement of angina in them has been questioned. This work sought to determine the incidence of typical angina, exertional and non-exertional chest pain and subsequent coronary prognosis in South Asian compared to White populations.

Methods A cohort study of 9775 (9195 White participants and 580 South Asian participants) civil servants aged 35–55 years in 1985–8 with seven phases of community follow-up over 18 years. Chest pain was categorised as typical angina, exertional chest pain and non-exertional chest pain using the Rose questionnaire. The prognostic outcome was a measure of coronary death and non-fatal myocardial infarction at phase 7 (2003-2004).

Results The South Asian participants had higher cumulative frequencies of typical angina by phase 7 (17.0% vs 11.3%, $\chi^2=16.93$, $p<0.001$) and exertional chest pain (15.4% vs 8.5%, $\chi^2=31.06$, $p<0.001$) compared to White participants but less non-exertional chest pain (24.6% vs 31.3%, $\chi^2=11.76$, $p=0.001$). In both ethnic groups, typical angina and exertional chest pain were associated with increased rates of coronary events when compared to those with no chest pain. Within those with any pain at baseline, South Asian participants had a worse long-term prognosis than White participants (typical angina HR 2.56 (1.36-4.84)).

Conclusions South Asian participants had a higher incidence of typical angina and exertional chest pain than White participants, and this was associated with an increased subsequent rate of coronary death and myocardial infarction compared to those with no chest pain. However, South Asian participants had a worse long-term prognosis than White participants within all types of chest pain.

5.2 Introduction

Prospective studies in healthy individuals comparing South Asian to White populations report a higher incidence of fatal outcomes¹²² and non-fatal outcomes such as myocardial infarction.¹²³ There are no studies comparing incidence of angina among South Asian compared to White populations.¹⁴⁵ Appropriate identification and management at early, incident symptomatic presentations of coronary disease such as angina may prevent or at least delay progression to more serious later-phase manifestations of coronary disease such as myocardial infarction and ultimately coronary death.

However, South Asian people may report atypical features when presenting with chest pain^{39 40 45} and angina measurement is reported to be inconsistent in South Asian people using questionnaires.³⁹ The comparative incidence of chest pain symptoms in South Asian and White populations and subsequent implications on prognosis has not been investigated in population-based studies.

5.3 Research objective to be investigated

This chapter sought to investigate specific research objective 1.

To determine the incidence and prognosis of angina in healthy South Asian and White populations.

5.4 Specific research questions

- i. What is the cumulative incidence of typical angina symptoms, exertional chest pain, and non-exertional chest pain in South Asian compared to White populations?
- ii. What is the association with coronary risk factors with different forms of chest pain in South Asian and White populations?
- iii. What are the rates of subsequent prognostic outcomes (coronary death and non-fatal myocardial infarction) of chest pain in South Asian and White populations?

5.5 Methods

5.5.1 Population

The Whitehall-II study is a prospective cohort of non-industrial civil servants aged 35–55 years who worked in the London offices of 20 civil service departments at baseline (1985–1988). Clinical examinations and questionnaires were administered at baseline, 1991–1993 (phase 3), 1997–1999 (phase 5), and 2003–2004 (phase 7), with questionnaires in 1989 (phase 2), 1995 (phase 4), and 2001 (phase 6). By 18 years at phase 7, follow-up for the whole cohort was 67%. 10308 people were recruited, 3413 women and 6895 men. The participants were all grades, from clerical and office support grades through middle-ranking executive grades up to senior administrative grades, differing widely in salary.

5.5.2 Ethnicity

Ethnicity was defined according to the Office for National Statistics 1991 census types (appendix 13.1). Participants self-reported their ethnicity at phase 5, and where this was missing, observer-assigned ethnicity from phase 1 was used. There was strong agreement between data on observer-assigned ethnicity and self-reported ethnicity - 93% of ascribed South Asian participants self-described themselves South Asian, 99.3% of self-ascribed White participants described themselves as White. Of the participants, 9195 were ascribed as White at phase 1 and 580 participants were grouped as South Asian.

5.5.3 Chest pain

At each of the seven phases over 18 years follow-up, symptoms of stable angina pectoris were assessed using the Rose questionnaire (appendix 13.3). Chest pain was defined in three mutually exclusive groups:

- “typical angina” if the pain was located over the sternum or in both the left chest and the left arm, was precipitated by exertion, caused the person to stop and went away in 10 minutes or less;
- ‘exertional chest pain’, based on the ‘possible’ classification as originally proposed by Cook et al,¹⁴⁶ being chest pain brought on by exertion but

not satisfying the additional criteria, such as location and relation to rest, necessary for a diagnosis of typical angina;

- ‘non-exertional chest pain’ was defined as those complaining of chest pain that had no relation to exertion.

```
STATA do-file- generation of chest pain groups at phase 1

gen rosedefinite=1 if chpuph==1 & (chpact==1|chpact==2)& chpstop==1 & chptime==1 &
(chploc==1|chploc==2)
recode rosedefinite . =0
replace rosedefinite=. if chpuph==.
label variable rosedefinite "new phase 1 typical"

gen rosepossible=1 if chpuph==1 & rosedefinite==0
recode rosepossible . =0
replace rosepossible=. if chpuph==.
label variable rosepossible "new phase 1 exertional"

gen atypicalpain=1 if chpain==1 & rosepossible==0 & rosedefinite==0
recode atypicalpain . =0
replace atypicalpain=. if chpain==.
label variable atypicalpain "nonexertional phase 1"

gen chestpain=1 if atypicalpain==1
replace chestpain=2 if rosepossible==1
replace chestpain=3 if rosedefinite==1
replace chestpain=0 if chpain==2
label variable chestpain "0 none 1 non-exertional 2 exertional 3 typical"
```

9184 White participants and 577 South Asian participants had data on chest pain at phase 1. By 18 year follow-up at phase 7, 41 South Asian participants and 525 White participants had died, and data on chest pain were available on 317 South Asian participants and 6268 White participants. No differences in baseline risk factor profile were found between those South Asian participants with follow-up for chest pain at phase 7 and those without. The rate of chest pain non-response on those who filled in the overall study questionnaire was low, inferring most of loss to follow-up for chest pain response was as a result of those not filling in the study questionnaire rather than not filling in the Rose angina section.

Baseline was defined as phases 1-3, as multiple reports of Rose angina are more likely to indicate the presence of disease,¹⁴⁷ and angina may come and go depending on concomitant control of symptoms at time of assessment. Those with typical angina at either phase 1, 2 or 3 were defined as baseline typical angina. Baseline exertional chest pain was similarly defined using exertional

chest pain at either phase 1,2 or 3, having excluded those who had complained of typical angina, and baseline non-exertional chest pain again was similarly defined, having excluded those who had complained of typical angina or exertional chest pain at one of the phases 1, 2 or 3.

```
STATA do-file- generation of baseline categories of chest pain, where z=phase 2, x=phase 3

gen earlytypical=1 if (chestpain==3|zchestpain==3|xchestpain==3)
recode earlytypical .=0

gen earlyexertional=1 if (chestpain==2|zchestpain==2|xchestpain==2)& earlytypical==0
recode earlyexertional .=0

gen earlyatypical=1 if (chestpain==1|zchestpain==1|xchestpain==1)& earlytypical==0 & earlyexertional==0
recode earlyatypical .=0

gen earlynopain=1 if (chestpain==0|zchestpain==0|xchestpain==0)& earlytypical==0 & earlyexertional==0
& earlyatypical==0
recode earlynopain .=0
```

5.5.4 Risk factors

At baseline, standardised assessments were made of smoking, hypertension (blood pressure higher than or equal to 130/85 mmHg or on antihypertensive medication), total cholesterol, body mass index (BMI), self reported diagnosis of diabetes, and family history (in parents or siblings) of onset of coronary heart disease before age 55 years. Metabolic syndrome was defined by the 2001 National Cholesterol Education Program Adult Treatment Panel-III criteria at phase 3 by the presence of three or more of: central obesity, elevated fasting blood triglycerides, reduced blood HDL cholesterol, elevated blood pressure, elevated fasting glucose.¹⁴⁸ This definition gave less emphasis to glucose intolerance and acknowledged the importance of central obesity - it included the presence of enlarged waist circumference in the set of diagnostic criteria for metabolic syndrome. It is a widely-used definition, though may become superseded by the more recently announced (2005) International Diabetes Federation definition.^j Validation of this measure is increasingly reported in the literature.¹⁴⁹

^j This insists on the presence of waist circumference. This new definition also recommends using ethnic-specific waist circumference cut-offs, and proposes a lower threshold for fasting blood glucose.

Impaired glucose tolerance was defined as a fasting plasma glucose <7 mmol/l and postload^k glucose ≥ 7.8 mmol/l (140 mg/dl) and <11.1 mmol/l. Civil service employment grade was used as a measure of socioeconomic position. On the basis of salary and work role, the civil service defines a hierarchy of employment grades, in three levels: unified grades 1-7 (high), executive officers (medium), and clerical and support staff (low).

5.5.5 *Follow-up*

The outcome in prognostic analyses was a combined measure of coronary death and non-fatal myocardial infarction by phase 7, the latest study phase for which events data are available. 99% of participants were flagged for mortality at the National Health Service Central Registry. Coronary death was defined by the International Classification of Diseases-Ninth Revision (ICD-9) code 410–414.¹⁵⁰ Based on all available data (from questionnaire, study ECGs, hospital acute ECGs and cardiac enzymes), non-fatal myocardial infarction was defined following MONICA criteria.¹ Classification of non-fatal myocardial infarction was carried out blind to other study data independently by two trained coders, with adjudication by a third in the (rare) event of disagreement.

5.5.6 *Statistical analysis*

Cumulative incidence was estimated with 95% confidence intervals of those who complained of typical, exertional and non-exertional chest pain through the six phases of the study following phase 1. Those who had complained for chest pain at one phase were then not counted in following phases. For baseline characteristics, continuous variables were presented as means with standard deviation and proportions as percentages. These baseline clinical and socio-demographic data were tabulated by ethnic group across types of chest pain, and tested for age-adjusted linear trend across those types, in South Asian

^k levels 2 hours after a 75-g oral glucose tolerance test

¹ The MONICA (Multinational MONItoring of trends and determinants in CARDiovascular disease) Project was established in the early 1980s in many centres around the world to monitor trends in cardiovascular diseases, and to relate these to risk factor changes in the population over a ten year period.

participants and in White participants, using the χ^2 test for linear trend for proportions and the analysis of variance for trend for continuous variables.

The relative risk of future coronary death and non-fatal myocardial infarction was examined among those with typical, exertional and non-exertional chest pain on at least one of the first three phases compared to those with no chest pain at any of these three early stages. Using the Cox's proportional hazards model, adjusted rates and 95% confidence intervals were calculated for outcomes and adjusted for age, sex, hypertension, blood cholesterol, ex/current smoker, BMI, diabetes, living alone, family history and grade at work. The relative risk of future coronary death and non-fatal myocardial infarction of South Asian versus White participants was calculated within each type of chest pain.

All analyses were performed using STATA (version 10; StataCorp, College Station, TX, USA).

5.6 Results

Irrespective of the type of chest pain, South Asian participants tended to be older, less likely to have smoked, more likely to be hypertensive and diabetic, more likely to live with a partner, have a higher prevalence of metabolic syndrome and be in lower grades of work than White participants (Table 17). Across the types of chest pain, there was an increasing prevalence of hypertension and higher cholesterol levels and trends towards more metabolic syndrome and higher body mass index with more typical chest pain.

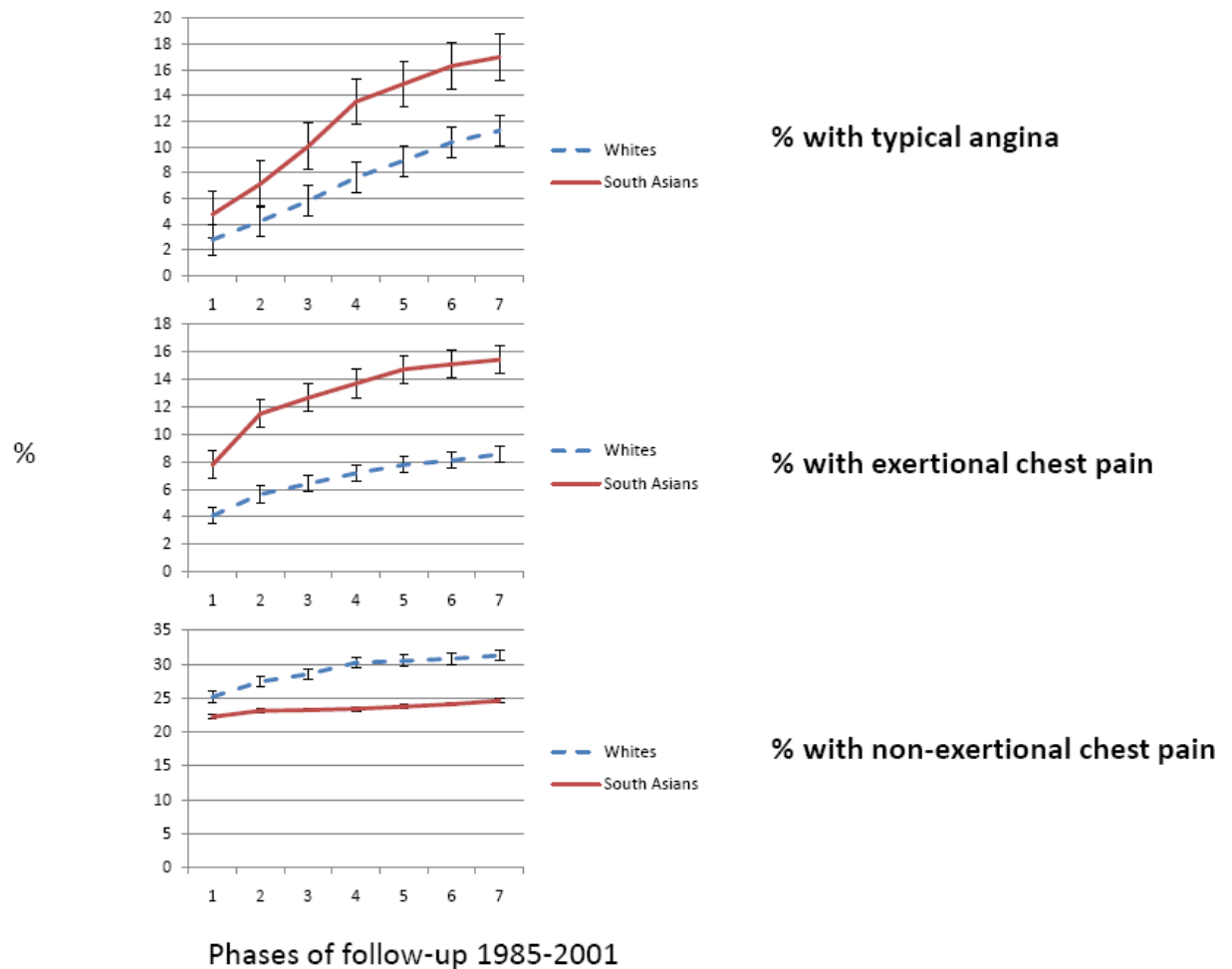
	Ethnic group	Whole cohort	No chest pain	Non-exertional chest pain	Exertional chest pain	Typical angina	P for trend across chest pain types
N	South Asian	580	312	134	73	58	
	White	9195	5444	2619	587	534	
Age in years (mean, (SD))	South Asian	45.65 (5.72)	45.26(5.99)	45.71(5.33)	46.14(5.71)	47.14(4.99)	0.115
	White	44.31 (6.08)	44.36(6.10)	43.77(5.94)	44.70(6.19)	45.90(6.11)	<0.001
Men	South Asian	357 (61.55)	183 (41.35)	100 (74.63)	45 (61.64)	27 (46.55)	0.482
	White	6309 (68.61)	3591 (65.96)	2019 (77.09)	387 (65.93)	308 (57.68)	0.726
Ex/current smoker	South Asian	190 (33.04)	96 (31.17)	50 (37.59)	28 (38.36)	16 (27.59)	0.758
	White	4767 (52.28)	2700 (50.05)	1425 (54.77)	334 (57.29)	300 (56.93)	<0.001
Hypertensive	South Asian	70 (12.07)	32 (10.26)	11 (8.21)	10 (13.70)	16 (27.59)	0.002
	White	714 (7.77)	410 (7.53)	168 (6.41)	52 (8.86)	83 (15.54)	<0.001
Cholesterol (mean (SD) in mmol/l)	South Asian	5.96 (1.24)	5.90(1.21)	5.94(1.23)	5.95(1.16)	6.39(1.48)	0.052
	White	5.97 (1.16)	5.94(1.18)	5.94(1.12)	6.09(1.19)	6.19 (1.17)	<0.001
Hyperglycaemic Diabetic	South Asian	22 (3.84)	9(2.93)	6(4.55)	4(5.48)	2(3.45)	0.464
	White	61 (0.67)	38(0.70)	14(0.54)	3(0.52)	6(1.13)	0.737
Impaired glucose tolerance	South Asian	46 (7.93)	25(8.01)	9(6.72)	7(9.59)	5(8.62)	0.784
	White	561 (6.10)	327(6.01)	157(5.99)	37(6.30)	40(7.49)	0.270
Metabolic syndrome	South Asian	66 (15.94)	34(15.89)	15(14.71)	6(11.76)	11(23.40)	0.516
	White	754 (10.58)	391(9.51)	214(10.11)	76(16.20)	73(16.98)	<0.001
BMI (mean (SD))	South Asian	24.44 (3.32)	24.26(3.42)	24.64(3.14)	24.49(2.93)	24.84(3.71)	0.537
	White	24.55 (3.45)	24.42(3.39)	24.46(3.23)	25.16(3.99)	25.65 (4.01)	<0.001
Living with partner	South Asian	487 (84.26)	256(82.58)	118 (88.06)	61(83.56)	50(86.21)	0.424
	White	6766 (73.85)	3995(73.61)	1987(76.22)	403(69.01)	375(70.36)	0.146
Family history	South Asian	227 (39.14)	115(36.86)	52(38.81)	32(43.84)	27(46.55)	0.106
	White	3599 (39.14)	2060(37.84)	1029(39.29)	247(42.08)	259(48.50)	<0.001
Job grade -low	South Asian	290 (50.00)	158(50.64)	55(41.04)	43(58.90)	32(55.17)	0.514
	White	1733 (18.85)	1095(20.11)	377(14.39)	124(21.12)	128(23.97)	0.703

The categories of chest pain total 9184 White and 577 South Asian participants who had data on chest pain at phase 1. The whole cohort comprises the 9195 White participants at phase 1 and the 580 South Asian participants. Data are n (%) unless otherwise specified. Test for trend is age-adjusted.

Table 17 Whitehall-II - Baseline characteristics in each chest pain type comparing South Asian and White participants

5.6.1 Incidence of different forms of chest pain by ethnic group

At baseline, South Asian participants had a higher prevalence of typical angina compared to White participants (4.8% vs 2.8%, $\chi^2= 5.50$, $p=0.019$) and exertional chest pain (7.8% vs 4.1%, $\chi^2= 14.97$, $p<0.001$) but not non-exertional chest pain (22.2% vs 25.2%, $\chi^2= 2.97$, $p=0.085$), as depicted in Figure 5. By phase 7, South Asian participants had higher cumulative frequencies of typical angina (17.0% vs 11.3%, $\chi^2=16.93$, $p<0.001$) and exertional chest pain (15.4% vs 8.5%, $\chi^2= 31.06$, $p<0.001$) compared to White participants but less non-exertional chest pain (24.6% vs 31.3%, $\chi^2=11.76$, $p=0.001$).



(Cumulative % with 95% CI bars)

Figure 5 Whitehall-II – Cumulative incidence of different types of chest pain by ethnic group over seven study phases

5.6.2 *Prognosis of chest pain*

During the mean follow-up of 15.1 years, 367 incident cases of total coronary events (49 in South Asian participants) occurred among the total cohort of participants who had been free from any coronary event at baseline. In the whole cohort, the South Asian participants was more likely than White participants to sustain the endpoint of coronary death and non-fatal myocardial infarction (HR in South Asian participants compared to White participants 2.22 (95% CI 1.59-3.09) adjusted for age, sex, hypertension, blood cholesterol, ex/current smoker, overweight, diabetes, living alone, family history and grade at work).

5.6.2.1 Prognosis within ethnic groups of those with pain compared to those with no chest pain

In both South Asian and White participants, those with baseline typical angina and exertional chest pain had a worse prognosis for the long-term coronary outcome compared to those with no baseline chest pain (in South Asian participants with typical angina (adjusted HR 4.67 (95% CI 2.12-10.30), Table 18). However, both South Asian and White participants who complained of baseline non-exertional chest pain did not have a worse prognosis compared to those who complained of no chest pain (in South Asian participants adjusted HR 1.34 (95% CI 0.56-3.22), Table 18).

5.6.2.2 Prognosis within types of pain for South Asian compared to White populations

Within those with typical angina at baseline, South Asian participants had a worse long-term prognosis than White participants (HR 2.56 (95% CI 1.36-4.84), Table 18). The South Asian participants also had a worse long-term prognosis than the White participants within the whole cohort (HR 2.22 (95% CI 1.59-3.09)) and in those with non-exertional chest pain, and there was a similar suggestion in those with exertional chest pain. There were no ethnic differences in long-term prognosis in the bigger group of participants that had no chest pain at baseline.

Study population	Ethnic group	N	Number of events by phase 7	Rate/1000 person years (95%CI)	HRs within ethnic groups compared to those with no chest pain		HRs within types of pain for South Asian compared to White participants (95%CI)	
					Age and sex-adjusted	Adjusted*	Age and sex-adjusted	Adjusted*
Whole cohort	White	9195	318	2.26 (2.03,2.53)	n/a	n/a	1	1
	South Asian	580	49	6.09 (4.60,8.06)	n/a	n/a	2.46 (1.82,3.32)	2.22 (1.59,3.09)
No chest pain	White	5444	138	1.67 (1.42,1.96)	1	1	1	1
	South Asian	312	15	3.44 (2.08,5.71)	1	1	1.92 (1.13,3.28)	1.58 (0.87,2.86)
Non-exertional chest pain	White	2619	80	1.95 (1.57,2.43)	1.13 (0.86,1.49)	1.16 (0.88,1.53)	1	1
	South Asian	134	9	4.68 (2.44,9.00)	1.24 (0.54,2.84)	1.34 (0.56,3.22)	2.10 (1.05,4.20)	2.17 (1.04,4.53)
Exertional chest pain	White	587	41	4.56 (3.36,6.19)	2.71 (1.91,3.84)	2.34 (1.64,3.32)	1	1
	South Asian	73	8	8.21 (4.11,16.4)	2.37 (1.01,5.60)	2.52 (1.02,6.18)	1.70 (0.79,3.65)	1.74 (0.75,4.03)
Typical angina	White	534	59	7.49 (5.80,9.66)	4.32 (3.18,5.87)	3.56 (2.59,4.88)	1	1
	South Asian	58	17	21.9 (13.6,35.3)	6.93 (3.40,14.10)	4.67 (2.12,10.30)	2.94 (1.71,5.06)	2.56 (1.36,4.84)

*adjusted for age, sex, hypertension, blood cholesterol, ex/current smoker, overweight, diabetes, living alone, family history and grade at work; n/a – not applicable

The study population of the whole cohort represents those at phase 1.

The study populations of the types of chest pain represent those who complained of these pains at phases 1, 2 or 3. The types are mutually exclusive, as those with exertional chest pain excluded those who had complained of typical angina at one of the phases 1, 2 or 3, and baseline non-exertional chest pain excluded those who had complained of typical angina or exertional chest pain at one of the phases 1, 2 or 3.

Table 18 Whitehall-II - Prognosis for coronary death and non-fatal myocardial infarction, comparing types of chest pain to those with no chest pain, and comparing South Asian to White participants by type of chest pain

5.6.3 Mortality of whole cohort

Overall incident coronary and cardiovascular mortality was higher in South Asian participants than among White participants, but all-cause mortality was not higher in South Asian participants than among White participants (Table 19). Overall incident coronary events (coronary death and non-fatal myocardial infarction) was higher in South Asian participants than among White participants.

Outcome	Ethnic group	Subjects	Number of events (To Sep 04)	Rate/1000 person years	Age-adjusted hazard ratio (95%CI)	P value
All – cause mortality	White	9189	525 (5.7%)	3.33	1	0.456
	South Asian	577	41 (7.1%)	4.16	1.13 (0.82-1.55)	
Cardiovascular death	White	9184	140 (1.5%)	0.89	1	<0.001
	South Asian	577	23 (4.0%)	2.34	2.34 (1.50-3.64)	
Coronary death	White	9184	80 (0.9%)	0.51	1	<0.001
	South Asian	577	21 (3.6%)	2.13	3.73 (2.30-6.03)	
Coronary death and NFMI	White	9164	318 (3.5%)	2.23	1	<0.001
	South Asian	576	49 (8.5%)	5.86	2.62 (1.94-3.54)	

Table 19 Whitehall-II – Incidence of whole cohort for differing outcomes, comparing South Asian to White participants

5.7 Discussion

5.7.1 Objective addressed

I found a higher cumulative incidence of typical angina and exertional chest pain in South Asian participants compared to White participants, in a study of almost 10000 people with detailed characterisation of symptoms of stable angina using the Rose questionnaire at seven time-points over 18 year follow-up. I found that in both South Asian and White participants, typical angina and exertional chest pain at baseline were strongly associated with increased rates of coronary events when compared to those with no chest pain, but that those with non-exertional chest pain did not have a worse prognosis compared to those with no chest pain. Thus, the Rose questionnaire was valid in predicting prognosis in the South Asian participants. The overall cohort revealed worse prognosis in South Asian participants compared to White participants and that within types of pain, all types of chest pain tended to predict a more adverse prognosis in South Asian

participants. South Asian participants with no chest pain at baseline were not at higher long-term risk than the White participants with no chest pain at baseline.

5.7.2 The burden of symptoms and their prognostic validity in South Asian populations

The diagnosis of angina is perceived to be more difficult in the South Asian population as they are often labelled as having 'atypical' pain when presenting with ischaemia.⁴⁰ Though angina on Rose questionnaire predicts mortality in European populations,¹⁵¹ its consistency in South Asian populations has been questioned in a cross-sectional study³⁹ and no studies have examined its ability to predict long-term coronary events in patients of South Asian origin. I now show here that cumulative incidence of typical angina as ascertained by Rose questionnaire is higher in South Asian compared to White participants, and that this angina has an adverse prognosis in both White and South Asian participants compared to those with no chest pain. Non-exertional chest pain was not higher in baseline prevalence or in cumulative incidence in South Asian compared to White participants. It was not associated with coronary events in either ethnic group when compared to those with no chest pain. These results suggest that the Rose angina questionnaire can, in both South Asian and White populations, discriminate between prognostically significant chest pain and chest pain that does not result in adverse cardiac outcomes.

5.7.3 The prognosis of chest pain symptoms in South Asian compared to White populations

South Asian participants had a worse long-term prognosis than White participants within the whole cohort and within all types of chest pain, and though there appeared to be no ethnic differences in long-term prognosis in the bigger group of participants that had no chest pain at baseline, it is conceivable that a lack of power may hide a worse prognosis in South Asian participants even in this group (HR 1.58 95% CI (0.87-2.86)).

Thus, though South Asian participants with non-exertional pain are at relatively less risk than those South Asian participants with typical angina, the finding that South Asian participants have a worse long-term prognosis than White participants within all types of chest pain (exertional chest pain not being

significant, though this may reflect lack of power) may be a reflection of their overall higher incidence of fatal coronary disease, and of non-fatal myocardial infarction. Thus the presence of non-exertional pain at baseline may be unrelated to these later events, as it does not constitute an incident coronary event as such.

Using the definitions of baseline chest pain in Whitehall-II illustrates the difficulty in defining an incident event, and hence in the calculation of prognosis. Phase 1 represents a point in time in the life of the participants, by which time some of the cohort may already have had chest pain prior to being included in the study. To truly detect the prognosis of incident angina requires a cohort in which recruitment of all participants occurs at the first time they complain of chest pain. Whitehall-II, as a prospective cohort study of healthy individuals, was primarily suited to the study of cumulative incidence following recruitment.

Richer data on how coronary risk factors were managed in primary care may also explain prognostic patterns. It is conceivable that South Asian participants with non-exertional pain were at higher risk than White populations with non-exertional pain due to differences in risk factor profile and their management of them in primary care. The clinical careers of people with angina evolve over time, punctuated by changes in morbidity and in healthcare response. The Whitehall II study, in common with other population based studies, is not able to characterise the detailed history of appropriateness of each management step in this career.

Finally, the use of the measures of chest pain at baseline for prognosis between ethnic groups may be inaccurate due to small numbers. Only 58 South Asian participants had typical chest pain at phases 1, 2 or 3 and this renders prognostic analyses comparing them with White participants with typical chest pain less precise.

5.7.4 Relation with clinical presentation and diagnosis and implications for clinicians

A higher incidence of angina among South Asian participants is consistent with their higher incidence of fatal coronary disease, and of non-fatal myocardial infarction. These results have implications on workload for primary care doctors,

chest pain clinics and secondary care investigation resources in areas of high concentrations of South Asian people. Adequate allocation of appropriate healthcare resources on a population level in such areas will be necessary, especially as the current rate of decline of angina prevalence is much lower compared to the more marked decline observed for mortality from myocardial infarction.¹⁵²

The prospective validity of the Rose questionnaire in South Asian populations for the prediction of adverse coronary events in those with typical angina compared to those with no chest pain highlights the importance of making the correct diagnosis from symptoms. It has been previously shown in this cohort that people reporting angina symptoms, but without a diagnosis, were at increased risk of death and poor subsequent physical functioning than those who did not report symptoms.¹⁵³ I was unable to extend this to my analyses due to low numbers of South Asian participants diagnosed with angina. Conceivably, those with typical angina who had been diagnosed with angina would do better than those with typical angina as yet undiagnosed.

5.7.5 Limitations

A strength of this work is that no previous cohort has reported on differences between South Asian and White populations in repeat measures of a standardised assessment of chest pain symptoms over long-term follow up. However, the 2003 Health Survey for England revealed that though the prevalence of angina in Pakistani men was significantly higher than the general population, this was not the case for Indian and Bangladeshi men.⁵⁸ The Whitehall-II study comprised mainly Indian people (74%, with 13% Sri Lankan, 10% Pakistani, and 3% Bangladeshi) and thus may underestimate the overall future risk of coronary disease for 'South Asians' if baseline levels of coronary disease are lower than a more representative South Asian population. This heterogeneity within the South Asian group could not be accounted for in our study. However, the Whitehall-II study, from previously published reports on baseline characteristics comparing its South Asian and White participants is,⁶² in

its marked social and ethnic differences in coronary heart disease, broadly comparable to other studies in the South Asian population in the UK.

5.7.6 Implications

This study reports a higher incidence of angina in South Asian participants, though the aetiology of this is not possible to investigate with this dataset. Diabetes is likely to contribute to the higher incidence of coronary disease in South Asian people and cumulative prevalence of diabetes in this study was significantly higher in South Asian than White participants (10.5% v 2.7% by phase 7). Using such a study design, with serial measures of chest pain in a cohort of diabetics would allow further investigation into the aetiology of angina.

Improved resolution of angina as an epidemiological variable will also allow its increased use as a non-fatal outcome. More long term prospective studies of chronic symptomatic conditions are needed, as increasingly these conditions represent the bulk of where coronary disease presents, shifting away from presenting acutely to secondary care. A better understanding of angina, increasingly the most common initial symptomatic manifestation of coronary disease,²⁹ will encourage better coding of this early clinical manifestation of coronary disease in primary care databases.

5.8 Conclusions

I have demonstrated here that South Asian people have a higher incidence of typical angina over long-term follow-up compared to White people, but that they did not have a higher incidence of chest pain that was non-exertional in nature. Typical angina as measured by the Rose angina questionnaire had a worse prognosis for coronary death and non-fatal myocardial infarction, but non-exertional chest pain did not in both South Asian and White people, when compared to those with no chest pain. My findings demonstrate that South Asian people have an increased incidence of prognostically-significant angina compared to White people.

5.9 Building to next chapter

I have shown that typical angina, as measured using the Rose questionnaire, is common in South Asian people and that both South Asian and White populations

with typical angina have a higher risk of adverse coronary outcomes than in those with no chest pain.

The Whitehall-II cohort is an observational cohort of mainly healthy participants with no account possible for the interaction of the participants with healthcare services. The Whitehall-II study pre-dates the widespread introduction of rapid access chest pain clinics in the UK and was an observational study with no intervention planned. My analyses showed that within all those with chest pain irrespective of type, South Asian people had a worse long-term prognosis than White people. However, whether a more equitable outcome of incident angina in South Asian and White populations would occur if assessed in a health care facility is not known.

For the next stage of this thesis, I planned to investigate the presentation, management and prognosis of this early stage of coronary disease at a rapid access chest pain clinic. These clinics are designed from the outset to assess those with recent-onset chest pain, and hence provide a source of incident symptoms. I wanted to continue to examine the theme of typicality of pain by ethnic group, and examine its prognosis as it presented to the clinical environment, and thus to examine how the typicality of pain between ethnic groups influence clinical management. Early and appropriate identification of angina will result in early and appropriate clinical management, and this will in turn affect prognosis.

The Rose questionnaire is a tool used mostly in epidemiological research, and often through self-report rather than direct interview. In the chest pain clinic, the patient presents with symptoms to the doctor. They are directed towards describing their chest pain using specific descriptors when questioned by the doctor seeing them. The doctor typically asks the patient about four components of the chest pain they are presenting with: character, site, duration and precipitating factors. I now aimed to quantify this verbal history and assess how such words were different between ethnic groups and whether these words, used in diagnosis, had any prognostic significance.

6 Prognosis of incident typical and atypical chest pain

6.1 Summary of chapter

Background South Asian people have been reported as being more likely than White people to report atypical angina yet less likely to undergo coronary angiography to investigate angina. This work sought to determine whether atypical symptoms of angina in South Asian populations predicted clinically important outcomes and influenced receipt of appropriate clinical management.

Methods 2189 South Asian participants (980 women) and 5605 White participants (2676 women) with new-onset chest pain of median age 54 (IQR 44-64) were prospectively recruited from six rapid access chest pain clinics in the UK and followed up for death due to coronary disease or admission with acute coronary syndrome over a mean of 5.0 years. Participants were also followed up for receipt of coronary angiography and revascularisation.

Results Atypical chest pain was reported by South Asian participants more than White participants (59.9% vs 52.5%, $p < 0.001$). Typical symptoms were predictive of a diagnosis of angina across ethnicity. Typical symptoms compared to atypical symptoms were associated with the coronary outcome in both South Asian and White participants (HR 1.58 (1.14-2.18), South Asian). In those with typical symptoms, South Asian participants were more likely to experience the coronary outcome (HR 1.41, 95% CI 1.04–1.91) but were less likely to receive angiography (HR 0.52 (95% CI 0.41-0.67; $p < 0.001$) and revascularisation than White participants.

Conclusions Typical chest pain compared to atypical chest pain was as likely to be associated with a worse prognosis in South Asian as in White populations. Systematic and potentially inequitable differences in management between ethnic groups could not be explained by differences in presentation of symptoms.

6.2 Introduction

South Asian people³⁹⁻⁴¹ and other minority ethnic groups^{42 43} with suspected ischaemia are more likely to report atypical features of chest pain. The description of symptoms, articulated by patients and recorded by doctors, remains a cornerstone of diagnosing stable angina pectoris, yet descriptions have been largely derived and validated against White men.³⁴

South Asian people are less likely than White people to undergo coronary angiography to investigate angina.⁶¹ It has been proposed that differences in how patients describe their symptoms may contribute to inequalities in medical care,^{40 63} because the diagnostic validity of symptoms plays an important role in deciding appropriate clinical management.⁴⁷

The previous chapter showed both South Asian and White populations with typical angina had a higher risk of adverse coronary outcomes than in those with no chest pain, and that South Asian people with chest pain may have a worse prognosis than White people. To examine the prognosis of true incident angina between South Asian and White populations ideally requires a cohort in which recruitment of all participants occurs at first onset of chest pain, and which takes into account the description of symptoms articulated.

6.3 Research objective to be investigated

This chapter sought to investigate specific research objective 2.

To determine in those presenting with incident chest pain whether differences exist in the description of symptoms between South Asian and White populations, and the association of symptom descriptors with prognosis and receipt of management strategies for chronic coronary disease.

6.4 Specific research questions

To:

- i. Is the description of angina pain as typical or atypical associated with coronary outcomes in White and South Asian populations?

- ii. Are differences in how populations of White and South Asian origin report their symptoms related to their ensuing clinical management?

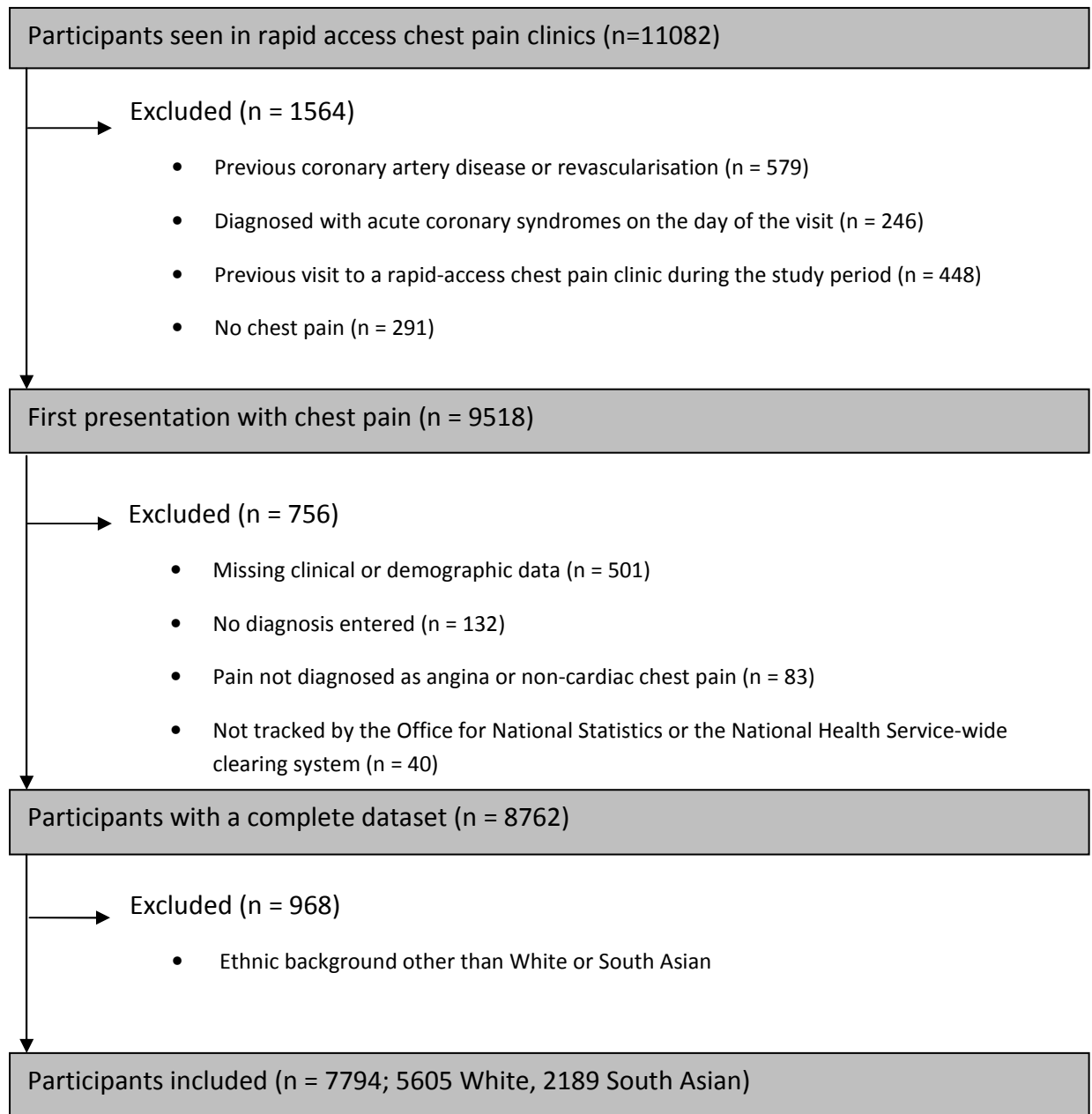
6.5 Methods

6.5.1 Population

11082 consecutive participants with recent-onset chest pain recruited in six rapid access chest pain clinics in the United Kingdom from 2 January 1996 to 31 December 2002 constituted the study population. These ambulatory care clinics are run by cardiology teams and accept same day referrals from family doctors of those in whom incident angina pectoris is suspected. Participants who had previously been investigated or diagnosed with coronary disease, or in whom acute, or unstable coronary syndromes were suspected were not eligible for referral to these clinics. Data were electronically recorded by the cardiologist using identical databases. Of those participants with no previous history of chest pain (n= 9518), I excluded re-attendances during the study period (n=448), participants without chest pain (n=291), participants diagnosed with acute coronary syndromes on the day of visit (n=246) and participants who reported previously diagnosed coronary heart disease or revascularisation procedure (n=579) so as to include incident chest pain patients only. I excluded participants with missing clinical and demographic data (n=501), participants for whom a diagnosis was either not entered (n=132) or not identified as angina or non-cardiac chest pain (n=83, e.g. having other diagnoses such as pericarditis) and those who were not traced by the Office for National Statistics or the National Health Service-wide clearing system (n=40).

Of the remaining 8762 participants with complete data and follow-up, I analysed the 7794 participants with an ethnic code of White or Asian (excluding 968 from other ethnic groups), which constituted the study group (Figure 6).

Figure 6 Chest pain clinic study - Recruitment of participants



6.5.2 *Ethnicity*

The cardiologist ascribed ethnicity as “Asian”, “White”, “black” or “other” during the consultation. In a validation study within the Newham chest pain clinic, I found that of 34 consecutive participants (25 South Asian), 88% self-assigned their ethnicity using the 2001 census classification in line with the assessment of the cardiologist (kappa statistic 0.766).

6.5.3 *Risk factors and treatment strategy*

Data on smoking status (no, ever/current), history of hypertension, history hypercholesterolemia/cholesterol level, history of diabetes and cardiac medication (aspirin, β -blocker, statin, nitrate, nicorandil, calcium-channel antagonist, ACE (angiotensin-converting enzyme) inhibitor) were recorded by the cardiologist and exercise electrocardiogram testing was performed if deemed appropriate by the cardiologist.

6.5.4 *Descriptors of chest pain*

Whilst taking the history from the participant, cardiologists recorded a descriptor for each of the following four components of chest pain:

- character (aching, constricting, stabbing, nondescript)
- site (central, left-sided, right-sided, submammary, epigastric, other)
- duration (seconds, < 5 minutes, 5–15 minutes, 15–30 minutes, hours or variable)
- precipitating factors (none, exercise, exercise and rest, stress, eating, other).

Health advocates trained to support the needs of those whose first language was not English were available if the participant did not attend with English-speaking friends/family members. For each component, one descriptor was selected from a drop-down menu (Table 20). Based on the Diamond-Forrester classification,³⁴ I considered typical pain to be that which the participant described as having a

constricting quality, being located centrally or on the left-side (which may have included radiation of the pain to the left shoulder or arm, a typical characteristic in some with angina) of the chest, lasting between a few seconds and 15 minutes, and being provoked by exercise (table below).

Table 20 Chest pain clinic study - Descriptors of four components of chest pain used by cardiologists and classification of their typicality

	Typical	Atypical	
Site	Central	√	
	Left sided	√	
	Right sided		√
	Sub-mammary		√
	Epigastric		√
	Other		√
Precipitating factor	Nothing		√
	Exercise	√	
	Exercise and rest	√	
	Stress		√
	Eating		√
	Other		√
Character	Aching		√
	Constricting	√	
	Stabbing		√
	Nondescript		√
Duration of episodes	Seconds		√
	<5 minutes	√	
	5-15 minutes	√	
	15-30 minutes		√
	Hours/variable		√

I used a “symptom score” to classify the participant’s description of pain as:

- typical (3 or more characteristics of typical pain) or
- atypical (2 or fewer characteristics).

The cardiologist also made a personal assessment of the participant’s overall symptoms as typical or atypical (“cardiologist summary”). At the end of the consultation, using information from other sources such as the full clinical

history, clinical examination and exercise electrocardiography, the cardiologist diagnosed the cause of the participant's chest pain as either angina or non-cardiac chest pain.

```
STATA do-file – generation of symptom score

gen typloc=1 if cplocation==1|cplocation==2
gen typdur=1 if cpduration==3|cpduration==2
gen typprec=1 if cproprovocation==2|cproprovocation==3
gen typqual=1 if cpquality==3

recode typloc .=0
recode typdur .=0
recode typprec .=0
recode typqual .=0

gen typacc=typloc+typdur+typprec+typqual
gen typicality=1 if typacc>=3
replace typicality=0 if typacc<3
label variable typicality " 1 typical 0 atypical"
```

6.5.5 Follow-up

Using unique National Health Service numbers, the study was able to monitor mortality among participants by use of data from the Office for National Statistics. The cohort was able to monitor hospital admissions, coronary angiography and revascularisation by use of the national Hospital Episode Statistics, supplied by the National Health Service Wide Clearing System. Successful matching was achieved for 99.5% of the cohort. Causes of death and admission to hospital were coded according to the International Classification of Diseases, 10th revision (ICD-10).

The combined primary outcome was death from coronary artery disease (ICD-10 codes I20-I25) and hospital admission due to an acute coronary syndrome (acute myocardial infarction, ICD-10 codes I21-I23) or unstable angina (ICD-10 codes I20.0–I20.9, I24.0, I24.8, I24.9) within five years. The management outcomes were receipt of coronary angiography as a confirmatory diagnostic test and subsequent coronary revascularisation (either percutaneous coronary intervention or coronary artery bypass surgery, whichever was first) within three years of a clinic visit.

6.5.6 *Statistical analysis*

When examining baseline clinical and chest pain characteristics, age was presented as a median with the inter-quartile range and compared between groups using Student's t-test, whilst proportions were compared using the χ^2 -statistic. To examine the probability of receiving a diagnosis of angina according to exercise ECG result, cardiologist summary or symptom score, likelihood ratios were used with 95% confidence intervals by ethnicity to test the likelihood that a positive exercise ECG or typical cardiologist summary or typical symptom score would be expected in a participant given a diagnosis of angina by the cardiologist. When calculating likelihood ratios for cardiologist summary and the symptom score, those participants with a positive exercise ECG were excluded (182 South Asian participant, 668 White participants) so as to remove the potential influence a positive exercise ECG may have on formulating a diagnosis of angina. To examine the prognostic validity of cardiologist summary and symptom score on coronary outcome, adjusted Cox proportional hazards regression were conducted by ethnicity. A hazard ratio less than 1 represents a better prognosis. Adjusted Cox proportional receipt of coronary angiography and revascularisation in those that had presented with typical descriptors and in those with atypical descriptors. In these analyses, a hazard ratio less than 1 represents a lower likelihood of receiving the procedure. Adjustments were made using age (as a continuous variable), sex, diabetes, smoking, hypertension, anti-anginal medication (β -blocker, calcium-channel antagonist, oral nitrate, nicorandil), secondary prevention medication (aspirin, statin, ACE inhibitor), revascularisation (PCI or CABG) and exercise ECG result (positive or negative).

6.6 Results

In total, the cohort included 7794 participants: 2676 White women, 2929 White men, 980 South Asian women and 1209 South Asian men. From tTable 21, South Asian women and men were younger than their White counterparts, with lower levels of smoking but a higher prevalence of diabetes mellitus.

		Women			Men		
		S Asian (n=980)	White (n=2676)	p	South Asian (n=1209)	White (n= 2929)	p
	Age in yrs, median(IQR)	50.6 (42-58)	57.6 (49-67)	<0.001	49.8 (41-59)	54.7 (45-65)	0.001
Risk factors	Smoker	35 (3.6%)	683 (25.5%)	<0.001	320 (26.3%)	924 (31.6%)	0.001
	Diabetes	209 (21.3%)	165 (6.1%)	<0.001	219 (18.1%)	207 (7.1%)	0.001
	Hypertension	367 (37.5%)	1017 (38.0%)	0.759	365 (30.2%)	875 (29.9%)	0.840
Medication	Secondary prevention						
	aspirin	232 (23.7%)	843 (31.5%)	<0.001	328 (27.1%)	1028 (35.1%)	<0.001
	statin	61 (6.2%)	371 (13.9%)	<0.001	117 (9.7%)	445 (15.2%)	<0.001
	ACE inhibitor	62 (6.3%)	171 (6.4%)	0.944	83 (6.9%)	213 (7.3%)	0.644
	Anti-anginals						
	β Blocker	155 (15.8%)	557 (20.8%)	0.001	214 (17.7%)	701 (23.9%)	<0.001
	Calcium antagonist	99 (10.1%)	474 (17.7%)	<0.001	102 (8.4%)	537 (18.3%)	<0.001
	Oral nitrate	67 (6.8%)	229 (8.6%)	0.091	94 (7.8%)	300 (10.2%)	0.014
	Nicorandil	3 (0.3%)	38 (1.4%)	0.005	9 (0.7%)	60 (2.1%)	0.003
Participant pain descriptors	Site						
	Central	402 (41.0%)	1592 (59.5%)		450 (37.2%)	1728 (59.0%)	
	Left sided	404 (41.2%)	583 (21.8%)		560 (46.3%)	804 (27.5%)	
	Right sided	40 (4.1%)	56 (2.0%)		50 (4.2%)	86 (2.9%)	
	Sub-mammary	64 (6.5%)	223 (8.3%)		103 (8.5%)	149 (5.1%)	
	Epigastric	69 (7.0%)	218 (8.2%)		44 (3.61%)	158 (5.4%)	
	Other	1 (0.1%)	7 (0.3%)	<0.001	2 (0.2%)	4 (0.1%)	<0.001
	Precipitating factor						
	Nothing	603 (61.5%)	1399 (52.3%)		765 (63.3%)	1524 (52.0%)	
	Exercise	173 (17.7%)	752 (28.1%)		216 (17.9%)	958 (32.7%)	
	Exercise and rest	142 (14.5%)	340 (12.7%)		164 (13.6%)	288 (9.8%)	
	Stress	29 (3.0%)	121 (4.5%)		27 (2.2%)	94 (3.2%)	
	Eating	32 (3.3%)	60 (2.2%)		34 (2.8%)	60 (2.1%)	
	Other	1 (0.1%)	4 (0.2%)	<0.001	3 (0.3%)	5 (0.2%)	<0.001
	Character						
	Aching	325 (33.2%)	1059 (39.6%)		407 (33.7%)	1110 (37.6%)	
	Constricting	230 (23.5%)	762 (28.5%)		295 (24.4%)	884 (30.2%)	
	Stabbing	269 (27.5%)	558 (20.9%)		303 (25.1%)	623 (21.3%)	
	Nondescript	156 (15.9%)	297 (11.1%)	<0.001	204 (16.9%)	322 (11.0%)	<0.001
	Duration of episodes						
	Seconds	39 (4.0%)	147 (5.5%)		69 (5.7%)	236 (8.1%)	
<5 minutes	156 (15.9%)	513 (19.2%)		230 (19.1%)	627 (21.4%)		
5-15 minutes	226 (23.1%)	699 (26.0%)		269 (22.5%)	733 (25.0%)		
15-30 minutes	123 (12.6%)	259 (9.7%)		129 (10.7%)	282 (9.6%)		
Hours/variable	436 (44.5%)	1058 (39.5%)	0.001	512 (42.0%)	1051 (35.9%)	<0.001	
Investigations	Exercise ECG						
	Positive	56 (12.8%)	200 (13.2%)	0.499	126 (17.3%)	468 (24.0%)	0.001
Symptom assessment	Cardiologist summary						
	Typical	163 (16.6%)	647 (24.2%)		193 (16.0%)	834 (28.5%)	
	Atypical	817 (83.4%)	2044 (75.8%)	<0.001	1016 (84.0%)	2095 (71.5%)	<0.001
	Symptom score						
	Typical	386 (39.4%)	1243 (46.5%)		492 (40.7%)	1509 (51.5%)	
	Atypical	594 (60.6%)	1433 (53.6%)	<0.001	717 (59.3%)	1420 (48.5%)	<0.001

Table 21 Chest pain clinic study - Baseline data and chest pain characteristics, comparing participants of South Asian origin with those of White origin by sex

(previous page)

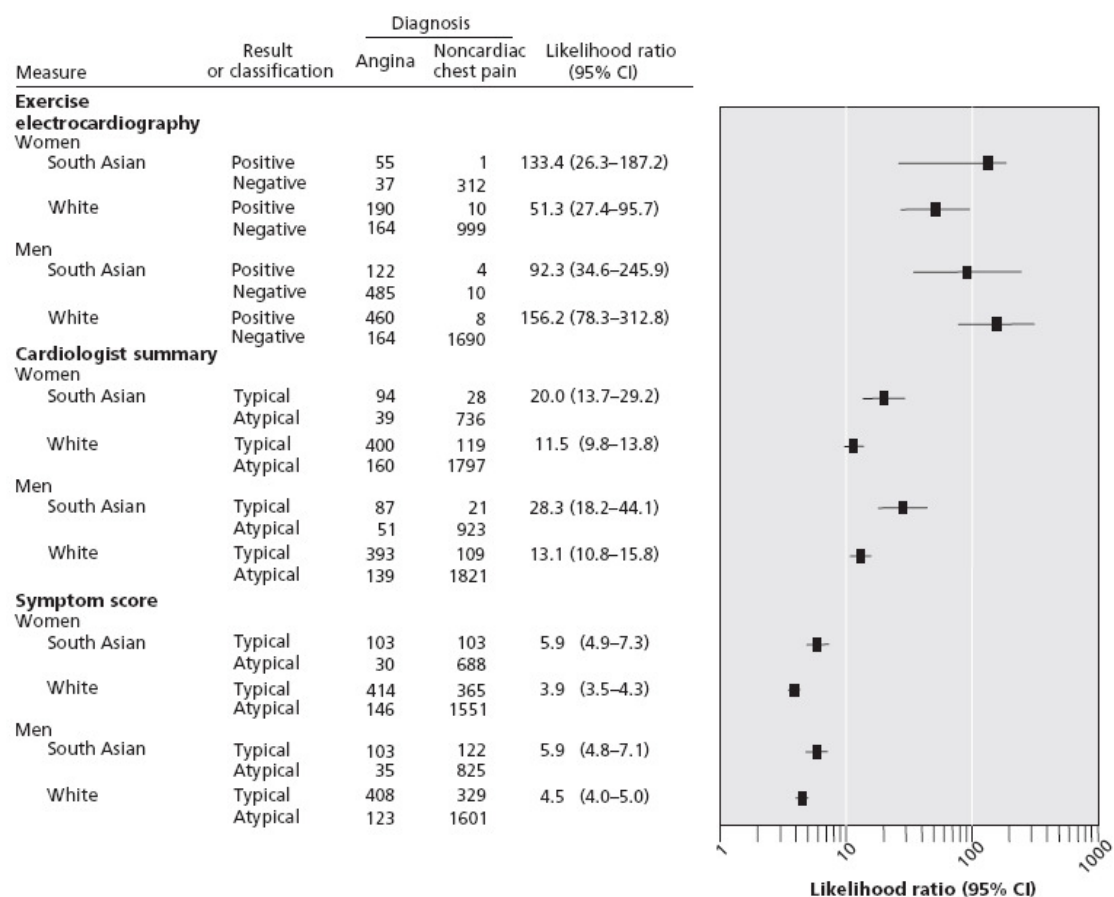
6.6.1 Chest pain descriptors

South Asian participants of both sexes were more likely to report atypical descriptors compared to White participants (Table 21). Their pain was less associated with exercise, more stabbing or non-descript than constricting and more likely to last hours or variable periods when compared to White participants. Though left-sided pain was included as typical in the symptoms score as it may code for the very typical sensation of chest pain radiating to the left arm, South Asian participants had chest pain that tended to be more left-sided than central. As left pain was not coded separately as left chest or left arm, it is not possible to discern whether this left chest pain is mostly atypical or mostly radiated typical pain in South Asian participants, though the pattern of results from the other descriptors hints to the former. Overall, atypical chest pain was reported by more South Asian participants than White participants (59.9% v. 52.5%, $p < 0.001$). South Asian participants of both sexes were more likely to have their symptoms described as atypical by the cardiologist, and less likely to be given a diagnosis of angina by the cardiologist. There was 73.3% agreement (kappa statistic 0.43) between the cardiologist summary and symptom score.

6.6.2 Symptoms and diagnosis

Neither sex nor ethnicity modified the association between the exercise ECG result and the diagnosis of angina, with high likelihood ratios (Figure 7) across sex and ethnicity. Hence, typical symptoms strongly predicted a positive exercise ECG result. After excluding patients with a positive exercise ECG which would have strongly influenced a diagnosis of angina, both the cardiologist summary and the symptom score of typical symptoms were still predictive of a diagnosis of angina across sex and ethnicity. Likelihood ratios were lower for the symptom score compared with cardiologist summary but remained well above 1.0.

Figure 7 Chest pain clinic study - Likelihood that exercise ECG result, cardiologist summary or symptom score leads to a diagnosis of angina, by sex and ethnicity



6.6.3 Symptoms and their validity in predicting prognosis

The overall prognosis for the combined coronary outcome in the cohort was no worse in South Asian compared to White participants (adjusted for age, sex, diabetes, smoking, hypertension and hypercholesterolaemia, HR 1.04 (95% CI 0.75-1.45)).

Typical symptoms predicted coronary outcome in South Asian participants as well as in White participants, using both the cardiologist summary and symptom score (Table 22).

Chest pain assessment		Chest pain description		Risk of coronary death or ACS	p**
		Typical	Atypical	HR*	
Cardiologist summary	South Asian	64/356	100/1833	1.97 (1.38-2.81)	0.353
	White	223/1481	151/4124	2.41 (1.91-3.05)	
Symptom score	South Asian	97/878	67/1311	1.58 (1.14-2.18)	0.902
	White	261/2663	113/2942	1.62 (1.29-2.05)	

Coronary outcome - death due to coronary heart disease or acute coronary or hospital admission with unstable angina
 *Hazard ratio for typical vs atypical (95%CI) adjusted for age, sex, diabetes, hypertension, smoking and revascularisation
 ** P for difference between two hazard ratios¹⁵⁴

Table 22 Chest pain clinic study - Typical compared to atypical chest pain as a predictor of coronary outcome in South Asian and in White participants

Within both those with typical symptoms and atypical symptoms, South Asian participants were no more likely to suffer the coronary outcome than White participants on unadjusted survival curves (Figure 8, unadjusted log rank test p=0.53 in typical category, p=0.88 for atypical).

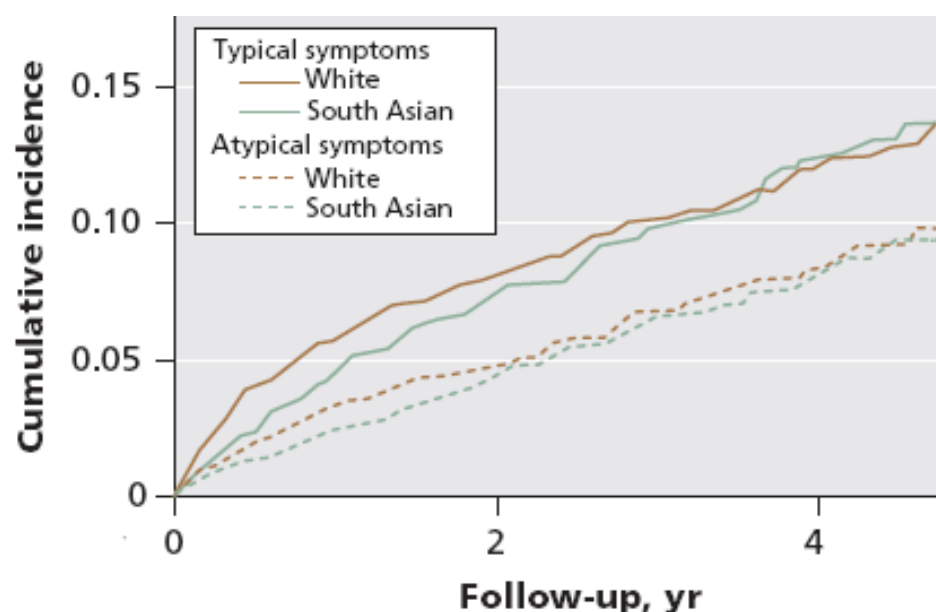


Figure 8 Chest pain clinic study - Typicality of chest pain according to symptom score comparing South Asian to White participants and cumulative probability of coronary death/ACS

Within those with typical symptoms, on examining adjusted Cox regression hazard ratios (Table 23) to take into account differences in baseline risk profile, South Asian participants with typical pain were as likely as White participants with typical pain to experience a coronary outcome for cardiologist summaries

(HR 1.27, 95% CI 0.89–1.81) and more likely with symptom scores (HR 1.41, 95% CI 1.04–1.91). Atypical pain had a similar prognostic value for coronary outcomes in South Asian participants compared to White participants. There was no interaction between sex and ethnic background (likelihood ratio for interaction: typical pain p=0.34; atypical pain p=0.76).

South Asian vs. White	Hazard ratio (95% CI)*		
	Coronary Angiography*	Revascularisation*	Coronary death or ACS**
Typical			
Cardiologist summary	0.58 (0.45-0.75)	0.52 (0.36-0.75)	1.27 (0.89-1.81)
Symptom score	0.52 (0.41-0.67)	0.53 (0.38-0.74)	1.41 (1.04-1.91)
Atypical			
Cardiologist summary	0.55 (0.38-0.78)	0.61 (0.35-1.05)	1.38 (0.94-2.02)
Symptom score	0.59 (0.39-0.88)	0.49 (0.24-1.00)	1.19 (0.73-1.92)

Coronary outcome - death due to coronary heart disease or acute coronary or hospital admission with unstable angina

* Adjusted for age, sex, diabetes, smoking, hypertension, secondary prevention/anti-anginals and exercise ECG result

** Adjusted for age, sex, diabetes, smoking, hypertension, secondary prevention medication, revascularisation and exercise ECG result

Table 23 Chest pain clinic study - Type of chest pain (typical and atypical) and subsequent receipt of angiography, receipt of revascularisation and prognosis in South Asian compared to White participants

6.6.4 Symptoms and their relation to clinical management

South Asian participants with typical or atypical pain were less likely than White participants with typical or atypical pain respectively to receive angiography and revascularisation (Table 23-typical symptom score, adjusted HR for angiography 0.52, 95% CI 0.41–0.67; adjusted HR for revascularisation 0.53, 95% CI 0.38–0.74). The adjustments were designed to be appropriate for the management outcome – the use of anti-anginal medication specifically important in progress to angiography and revascularisation. Further analyses showed that these results were also independent of whether or not the cardiologist had made the diagnosis of angina – by including only those in whom the diagnosis of angina was made, South Asian participants with typical pain were still less likely than White participants with typical pain to receive angiography and revascularisation (typical cardiologist summary, adjusted HR for angiography

0.59, 95% CI 0.45–0.76; adjusted HR for revascularisation 0.49, 95% CI 0.34–0.72).

Revascularisation rates were higher among patients who reported typical symptoms than among those who reported atypical symptoms (women, adjusted HR for revascularisation 3.86, 95% CI 2.35–6.35; South Asian participants, adjusted HR 3.16, 95% CI 1.93–5.19).

6.6.5 The impact of diagnosis on prognosis

In both those diagnosed with angina and those not, the overall prognosis for coronary death in the cohort was no worse in South Asian participants compared to White participants (diagnosed as angina, HR 1.20 (95% CI 0.88–1.64) adjusted for age, sex, diabetes, smoking, hypertension, secondary prevention and exercise ECG result).

6.6.5.1 The symptom score

I defined typical pain as three or more of these characteristics and atypical pain two or fewer (the ‘symptom score’) to make a binary descriptive variable of chest pain. I did not analyse as per the three types initially described by Diamond and Forrester (non-cardiac, atypical, typical) even though the data collection form did allow the cardiologist to assess the symptoms as non-cardiac, atypical and typical. Investigating these categories, ‘atypical’ behaved similarly to ‘non-cardiac’, as those with atypical pain did not have higher hazard ratios for risk of coronary outcome compared to ‘non-cardiac’ (Table 24). The Diamond and Forrester classification is rarely used by cardiologists, most preferring to assess typical or atypical in the real-world clinical setting. Hence, I used a binary symptom score.

Cardiologist assessment symptoms	Male		Female	
	South Asian (n=1219)	White (n=2959)	South Asian (n=986)	White (n=2704)
Non-cardiac	1	1	1	1
Typical	3.28 (1.42-7.58)	7.04 (2.81-17.67)	8.90 (0.92-86.43)	5.04 (1.76-14.41)
Atypical	1.19 (0.57-2.52)	1.57 (0.61-4.05)	4.85 (0.59-39.70)	1.11 (0.37-3.35)

Table 24 Chest pain clinic study - Non-cardiac compared to typical and atypical chest pain as a predictor of coronary outcome in South Asian and White participants by sex

In the initial exploration of the database, I tried to ascertain whether individual descriptors within the components of chest pain might be markers of prognosis (e.g. central chest pain alone). However, numbers within each descriptor type were too small and from a clinical point of view, most cardiologists tend to build a picture of typicality of symptoms from a constellation of features rather than one feature itself. My early analyses did however show me the validity of the Diamond and Forrester classification (Table 25). When examining character, constricting descriptors had a worse prognosis than aching, stabbing and non-descript. Similarly, descriptors that were central in location and precipitated by exercise had the worse prognosis within their components of chest pain.

		Male		Female	
		South Asian (n=1219)	White (n=2959)	South Asian (n=986)	White (n=2704)
Character	Aching	0.36 (0.15-0.82)	0.55 (0.33-0.91)	-	0.71 (0.36-1.41)
	Stabbing	0.53 (0.25-1.15)	0.32 (0.16-0.66)	-	0.36 (0.13-0.95)
	Constricting	1	1	1	1
	Nondescript	0.78 (0.36-1.69)	0.48 (0.22-1.01)	-	1.02 (0.45-2.31)
Site	Central	1	1	1	1
	Left sided	0.60 (0.33-1.09)	0.55 (0.32-0.95)	0.84 (0.24-2.91)	0.37 (0.16-0.88)
Precipitating factor	Nothing	1	1	1	1
	Exercise	2.85 (1.41-5.75)	3.77 (2.33-6.12)	2.85 (0.48-17.11)	8.86 (3.90-20.14)
	Exercise and rest	1.91 (0.89-4.09)	2.90 (1.45-5.79)	5.63 (1.34-23.76)	5.63 (2.10-15.15)
Duration	Seconds	Numbers too small for analysis			
	1-5 minutes				
	5-15 minutes				
	15-30 minutes				
	Hours/ Variable				

Unadjusted hazard ratios (95%CI); HR>1 indicates poorer prognosis.

Table 25 Chest pain clinic study – Individual chest pain descriptor and risk of coronary outcome in South Asian and White participants by sex

6.6.5.2 Symptoms and risk factors in prediction of prognosis

I examined further the effect of high coronary risk (having two or more of the risk factors: smoking, hypertensive, diabetic, or hypercholesterolemia) versus low coronary risk on outcomes in the whole cohort. High coronary risk was a predictor of outcomes in the whole cohort of coronary outcome as would be expected (age and sex-adjusted HR 1.41 (1.08-1.85)). Limiting analyses to South Asian participants with atypical pain, high coronary risk compared to low coronary risk remained a predictor of outcomes (age and sex-adjusted HR 3.22 (1.22-8.55)). This was rendered non-significant on adjustment for receipt of secondary prevention therapy but not coronary revascularisation (Table 26). Thus in South Asian people with a profile of high coronary risk but with atypical pain, management should be concentrated on secondary prevention not revascularisation. The symptom score thus highlights to the general practitioner those people irrespective of ethnic group, in whom referral to a chest pain clinic is appropriate.

	Adjusted for age and sex	Adjusted for age, sex and revascularisation	Adjusted for age, sex and secondary prevention
South Asian person with atypical pain	3.22 (1.22-8.55)	2.82 (1.05-7.56)	2.49 (0.91-6.85)

Coronary outcome - death due to coronary heart disease or acute coronary or hospital admission with unstable angina

*Hazard ratio for typical vs atypical (95%CI) adjusted for age, sex or ethnicity, diabetes, hypertension, smoking and revascularisation

High coronary risk = two or more of the risk factors: smoking, hypertensive, diabetic, or hypercholesterolemia

Table 26 Chest pain clinic study - High coronary risk compared to low coronary risk in South Asian participants with atypical pain as a predictor of coronary outcome, adjusted for management strategy

6.7 Discussion

6.7.1 Objective addressed

In a study of over 7000 consecutive participants presenting to a rapid access chest pain clinic with detailed data on symptom characterisation, typical chest pain compared to atypical chest pain was as likely to be associated with a worse prognosis in South Asian as in White participants. South Asian participants with prognostically significant angina pectoris did not present atypically. Systematic and potentially inequitable differences in management between ethnic groups

could not be explained by differences in presentation of symptoms. The overall prognosis for coronary death in the cohort was no worse in South Asian compared to White participants.

The central diagnostic cannon of stable angina³⁴ for the last three decades, which has assessed pre-test probability of coronary disease using symptom typicality, age and sex, has now had its contemporary validity in South Asian people demonstrated by this study.

6.7.2 Symptoms in South Asian people

I found that typical symptoms were predictive of a diagnosis of angina across ethnicity. Furthermore, typical symptoms were predictive of coronary outcomes in South Asian participants when they were compared to atypical presentations. Although South Asian participants attending the chest pain clinic did report a marked excess of atypical symptoms, the rate of subsequent adverse coronary outcomes in this group was similar in White and South Asian participants. Since both doctors and patients may be aware that in the general population coronary heart disease mortality is higher in South Asian people,^{10 155} my findings might be explained by a lower threshold for referral of South Asian people from primary care to a chest pain clinic with any chest pain symptoms, hence reversing the possibility of selection bias favouring white patients. Indeed, a previous survey found some evidence that South Asian people with chest pain may be more willing to seek care.⁴¹

These results contrasted with the Whitehall-II findings that revealed a worse prognosis in South Asian compared to White populations within each type of chest pain. Whitehall-II was a healthy population rather than clinical cohort, and thus it is conceivable that those South Asian participants with typical angina in the early stages of Whitehall-II went undiagnosed and hence unmanaged. Furthermore, a chest pain clinic provides a more reliable measure of incidence, as it is designed to capture recent-onset chest pain which Whitehall-II was not. The chest pain clinic, with its detailed coding of the description of symptoms by cardiologists in a clinic designed for capturing incident angina, shows that incident atypical chest pain in

South Asian participants does not have a worse prognosis than in White participants.

Chest pain characteristics, and their perception, have been compared in different ethnic groups.^{42 43} South Asian, compared to White populations, report a higher likelihood of seeking care.⁴¹ African-American people may be more likely to attribute their symptoms to a non-cardiac source than White people but were not more likely to have atypical symptoms in a prospective study based in an emergency department.¹⁵⁶ African-American people have also been reported to complain more of shortness of breath than White people when presenting for coronary angiography.¹⁵⁷

6.7.3 Typicality of symptoms and other explanations for inequalities in management

I found lower rates of coronary angiography and revascularisation among South Asian participants compared with White participants. This could not be fully explained by the presence of typical or atypical symptoms, as even South Asian participants with typical pain were less likely to undergo diagnostic and therapeutic invasive procedures. Studies of inequalities in invasive management of angina among South Asian people have lacked details about pain symptoms. It is also unlikely that differences in symptom severity explain this under-management because functional impact and tendency to seek care are higher among South Asian people with chest pain.⁴¹

South Asian and White people may differ in their understanding of the risks and benefits of revascularisation. Written communication in English, waiting lists, and repeated out-patient assessments may represent barriers for South Asian people trying to negotiate the administrative hurdles towards revascularisation. Ethnic groups may also differ in willingness to undergo revascularisation, with studies from the United States reporting that Black and White people have different preferences for treatment.¹⁵⁸

Unmeasured factors may account for the under-management observed. The degree of co-morbidities was not well-captured on this database and referral selection

may depend on interactions between co-morbidities. As an example, patients with aortic valve stenosis causing chest pain would have been more likely to be referred for cardiac catheterisation but less so as renal function progressively declines due to perceived surgical operative risk. Further social factors such as employment, language barriers, and patient preferences were not available as measures in these data. The cohort did not have data on refusal of revascularisation, nor on the efficacy of ensuing medical treatment with anti-anginal drugs alone. The factors comprising angiography decision making are thus complex, prognostically important, and often immeasurable.

6.7.4 Clinical implications of history taking

A history of typical symptoms was based solely on pre-defined response types to four questions – character, site, duration and precipitating factors. Typical pain was associated with a diagnosis of angina and worse prognosis for coronary outcomes in South Asian participants compared to those with a history of atypical symptoms. This symptom score could potentially be quickly elicited from a history taken by the general practitioner in order to decide upon referral to a chest pain clinic in the place of more detailed risk scores. The cardiologist summary demonstrated stronger associations with a diagnosis of angina, or risk of coronary outcomes on follow-up, than did the symptom score. This may reflect the incorporation of risk factor information, and clinical experience into the estimate of pre-test disease likelihood. Though weaker, the simpler symptom score remained predictive of outcomes. This will encourage the general practitioner that a simple and quick history eliciting these descriptors of chest pain is an effective means to determining the appropriateness for referral to a cardiologist irrespective of ethnicity. This work helps to guide the general practitioner that the management of the patient with atypical pain but multiple coronary risk factors is to focus on the risk factors, not the atypical pain.

6.7.5 Limitations

A major strength of this study is the detailed description of chest pain among a large number of participants with recent onset symptoms, without previous investigation, myocardial infarction or revascularisation, at the interface of

primary and secondary care. The high proportion of South Asian participants in the study reflects the high concentration of South Asian people in the areas where the chest pain clinics were located, and thus gives a realistic picture of likely disease burden and potential demand on healthcare services in areas with a high proportion of South Asian people in the local population.

Several limitations should however be considered in interpreting these findings. First, the recorded history may have been biased by the knowledge of the exercise ECG findings; for this reason, I excluded those with an abnormal exercise ECG when assessing diagnosis of angina.

Second, the category of South Asian encompasses different language, religions and cultural groups, amongst whom cardiovascular risk profile differ.²⁰ Further research is required to test whether symptom validity differs between Bangladeshi, Indian, Pakistani or Sri Lankan people.

Third, data were not available on the findings of subsequent coronary angiography if it took place. As revascularisation is largely driven by the severity of angiographic disease, this data may have in part explained why revascularisation was not undertaken in some.

Fourth, though data entry for smoking status, history of hypertension and diabetes and medication were 100% complete, history of hypercholesterolemia was unknown in 68.49% of the cohort and 78.4% did not have a cholesterol level - hence this variable was not entered into the multi-variate analyses by symptom category model. Adding hypercholesterolemia or statin therapy into the prognostic multi-variate analyses symptom category did not significantly alter the direction nor strength of the hazard ratios.

Finally, when examining prognosis for coronary death in South Asian compared to White participants by chest pain symptoms category, increased power would have excluded a differential outcome between ethnic groups more confidently. With all four summary estimates for the coronary outcome to the right of 1 (Table 23), it

may be that lack of power hides worse outcomes for South Asian participants irrespective of presenting symptomatology similar to that observed in Whitehall-II.

6.7.6 Implications

Better coding of the symptoms articulated by the patient with chest pain may aid in the diagnostic process for angina. A potential limitation of this quantitative study is that the actual words used by patients, their meaning and context were not reported. This was addressed in an ethnographic qualitative study of 59 clinic consultations performed alongside this study by colleagues at the Newham site to understand how the chest pain classification and diagnosis were reached.¹⁵⁹ They found that symptom histories represented a complex negotiation between cardiologist and patient, with much ambiguity and re-telling. There was little evidence that this negotiation was patterned by sex or ethnicity. Importantly, none of the South Asian patients in this study relied on translators; the minority who needed help with English were accompanied by a younger family member. This work relied on the pre-specified coding in the database; it is likely that doctors may record in free text further relevant details of symptoms pertinent to the diagnosis of angina. Electronic processing of this natural language might aid the identification of patients with angina,¹⁶⁰ though this would be dependent on adequate documentation of the history by the doctor.

6.8 Conclusions

South Asian people with typical chest pain were found to be at increased risk of adverse coronary outcomes compared with those who presented with atypical pain. South Asian people with prognostically important angina pectoris did not present atypically, and differences in symptom description did not account for their lower rates of coronary angiography and revascularisation compared with White people. Thus, symptoms of chest pain are valid diagnostic and potentially important prognostic tools across ethnic backgrounds. Further study should examine why South Asian people with the same prognosis as White people receive poorer care.

6.9 Building to next chapter

I have shown that typical angina in South Asian populations, when ascertained by the words articulated by a patient to a specialist doctor, was valid in predicting a poorer prognosis than chest pain that is less typical of angina. By building a simple measurement tool from the clinical history, I used facets from normal clinical practice to show that history-taking is as valid in South Asian people as it is in White people, and that atypical chest pain, commoner in South Asian people, has a better prognosis than typical angina.

Overall prognosis in South Asian compared to White populations was not worse in this cohort. This contrasts with the findings of Whitehall-II, which demonstrated a worse prognosis in South Asian people compared to White people in all types of chest pain. Hence, the results of analysing this cohort, at the first stage of contact with the health services along the natural history of coronary disease, demonstrate that early clinical assessment may be able to delay the natural course of coronary disease. However, there are no randomised trials comparing this rapid access chest pain clinic model for the assessment of undifferentiated chest pain to older models of healthcare such as the out-patient cardiology service to definitively prove this.

However, under-treatment still prevailed in this cohort. The next stage of this thesis sought to study patients with chronic chest pain in need of specialist secondary care management. I wanted to continue to investigate prognosis, but examine both non-fatal and fatal outcomes. Specifically, I wanted to move onto symptomatic prognosis. If prognosis for fatal events in incident angina is relatively equitable between ethnic groups presenting to a chest pain clinic, I sought to investigate whether similar equity existed in how chronic angina improved with management strategies instigated in secondary care. Such symptomatic, non-fatal outcomes are important to the quality of life of the patient with chronic symptoms as well as to providing an overall picture of prognosis of coronary disease in South Asian compared to White populations. I will thus – in addition to prognosis for serious coronary clinical events such as myocardial infarction and death, now examine symptomatic prognosis.

7 Symptomatic outcomes following coronary angiography in patients with chronic stable angina

7.1 Summary of chapter

Background In patients with angina, the overall prognosis for coronary death is no worse in South Asian compared to White populations. However, it is not known whether there are disparities in symptomatic outcomes between South Asian and White populations from clinical management strategies in those with angina.

Methods Six-year prospective cohort study to determine whether improvement of angina symptoms differs between South Asian and White patients following revascularisation or medical management.

Results 43.9% of South Asian patients reported improvement in angina at six years compared with 60.3% of White patients (age-adjusted odds ratio 0.56, 95% CI 0.41-0.76, OR adjusted for diabetes, hypertension, smoking, number of diseased vessels, left ventricular function and social class 0.59, 95% CI 0.41-0.85). Similar proportions of White and South Asian patients underwent percutaneous coronary intervention (PCI) (19.6% vs 19.9%) and coronary artery bypass surgery (CABG) (32.8% vs 30.1%). South Asian patients were less likely to report improved angina after PCI (OR 0.19, 95% CI 0.06-0.56) or CABG (OR 0.36, 95% CI 0.17-0.74). There was less evidence of ethnic differences in angina improvement when treatment was medical (OR 0.87, 95% CI 0.48-1.57).

Conclusions South Asian patients had poorer symptomatic prognosis following coronary angiography, being less likely to experience long-term improvements in angina than White patients after receipt of revascularisation. That prognosis for fatal events is no worse in South Asian populations but that prognosis for morbidity outcomes may be worse than in White populations adds to the overall picture of prognosis for coronary disease between these ethnic groups.

7.2 Introduction

Angina is the most common initial manifestation of coronary heart disease,²⁹ a significant burden in primary care³¹ and has considerable economic implications.³² The Health Survey for England on minority health reported that the prevalence of angina pectoris may be higher in South Asian people.¹⁶¹ In these patients with exertional angina, prognosis for outcomes such as myocardial infarction and death is not improved by coronary revascularisation.

The previous chapter showed that, in patients with incident angina, the overall prognosis for coronary death was no worse in South Asian compared to White populations. It also found lower rates of revascularisation among South Asian patients compared with White patients. If revascularisation appears most suited for rapid symptom control rather than in improving prognosis for fatal outcomes, to fully examine prognosis of coronary disease in South Asian patients compared with White patients requires the study of symptomatic outcomes for those with angina.

Ethnic disparities in clinical outcomes following revascularisation have been reported in African-Americans.⁷¹ There is little evidence on morbidity outcomes in South Asian patients compared with White patients following presentation with angina, such as change in symptoms following treatment, and whether differing strategies of clinical management equally improve symptom burden by ethnic groups.

7.3 Research objective to be investigated

This chapter sought to investigate specific research objective 3.

To determine impact on symptomatic prognostic outcomes (change in angina severity) in South Asians and White populations from different management strategies for chronic angina.

7.4 Specific research questions

- i. Does the improvement of angina differ between South Asian and White patients six years following coronary angiography?
- ii. Do differing treatment modalities affect improvement of angina differentially by ethnic group?
- iii. Do South Asian and White patients appropriate for revascularisation report improved angina at six years?

7.5 Methods

7.5.1 Population

4121 consecutive patients were eligible for inclusion in the ACRE (Appropriateness of Coronary Revascularisation) study if they underwent coronary angiography at the Barts and London Hospitals Trust, London between 15 April 1996 and 14 April 1997. There were no exclusion criteria and written informed patient consent was obtained.

7.5.2 Ethnicity

Self-assigned ethnicity was based on the 1991 census classification by questionnaire on the day of index coronary angiography and identified 424 South Asian patients. For patients with missing data, given and family names were cross matched on a database of 15 000 names used to identify South Asian patients in routine data from east London.¹⁴¹ This database identified a further 78 South Asian patients. This system was considered valid because the name database is highly specific (99%); the name assigned and self-assigned methods identified similar proportions of South Asian people (15.6% and 12.8%, respectively) and confining the analyses to those with self assigned ethnicity did not affect the results.

7.5.3 Assessment of angina status at baseline and follow-up

7.5.3.1 Canadian Cardiovascular Society classification angina

On the day of index coronary angiography, patients completed a questionnaire about their general health, coronary heart disease risk factors and angina

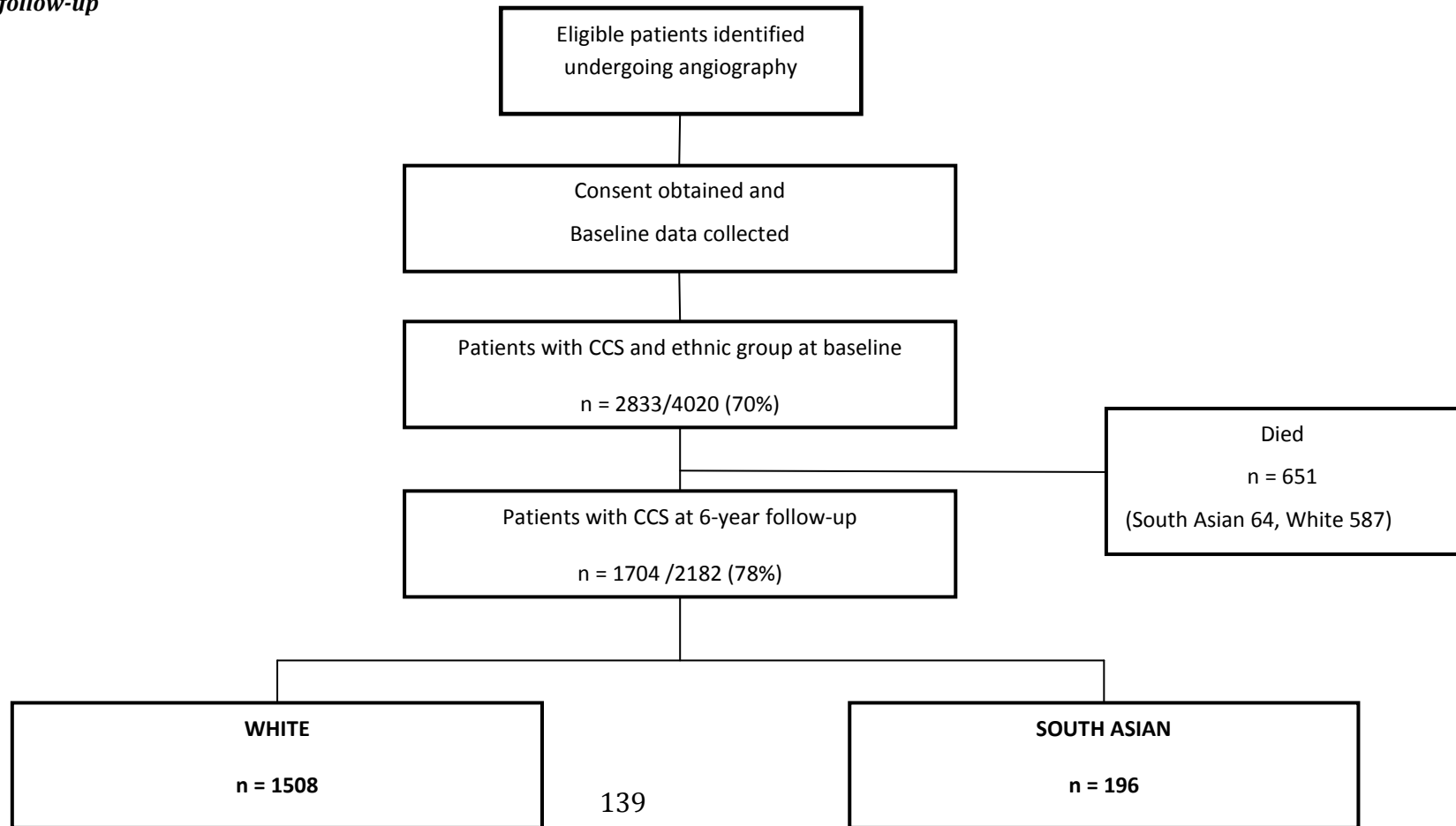
symptoms (data available for 3301/4020, 82% response rate) using the Canadian Cardiovascular Society classification.

Canadian Cardiovascular Society Functional Classification of Angina		
Class	Activity Evoking Angina	Limits to Physical Activity
I	Prolonged exertion	None
II	Walking > 2 blocks or > 1 flight of stairs	Slight
III	Walking < 2 blocks or < 1 flight of stairs	Marked
IV	Minimal or at rest	Severe

2833 of the 4020 (70%) had data on both CCS angina and ethnicity.

At follow-up, all patients who were alive and had consented to follow-up were sent a questionnaire asking about their angina (mean date 1st October 2002, response rate 78%). CCS for angina class was available at both baseline and follow-up in 1508 White patients and 196 South Asian patients (Figure 9). The patients' general practitioners were also sent a questionnaire at time of follow-up asking whether the patient had a current diagnosis of angina in order to cross-check patient questionnaire responses for angina.

Figure 9 ACRE - Recruitment of patients with chest pain data at baseline and follow-up



At follow-up (Table 27), presence of angina on CCS classification (I-IV) was associated with general practitioner diagnosis of angina in both White ($\chi^2=105$, $p<0.001$) and South Asian patients ($\chi^2=4.0$, $p=0.045$). CCS was also strongly associated with nitrate prescription ($\chi^2=114$ in White patients, 15.3 in South Asian patients, $p<0.001$ in both ethnic groups).

Ethnicity	CCS class (angina)	N	Nitrate prescription	P	N	GP diagnosis of angina	p
White	0 (no)	592	162(27.36)	<0.001	590	70(11.86)	<0.001
	I-IV (yes)	727	412(56.67)		720	264(36.67)	
South Asian	0 (no)	44	6 (13.64)	<0.001	43	9 (20.93)	0.045
	I-IV (yes)	98	47 (47.96)		97	37 (38.14)	

(%)

Table 27 ACRE - Presence of angina or not by CCS in White and South Asian patients at follow-up cross-tabulated to data on nitrate prescription GP diagnosis of angina on general practitioner questionnaire at follow-up

It has also previously been reported in this cohort that CCS class was linearly associated with angiographic findings, revascularisation rates, mortality and nonfatal myocardial infarction.⁵⁷ In age-adjusted analyses, a higher CCS class was associated with an increased number of diseased vessels and worse left ventricular function. After adjusting for age, sex, smoking, history of hypertension, diabetes, number of diseased vessels, left ventricular function, use of aspirin, beta-blockers or statins, and revascularisation status (for death and nonfatal myocardial infarction), a higher CCS class was linearly associated with higher coronary angioplasty ($P<0.001$) and bypass graft ($P=0.03$) rates, and higher all-cause mortality and nonfatal myocardial infarction ($P<0.001$; CCS IV versus I: hazard ratio 2.44, 95% CI 1.46 to 4.09).

7.5.3.2 Rose angina questionnaire

Cardiac symptoms using questions derived from the Rose angina questionnaire were also sought. However, the completion rate was significantly lower than for CCS in both ethnic groups (60% in South Asian patients, 69.8% in White patients).

7.5.4 *Baseline clinical details*

On the day of coronary angiography, eligible patients were identified by examination of ward admission and catheter laboratory logbooks. Data were extracted on clinical presentation, present medications, past history of diabetes, smoking and hypertension, family history of coronary disease (heart attack, angina or sudden cardiac death in parent/sibling aged under 60), occupation (to assign social class according to the Registrar General's classification^m) and education from case notes by trained nurses using standardised recording forms. The number of diseased vessels at angiography was calculated from the severity of disease in each of 27 coronary artery segments (as defined by the Coronary Artery Surgery Study¹⁶²). Left ventricular function was assessed by ventriculography.

7.5.5 *Appropriateness ratings*

A nine member expert panel (four cardiologists, three cardiothoracic surgeons, a general doctor, and a primary care doctor) was convened to rate the appropriateness of PCI and CABG. Using a technique developed by the RAND corporation in the USA,⁵⁹ the expert panel rated 2178 mutually exclusive indications for coronary angiography. A specific indication was defined by logical combinations of clinical presentation, test results, and current treatment. Median scores ranged from 1-9, with 1-3 being inappropriate, 4-6 uncertain, and 7-9 appropriate. Angiography was "inappropriate" when risks exceeded benefits and

^m An official scheme of class analysis used in British surveys and censuses, though increasingly being supplanted by newer classifications. It grouped occupations into five socio-economic classes with the implication that occupation was a meaningful indicator of social welfare.

I Professional occupations—e.g. doctors and lawyers.

II Managerial and lower professional occupations—e.g. managers and teachers.

IIIN Non-manual skilled occupations—e.g. office workers.

IIIM Manual skilled occupations—e.g. bricklayers, coalminers.

IV Semi-skilled occupations—e.g. postal workers.

V Unskilled occupations—e.g. porters, dustmen.

"uncertain" when benefits and risks approximated equality or when the expert panel was divided in its judgement.

7.5.6 *Angiographic findings*

These were obtained from the free text angiogram report held in the case notes and coded blind to the clinical details by a trained coder. The number of diseased vessels was calculated from the severity of disease as defined by the Coronary Artery Surgery Study.^{162 163}

7.5.7 *Follow up for mortality and hospitalisation*

At baseline, 99% of patients were flagged for mortality by the Office for National Statistics and were followed up until 14 October 2003. Patients were flagged with the National Health Service-Wide Clearing Service for all-cause hospital inpatient admissions since the date of their index coronary angiogram until 1st October 2002, matched on NHS number, or date of birth, postcode and sex. Details on hospital admission such as revascularisation procedures and non-fatal myocardial infarction (ICD-10 code 121) were collected from case notes and from the Patient Administration Systems from the 13 referring hospitals.

7.5.8 *Statistical analysis*

To measure course of angina, follow-up angina score was subtracted from baseline angina score (both 0 to +4). Then, the change in angina was coded as

- 0 if angina class had not changed or worsened from baseline to follow-up (-4 to 0), and
- 1 (+1 to +4) if angina had improved.

STATA do-file – generation of angina change

```
gen diff_angina=pccs-ccscoded
gen change_angina=diff_angina
recode change_angina -4/0=0 1/4=1
label var change_angina "change in angina status"
label define change_angina 0 "worse/none" 1 "improved"

where
    pccs= CCS angina at baseline
    ccscoded=CCS angina at follow-up
```

All covariates that were significantly associated with change in angina in the univariate analysis were included in the main analysis. Logistic regression analysis was conducted to examine the relationship between ethnicity and change in angina class. The likelihood ratio test was used to select covariates for the final model (at a threshold of $p < 0.1$). Findings are presented as odds ratios with 95% confidence intervals. Survival analysis was performed to examine the association of change in angina class and death. Kaplan Meier curves were plotted as a measure of absolute risk and Cox proportional hazards regression conducted for relative risk differences. Confounders included in the Cox regression were hypertension, smoking, number of diseased vessels, left ventricular function and social class.

7.6 Results

7.6.1 Baseline correlates of angina

In order to validate the measure of angina across both ethnic groups, I examined angina class versus baseline variables. South Asian patients with worse angina (higher angina class) were more likely to smoke, have lower mean systolic blood pressure, be in a lower social class, have a higher body mass index, have a history of heart failure, and have a higher doctor-defined angina class (Table 28). White patients with worse angina revealed similar trends, and were in addition more likely to have diabetes, a history of myocardial infarction and be on calcium antagonists, nitrates or ACE inhibitors. There was no evidence of any significant differences between the trends in White patients and the trends in South Asian patients (p for interaction column).

Table 28 ACRE - Baseline characteristics in each angina class, in South Asian and White patients

Ethnic group	South Asian					White					
	CCS class	I (N=10)	III (N=71)	III (N=128)	IV (N=125)	P for trend	I (N=166)	III (N=446)	III (N=685)	IV (N=905)	P for trend
Age (mean, years)	56.2	54.0	55.9	56.5	0.150	58.4	60.3	61.5	61.8	<0.001	0.998
Men	7 (70)	52 (73)	106 (83)	93 (74)	0.905	139 (84)	324 (73)	518 (76)	590 (65)	<0.001	0.089
Ever smoked	2 (22)	29 (42)	60 (48)	65 (56)	0.014	113 (69)	306 (70)	488 (73)	674 (77)	0.001	0.217
Hypertensive	3 (30)	26 (37)	50 (39)	54 (43)	0.317	49 (30)	145 (33)	200 (29)	287 (32)	0.837	0.323
Systolic blood pressure (mmHg)	141.2	135.7	133.2	130.6	0.051	134.5	136.3	134.3	132.5	0.009	0.308
Total cholesterol (mean,mmol/l)	5.69	5.80	5.53	5.61	0.458	5.48	5.67	5.65	5.63	0.501	0.303
Diabetes	3 (30)	18 (25)	42 (33)	45 (36)	0.280	12 (7)	35 (8)	71 (10)	102 (11)	0.033	0.880
Body Mass Index (mean, kg/m2)	25.3	25.8	25.6	26.7	0.092	27.6	27.1	27.2	28.1	0.002	0.536
Family history coronary disease	3 (33)	28 (42)	38 (34)	38 (35)	0.584	82 (52)	182 (43)	285 (45)	436 (51)	0.052	0.260
Lower social class	3 (43)	42 (61)	79 (68)	87 (73)	0.047	91 (56)	235 (54)	377 (57)	519 (59)	0.089	0.121
Left school <16	3 (43)	33 (58)	61 (62)	41 (44)	0.186	28 (18)	66 (16)	91 (14)	94 (11)	0.013	0.751
Medication											
Aspirin	8 (80)	53 (75)	94 (73)	95 (76)	0.898	136 (82)	334 (75)	511 (75)	691 (76)	0.726	0.784
ACE inhibitor	1 (10)	18 (25)	33 (26)	28 (22)	0.839	27 (16)	90 (20)	138 (20)	210 (23)	0.040	0.451
Statin	0	11 (15)	21 (16)	18 (14)	0.733	35 (21)	107 (24)	151 (22)	193 (21)	0.751	0.605
Beta-blocker	5 (50)	37 (52)	56 (44)	56 (45)	0.539	82 (49)	229 (51)	331 (48)	374 (41)	0.002	0.773
Calcium antagonist	5 (50)	32 (45)	60 (47)	73 (58)	0.153	76 (46)	212 (48)	316 (46)	540 (60)	<0.001	0.907
Nitrate	5 (50)	34 (48)	76 (59)	70 (56)	0.505	78 (47)	282 (63)	431 (63)	657 (73)	<0.001	0.221
Clinical presentation											
Previous myocardial infarction	5 (50)	29 (41)	51 (40)	55 (44)	0.897	62 (37)	163 (37)	295 (43)	399 (44)	0.006	0.518
Higher doctor-defined CCS (III-IV)	2 (22)	20 (30)	56 (47)	68 (63)	<0.001	23 (15)	110 (26)	245 (41)	501 (60)	<0.001	0.739
Previous percutaneous coronary intervention	1 (10)	3 (4)	9 (7)	13 (10)	0.230	15 (9)	27 (6)	45 (7)	117 (13)	<0.001	0.909
Previous CABG	1 (10)	1 (1)	8 (6)	20 (16)	0.003	12 (7)	29 (7)	67 (10)	148 (16)	<0.001	0.125
Angiographic findings											
Zero/mild/moderate diseased vessels	3 (30)	22 (31)	35 (27)	32 (26)	0.943	35 (21)	110 (25)	144 (21)	224 (25)	0.301	0.716
1 diseased vessel	4 (40)	18 (26)	30 (23)	27 (22)		51 (31)	118 (27)	207 (30)	229 (25)		
2 diseased vessels	2 (20)	19 (27)	27 (21)	18 (15)		32 (19)	87 (20)	142 (21)	181 (20)		
3 diseased vessels/LMS	1 (10)	11 (16)	36 (28)	45 (37)		48 (29)	128 (29)	187 (28)	265 (29)		
Impaired left ventricle	1 (13)	6 (10)	30 (28)	29 (31)	0.136	24 (19)	80 (22)	125 (22)	168 (23)		0.366

P value for trend is age-standardised. Values for categorical variables are numbers of patients with percentages of total number with data for that variable (all cells were more than 75% complete for data); continuous variables are as stated. P value for interaction examines whether trends across CCS by ethnic group are different, a high p value implying no significant difference and thus suggesting equivalent trends in both ethnic groups, hence taking into account smaller numbers in the South Asian group. Table does not include patients CCS=0 (n=32 for South Asian patients, 265 for White patients).

7.6.2 Mortality and relationship with angina status

Worse angina at baseline was associated with higher rates of all-cause mortality in both South Asian (log-rank test $p= 0.009$) and White patients (log-rank test $p<0.001$) on survival analysis (Figure 10).

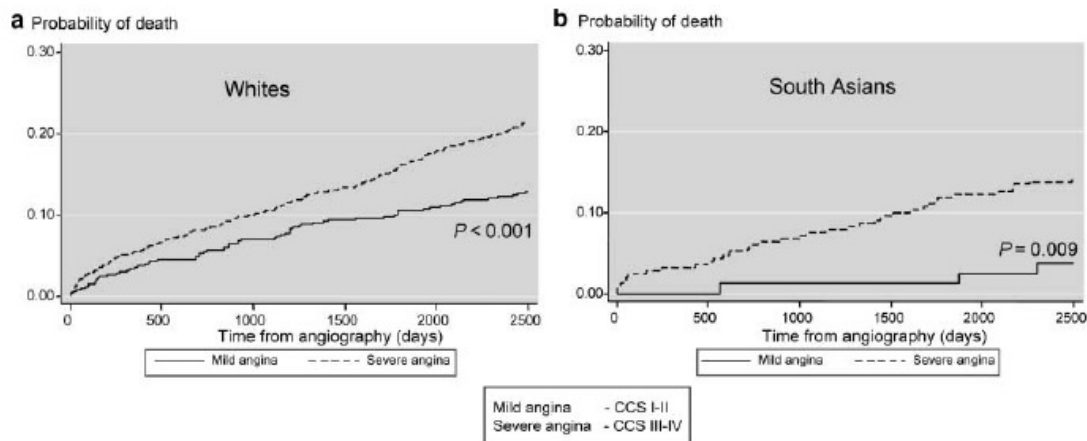


Figure 10 ACRE - Mild compared to severe baseline angina and risk of future all-cause mortality, in White and South Asian patients

7.6.3 Change in angina status between ethnic groups

The mean baseline CCS class was 2.83 (SD 1.18) in South Asian and 2.73 (SD 1.30) in White patients (two sample t test = -1.40, $p= 0.162$). At six-year follow-up, means were 2.13 (SD 1.62) and 1.44 (SD 1.56) respectively (two sample t test = -6.45, $p<0.001$, Figure 11).

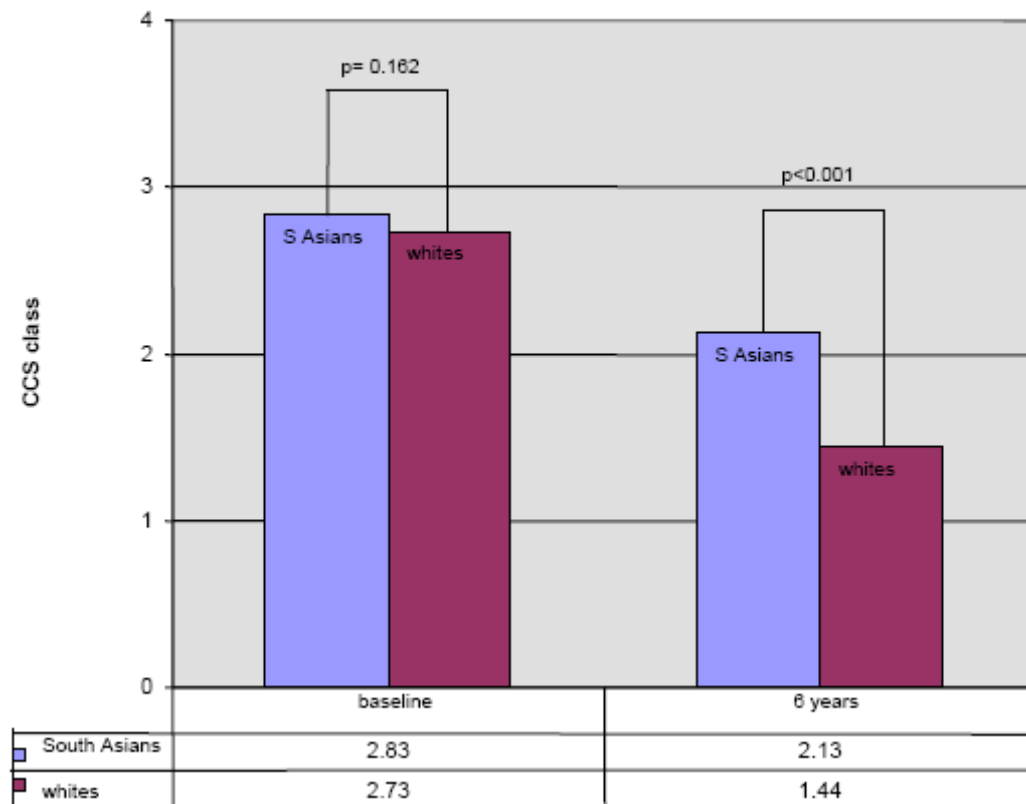


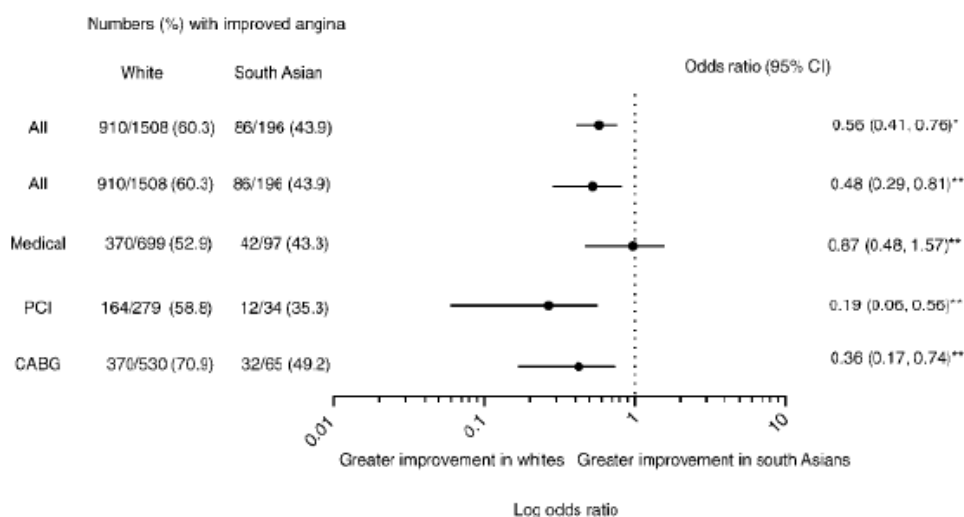
Figure 11 ACRE - Mean Canadian Cardiovascular Score of angina at baseline and 6-year follow-up, in White and South Asian patients

Consistent with this, South Asian patients were more likely to have a diagnosis of angina on the six-year follow-up general practitioner questionnaire than White patients (71/216 (32.9%) vs. 403/1691 (23.8%), age-adjusted OR 1.52, 95% CI 1.11-2.07).

Fewer South Asian patients (43.9% (86/196)) reported an improvement in angina at six years compared to White patients (60.3% (910/1508)), age-adjusted OR 0.56, 95% CI 0.41-0.76). Adjusting for diabetes, hypertension, smoking, number of diseased vessels, left ventricular function and social class did not attenuate this finding (Figure 12).

Figure 12 ACRE - Odds of improvement of angina in South Asians compared with White patients within whole study patient and by management strategy post-angiography

(Medical management strategy –use of oral medication alone (such as anti-anginal medication))



*Age adjusted

**Adjusted for age, diabetes, hypertension, the number of diseased vessels, total cholesterol, left-ventricular function and social class

7.6.4 Angina status and relation to revascularisation

Similar proportions of each ethnic group underwent percutaneous coronary intervention (South Asian 19.9% (100/502), White 19.6% (583/2974)) and CABG (South Asian 30.1% (151/502), White 32.8% (974/2974)) following angiography. Stratifying on management post-angiography, South Asian patients were less likely to report improved angina after PCI (OR 0.19, 95% CI 0.06-0.56) and CABG (OR 0.36, 95% CI 0.17-0.7, Figure 12). However, there was less evidence for ethnic differences in angina improvement if treated medically by medication alone.

7.6.5 Angina status, appropriateness for revascularisation and relation to revascularisation

Confining analyses to those patients judged appropriate for revascularisation, South Asian patients still reported less improvement in angina at six years compared to White patients (fully-adjusted OR 0.42, 95% CI 0.23-0.76).

The ACRE study has previously reported that the overall rate of revascularisation is lower among South Asian than White patients.⁶¹ In this

paper, there was no difference between South Asian and White patients in the proportions that were rated by the panel as appropriate for revascularisation (72% v 68%) but among patients deemed appropriate for angioplasty, South Asian patients were less likely to receive it than White patients.

7.6.6 Risk of myocardial infarction and death

There was no statistically significant difference in the rates of non-fatal myocardial infarction between South Asian and White patients (Table 29). South Asian patients had a statistically significantly lower rate of all-cause and coronary death. However, when adjusting for age, these differences were rendered non-significant.

	Ethnic group	Number of events	Rate/1000 person years (95%CI)	Hazard ratio (95%CI)	P
Myocardial infarction	White	275	13.90 (12.35-15.64)	1	0.447
	South Asian	41	12.25 (9.02-16.64)	0.88 (0.63-1.22)	
<i>adjusted for age</i>	White			1	0.400
	South Asian			0.87 (0.62-1.21)	
All-cause mortality	White	587	31.42 (28.98-34.06)	1	<0.001
	South Asian	64	19.56 (15.30-24.98)	0.62 (0.48-0.81)	
<i>adjusted for age</i>	White			1	0.460
	South Asian			0.91 (0.70-1.18)	
Coronary mortality	White patients	263	17.24 (15.28-19.45)	1	0.031
	South Asians	31	11.34 (7.98-16.13)	0.66 (0.46-0.96)	
<i>adjusted for age</i>	White			1	0.720
	South Asian			0.93 (0.64-1.36)	

Table 29 ACRE - Numbers of outcomes (myocardial infarction and death (all cause/coronary)), rates and hazard ratios (crude/adjusted for age) in South Asian compared with White patients

7.7 Discussion

7.7.1 Objective addressed

This is the first study to report on long-term differences between South Asian and White patients in symptomatic outcomes of coronary disease. My findings reveal that South Asians patients were less likely to experience long-term improvement in angina following coronary revascularisation when compared to White patients, despite similar rates of infarction and death.

In those with angina, revascularisation appears most suited for rapid symptom control rather than in improving prognosis for fatal outcomes. Thus this work used a symptomatic outcome, and found relief of angina to be worse in South Asian compared to White patients. Such symptomatic outcomes add to the overall picture of prognosis of coronary disease in South Asian compared with White populations, as relief of angina determines return to work and perceived health status.⁴⁸ By ignoring 'symptomatic prognosis', an incomplete picture of prognosis is painted, which appears equitable between ethnic groups when examining case fatality alone.

7.7.2 Why does angina improve less in South Asian patients after revascularisation?

I tested whether South Asian patients undergoing revascularisation were less appropriate candidates for the procedure. Using pre-defined and validated definition of appropriateness, I still found a lesser improvement in angina amongst South Asian compared with White patients.

South Asian populations may have smaller coronary arteries compared to White populations,¹⁶⁴ though this may be explained by body size.⁷² Revascularisation of smaller coronary arteries has been associated with less favourable clinical outcomes¹⁶⁵ and I found that the rate of repeat percutaneous coronary interventions in South Asian patients was higher than among White patients (OR 1.70, 95% CI 1.01-2.86). Diabetes may also alter the perception of cardiac pain if associated with neuropathy.¹⁶⁶ However, after adjusting for the higher prevalence of diabetes and lower body mass index in South Asian patients in ACRE compared to White patients, this did not attenuate the observed differences in angina improvement between the ethnic groups. Adjustments were also made for other coronary risk factors, though an association between these risk factors and symptom persistence has not found in previous studies.¹⁴⁷ I also adjusted for the number of diseased coronary vessels, as persistence of angina may be a marker of disease severity such as increased atherosclerotic burden.³⁸

Overall, the reasons for the lesser improvement in angina in South Asian patients compared to White patients could not be fully elucidated by this study.

7.7.3 Limitations

I acknowledge the inherent difficulty in measuring angina in any ethnic group, especially via a questionnaire written in English. However, several lines of evidence suggest that the ethnic differences in symptoms I report are likely to be robust. Firstly, South Asian patients had a higher prevalence of primary care doctor-diagnosed angina at six years; secondly, increasing angina as measured by CCS at baseline was associated with worsening patterns in other baseline clinical measures and higher rates of prospective all-cause mortality; thirdly, there were no important differences in non-response bias between ethnic groups in those responding and not responding to the questionnaire and finally, analyses with angina diagnosis obtained from the Rose questionnaire yielded similar results, with South Asian patients reporting a trend towards less improvement in angina compared with White patients (age-adjusted OR 0.68, 95% CI 0.41-1.11). The importance of symptomatic outcomes should be underlined. Angina patients with similar functional limitation vary considerably in tolerance of their symptoms, which in turn influences the management instigated by their doctor.³³ The presence of chest pain in primary care patients is associated with poorer functional status, especially in role functioning.¹⁶⁷ Patient-defined measures thus need to be developed to take into account the fact that patients and clinicians differ in regard to the distress caused by symptoms.

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The ACRE study could not discriminate the differing peoples within the South Asian term and evidence exists of differences in coronary risk factors between these peoples.²⁰ Though ACRE did have details on individual South Asian nationality, numbers were too small with which to carry out comparative analyses. There is however less evidence on differences in symptoms of angina between these peoples.

Conceivably, if one ethnic group had higher coronary mortality than the other, then angina follow-up data may have been biased by the lack of data from those

who had died, who may have had lesser improvement in angina had they survived. A greater proportion of White patients had died by six years compared to South Asian patients. However, by excluding all those that had died, I found that in those that survived to six years there was still a lesser improvement in angina in South Asian patients than White patients (OR 0.49, 95% CI 0.31-0.78, adjusting for diabetes, hypertension, smoking, number of diseased vessels, left ventricular function and social class). The relative numbers who had died compared to those that survived remained low in both ethnic groups and would thus not have significantly biased the overall finding of less improvement of angina in South Asian patients compared to White patients at follow-up.

As a prospectively recruited clinical cohort, all patients who consecutively attended for angiography over the recruitment phase were included – this eliminates selection bias in following up those selected for angiography, though it cannot taken into account possible selection bias in the selection process for angiography. South Asian people with angina pectoris had lower rates of coronary angiography compared with White people in the Chest Pain Clinic study, a study of incident angina. However, chronic angina is more likely to sway the cardiologist in favour of coronary angiography. The time from initial symptoms to ultimately receiving coronary angiography may be longer in South Asian people, especially in light of their increased number of interactions with healthcare professionals prior to receiving coronary angiography than White people,⁶¹ but when faced with chronic, persistent symptoms they may not under-investigated in the long-term. Unmeasured factors may account for the under-management observed in the Chest Pain Clinic study, such as comorbidity, patient preferences and the efficacy of ensuing medical treatment with anti-anginal drugs alone which may have rendered coronary angiography unnecessary.

7.7.4 Implications

Few studies examine morbidity, symptomatic outcomes following revascularisation and our study revealed no differences in long-term mortality between these two ethnic groups following angiography. Coronary revascularisation for angina, either by PCI or CABG, is performed primarily for relief of symptoms yet in this study did not improve angina among South Asian patients as much as it did for White patients. Hence, studying symptomatic outcomes by ethnicity may be of more importance than case fatality alone in the study of the prognosis of chronic stable angina.

It would have been of interest to ascertain whether in ACRE, typicality of symptoms was prognostically related to better symptomatic outcomes, had the data been available. However, in the Chest Pain Clinic study of the previous chapter, South Asian participants were under-treated by revascularisation compared to White participants irrespective of typicality of symptoms. This was despite descriptors of chest pain being used equally across ethnic group in making a diagnosis of angina and being equally predictive of coronary events. Thus, atypical presentation of chest pain at initial presentation may not have accounted for the longer-term poorer symptomatic outcomes in South Asian patients in ACRE.

7.8 Conclusions

I found that South Asian patients were less likely to have improved angina than White patients six years after undergoing coronary revascularisation, even after having taken into account appropriateness for revascularisation and differences in clinical characteristics. The use of a symptomatic outcome adds to the overall picture of prognosis of coronary disease in South Asian compared with White populations, as whilst prognosis for fatal events is no worse in South Asian patients with chronic stable angina, prognosis for morbidity, symptomatic outcomes may be.

7.9 Building to next chapter

I have shown that, in patients undergoing coronary angiography, South Asian patients had no worse a prognosis for 'hard' outcomes such as myocardial infarction and death compared to white patients, but that symptomatic prognosis was worse in ACRE. This was not accounted for by under-treatment, which still prevailed in this cohort as it did in the Chest Pain Clinic study.

The next stage of this thesis sought to study patients with acute chest pain as an emergency presenting to secondary care. I wanted to continue to examine prognosis at this more serious manifestation of coronary disease, and examine whether mortality differed between ethnic groups. The heterogeneous nature of acute coronary syndromes would be considered as prognosis will depend on the severity of disease at presentation. There are no contemporary studies that have examined prognosis between ethnic groups using the newer definitions of myocardial infarction incorporating troponin level. Furthermore, prevalence of diabetes, socio-environmental factors and management strategy, which differed between White and South Asian participants in the previous two cohorts of this thesis, may further influence prognosis differentially between ethnic groups. Diabetes in South Asians may have increased potency in causing ensuing disease, and since these acutely unwell patients are most likely to derive the greatest benefit from intensive therapy, under-treatment here will significantly affect future risk of death.

Thus I sought to investigate whether ethnic differences existed in prognosis of acute chest pain, and to consider the effect of not only biological differences but also severity of disease at presentation and socio-environmental and clinical management measures.

8 The prognosis of acute coronary syndromes

8.1 Summary of chapter

Background Understanding the prognosis of acute coronary syndromes (ACS) in South Asian compared to White populations necessitates adequate differentiation of ACS type and assessment of degree of disease severity at presentation, and consideration of factors such as diabetes, social environment and clinical management that may confound prognostic analyses by ethnicity.

Methods 3037 South Asian and 68843 White patients admitted with acute coronary syndrome in 2004 in England and Wales were followed up for all-cause death at one year. Prognostic analyses were further stratified by risk factors, clinical management strategies and socio-demographic characteristics.

Results South Asian patients were younger than White patients, and were more likely to be men, less likely to smoke, but were more likely to be hypertensive or diabetic. South Asian patients were not more likely to be under-treated. One-year risk-factor adjusted survival in South Asian patients was marginally better than White patients at one year (HR (95% CI) 0.83 (0.71-0.97)). Stratifying on risk factors, clinical management strategies and socio-environmental characteristics did not appear to confer a worse prognosis in South Asian compared to White patients.

Conclusions Survival following acute coronary syndromes was no worse in South Asian compared to White patients. Diabetes, was not associated with a higher relative risk in South Asian compared to White patients, nor were any other risk factors, clinical management strategies and socio-environmental characteristics.

8.2 Introduction

Studies examining prognosis of myocardial infarction between South Asians and White populations are conflicting. Some report a better prognosis,¹²³ others an equitable prognosis¹²⁶ and others a worse prognosis⁹⁶ in South Asian compared to White populations. To understand the prognosis of acute coronary syndromes in full, its different phenotypes need to be taken into account as they will differ in degree of disease severity and will hence affect any explanation the prognosis of acute coronary disease may have for the higher coronary mortality rate in South Asian compared to White populations.

Prognosis of acute coronary syndromes is also affected by a range of factors that range from biological risk factors through socio-environmental factors to differences in clinical management. Certain risk factors such as diabetes mellitus may be more potent in causing an adverse prognosis in South Asian compared to in White populations.⁹³ Furthermore, some,⁶¹ but not all^{57 62 169} studies, suggest that underuse of effective medical treatments is more common among South Asian people and that underuse may be associated with the deprived areas South Asian people live in.²⁹

8.3 Research objective to be investigated

This chapter sought to investigate specific research objective 4.

To compare fatal prognostic outcomes of acute coronary syndromes in South Asian and White populations and assess factors underlying prognosis.

8.4 Specific research questions

- i. Do South Asian patients suffer an increased case fatality compared to White patients when presenting with acute coronary syndromes?
- ii. Do the new definitions of myocardial infarction using troponin in prognostic analyses affect outcomes differentially by ethnic group?
- iii. What is the impact of differences of risk factors, clinical management and socio-environmental characteristics at baseline in South Asian compared to White patients on ensuing prognosis?

8.5 Methods

The Myocardial Infarction National Audit Project (MINAP) is a registry of all patients with an acute coronary syndrome who have been admitted to all 230 hospitals in England and Wales.¹³⁴ A standardised data collection form is used by all hospitals. MINAP uses a highly secure electronic data entry transmission and analysis system developed by the Central Cardiac Audit Database group to collect and analyse records of patients with all types of acute coronary syndrome.¹⁷⁰ The study monitors mortality among patients by linkage with the Office of National Statistics using the National Health Service number unique to each patient.

MINAP data for all patients with first admission with ACS during the year 2004 in England and Wales was used. Of 91684 patients, there were 68843 who were coded White and 3037 Asian. The definitions of admission variables were as follows:

- Smoking: ex- and current smokers
- Diabetes: known and newly-diagnosed cases
- Hyperlipidaemia: previously treated hypercholesterolaemia
- Medication: whether or not the patient was already taking an aspirin, statin, beta-blocker or ACE inhibitor

Further data were available on

- peak troponin level
- area deprivation (Index of Multiple Deprivation (IMD) 2000 score, see appendix 13.7.1)
- the distance the patient lived from the hospital
- whether admitting hospital had Membership of Association of UK University Hospitals
- receipt of in-patient coronary angiography.

8.6 Statistical analysis

Admission characteristics were examined by ethnic groups in risk factors, clinical management and socio-environmental characteristics. χ^2 tests were conducted to compare proportions, two-sample t tests for continuous variables. Admission characteristics were then examined between ethnic groups using the ACS types.

For prognostic analyses, Cox proportional hazards regression was performed to assess risk of all-cause death at one year. Adjustments for age (as a continuous variable), sex, hypertension, hyperlipidaemia, smoking and diabetes were made. These analyses were repeated for each ACS type. Analyses in the whole cohort were then stratified by admission factors (age above/below 65, sex, presence or absence of individual coronary risk factors, disease severity, clinical management factors and social environment) and formally examined as to whether a statistical difference existed between hazard ratios of each strata with the Bland-Altman two-tailed test of interaction.¹⁵⁴

The choice of cut-off level for a significant level of troponin varies between previously published trials, though as a cut-off level between 0.1 and 0.2 $\mu\text{g/L}$ has been proposed to identify patients at higher risk in most trials,^{77 171-173} 0.1 was used. For deprivation, quartiles were used, and examined highest quartile against lowest quartile. For distance from hospital, analyses were examined around the median of 7.6km.

8.7 Results

8.7.1 Admission characteristics of whole cohort

South Asian patients were younger than White patients, and were more likely to be men (Table 30). They were less likely to smoke, but more likely to be hypertensive or diabetic. South Asian patients were more likely to live in more deprived areas, but lived closer to hospitals and were more likely to use a teaching hospital. South Asian patients did not have higher troponins than White patients. South Asian patients were on more medications on arrival to hospital – the proportion having only one or less of aspirin, statin, beta-blocker or ACE inhibitor was lower than in White patients. They were also more likely to have a

coronary angiogram performed as an in-patient. Regarding the ACS types, similar proportions of South Asian and White patients were observed for STEMI, though there were increased numbers of troponin-negative ACSs in South Asian patients and fewer NSTEMIs.

Ethnic group		South Asian	White	
Risk factors				
				<i>p</i>
Age	Mean, SD	61.56 (13.6)	69.47 (13.2)	<0.001
	Over 65	1118 (37.4%)	41595 (60.3%)	<0.001
Sex	Men	2261 (74.3%)	43746 (63.3%)	<0.001
Smoking	Yes	1152 (47.7%)	39308 (71.7%)	<0.001
Hypertension	Yes	1493 (52.9%)	29051 (45.2%)	<0.001
Hyperlipidaemia	Yes	1098 (41.5%)	17868 (29.2%)	<0.001
Diabetes	Yes	1219 (43.8%)	11417 (18.0%)	<0.001
Disease severity				
Troponin ≥0.1	Yes	1271 (52.3%)	32267 (56.9%)	<0.001
Social environment				
Deprivation score quartile	Most deprived	328 (48.4%)	3341 (24.1%)	<0.001
Distance from hospital	Far (≥7.6km)	97 (14.1%)	7583 (51.2%)	<0.001
Teaching hospital	No	2010 (66.2%)	55890 (81.2%)	<0.001
Clinical management				
Treatment	0-1 drugs (fewer)	617 (20.3%)	17739 (25.8%)	<0.001
In-patient angiogram done	No	1095 (44.6%)	29076 (59.9%)	<0.001
Final diagnosis				
STEMI		870 (33.5%)	18684 (32.2%)	<0.001
NSTEMI/Trop +ve		1318 (50.8%)	34711 (59.8%)	
Trop -ve		408 (15.7%)	4654 (8.0%)	

% - percentages represent the proportion of those with this entry for this field out of total number available for the field
 Drugs - aspirin, statin, beta-blocker or ACE inhibitor

Table 30 MINAP - Admission data in South Asian and White patients, in 2004

8.7.2 Admission characteristics of types of acute coronary syndromes

Admission characteristics were examined by ACS type in South Asian and White patients (Table 31). Within all three types, South Asian compared to White patients were younger, more likely to be men, smoked less, were more likely to be hypertensive and diabetic, were more likely to live in more deprived areas but

closer to hospitals and were not more likely to be under-treated. This was consistent with the admission findings for the whole cohort (Table 30).

Examining across the three types, STEMI had higher troponins than NSTEMIs, in turn higher than troponin-negative ACSs, and there was more in-patient coronary angiography of patients with STEMI and NSTEMI than in those with troponin-negative ACS. STEMI and NSTEMI patients were on more medication on arrival than troponin-negative ACS patients.

ACS Type		STEMI		NSTEMI/Troponin +ve		Troponin -ve	
Ethnic group		South Asian	White	South Asian	White	South Asian	White
N		870	18684	1318	34711	408	4654
Risk factors							
Age	Mean, SD	60.08 (12.7)	66.30 (13.0)	64.26 (12.7)	72.41 (12.9)	60.26 (12.1)	66.72 (12.5)
	Over 65	318 (37.2)	10138 (54.8)	681 (52.3)	25178 (75.3)	163 (41.5)	2658 (57.6)
Sex	Men	668 (77.2)	12983 (69.7)	979 (74.5)	21039 (60.8)	290 (71.6)	2901 (62.7)
Smoking	Yes	365 (50.9)	11805 (75.9)	478 (46.1)	19099 (70.3)	148 (47.7)	2751 (71.5)
Hypertension	Yes	344 (43.3)	6884 (40.0)	685 (55.9)	15581 (47.7)	257 (64.4)	2378 (53.4)
Hyperlipidaemia	Yes	229 (31.0)	4175 (25.6)	460 (40.0)	8788 (28.0)	239 (64.8)	2066 (48.1)
Diabetes	Yes	309 (37.7)	2320 (13.5)	575 (47.3)	6761 (20.9)	168 (48.0)	784 (17.7)
Disease severity							
Troponin ≥0.1	Yes	511 (92.6)	13036 (94.1)	722 (60.4)	18091 (56.7)	1 (0.28)	30 (0.76)
Social environment							
Deprivation score quartile	Most deprived	286 (81.3)	2925 (48.9)	42 (80.8)	416 (46.4)	-	-
Distance from hospital	Far (≥7.6km)	84 (14.0)	6535 (50.9)	11 (12.9)	965 (52.2)	-	-
Teaching hospital	No	604 (69.4)	14792 (79.2)	975 (74.0)	28868 (83.2)	211 (51.7)	3788 (81.4)
Clinical management							
Treatment	0-1 drugs (fewer)	149 (17.1)	3370 (18.0)	227 (17.2)	7848 (22.6)	371 (90.9)	3,815 (82.0)
In-patient angiogram done	No	233 (34.5)	7179 (53.2)	395 (37.0)	13916 (57.0)	221 (58.6)	2031 (60.1)

()-percentages representing the proportion of those with this entry for this field out of total number available for the field

-no data available Drugs - aspirin, statin, beta-blocker or ACE inhibitor

Table 31 MINAP - Admission characteristics in each type of acute coronary syndrome in South Asian compared to White patients

8.7.3 Prognosis in whole cohort

Of 68843 White patients, 12823 had died at one year (rate/1000 person years (95%CI) - 0.64 (0.63-0.65)). Of 3037 South Asian patients, 286 had died at one year (rate/CI 0.33 (0.29-0.37)).

The hazard ratios (and 95% CIs) on cox regression analysis comparing South Asian with White patients were:

Crude	0.53 (0.47-0.59)
Age-adjusted	0.92 (0.82-1.04)
Adjusted for sex, hypertension, hyperlipidaemia, smoking, diabetes	0.83 (0.71-0.97)

Thus, crude survival in South Asian patients was markedly better than White patients at one year, and only marginally better after adjustment for age and of risk factors (HR 0.83 (95% CI 0.71-0.97)). Further adjustment for factors such as troponin level and treatment did not alter this result (HR 0.84 (95% CI 0.71-1.00)). Adjustment for age and deprivation score revealed that survival in South Asian patients was similar to White patients (HR 0.97 (95% CI 0.73-1.28)).

8.7.4 Prognosis by acute coronary syndrome type

Prognosis was examined by ACS type comparing South Asian with White patients (Figure 13). Though there was a trend towards better survival in South Asian patients on crude analyses in all three ACS types as for the whole cohort, on multi-variate adjustment, survival was similar in South Asian compared with White patients for each ACS type.

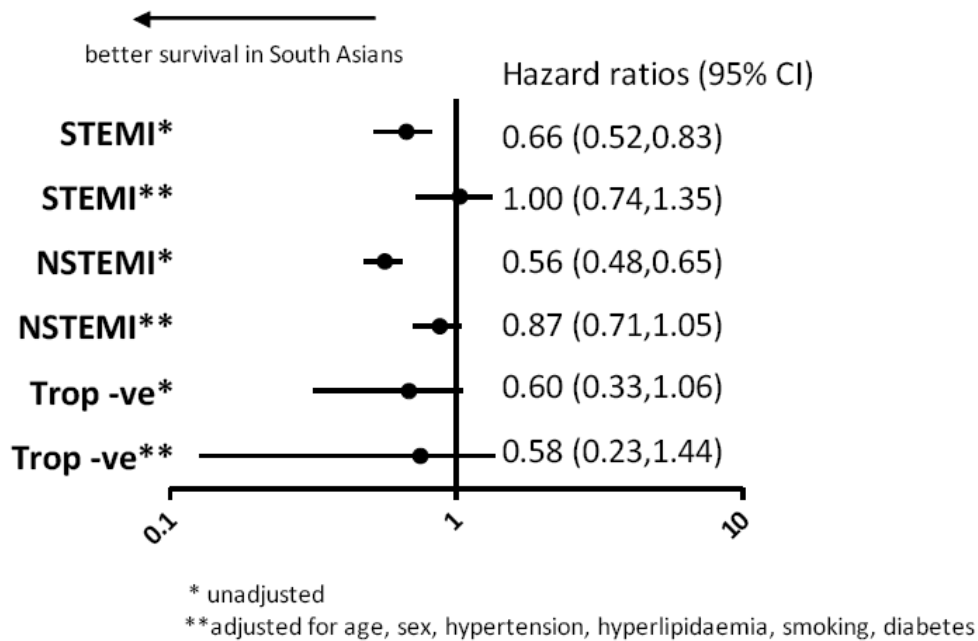


Figure 13 MINAP - Risk in South Asian compared to White patients within each type of acute coronary syndrome of all-cause mortality at one year

South Asian patients were noted to have more troponin-negative ACS admissions than White patients. I thus examined prognosis for STEMI/NSTEMI combined, excluding troponin-negative ACS admissions, and found that survival remained no worse in South Asian patients compared with White patients (HR 0.87 (95% CI 0.74-1.01), adjusted for age, sex, hypertension, hyperlipidaemia, smoking, diabetes).

8.7.5 Prognosis among diabetics

The potency of diabetes for causing coronary disease was examined by investigating the risk of one year death in patients with diabetes compared to patients without diabetes within each ethnic group for the whole cohort.

The hazard ratios on cox regression analysis in patients with diabetes compared to patients without diabetes, in South Asian and in White patients are depicted in Table 32. Diabetes in South Asian patients was associated with a poorer prognosis than in those South Asian patients who were not diabetic (adjusted HR 1.60 (95% CI 1.18-2.17)). A similarly poor prognosis was observed in White patients with diabetes compared to White patients without diabetes (adjusted

HR 1.50(95% CI 1.42-1.57)). Hence, diabetes was as potent in causing future adverse outcomes in South Asian and White patients.

Ethnic group	Diabetes	Number of events/Number	Rate/1000 person years (95%CI)	HR (95%CI)	
				Crude	Adjusted**
South Asian	Yes	155/1213 (12.8%)	0.44 (0.38-0.52)	1.97	1.60
	No	101/1554 (6.5%)	0.22 (0.18-0.27)	(1.53-2.53)*	(1.18-2.17)**
White	Yes	2874/11293 (25%)	0.91 (0.88-0.94)	1.52	1.50
	No	8894/51549(17.3%)	0.58 (0.57-0.60)	(1.45-1.58)*	(1.42-1.57)**

**Adjusted for age, sex, hypertension, hyperlipidaemia, smoking

Drugs - aspirin, statin, beta-blocker or ACE inhibitor

Table 32 MINAP - Risk in patients with diabetes compared to patients without diabetes of all-cause mortality at one year, in South Asian and White patients

8.7.6 Stratifying prognosis by admission characteristics

Table 33 reveals age-adjusted stratified analyses for risk of death at one year comparing South Asian and White patients.

8.7.6.1 Diabetes and other risk factors:

When examining survival within diabetic status, South Asian patients had a better survival compared to White patients irrespective of diabetic status (HR in patients with diabetes 0.75 (95% CI 0.63-0.88)).

Further adjusting the analyses within diabetics for sex, smoking, hypertension and hyperlipidaemia did not change the better survival observed in South Asian compared to White patients (HR 0.77(95% CI 0.63-0.94), table below). When additionally adjusting for receipt of aspirin, statin, beta-blocker or ACE inhibitor, South Asian and White patients had a similar survival. 82% of South Asian patients with diabetes were on two or more of these medications compared to 76% of White patients with diabetes (χ^2 20.41, $p < 0.001$).

		Age-adjusted	*Model 1	**Model 2
Diabetes	Yes	0.75 (0.63-0.88)	0.77(0.63-0.94)	0.81 (0.67-1.00)
	No	0.78 (0.64-0.95)	0.82(0.65-1.04)	0.83 (0.65-1.05)

*Model 1 - adjusted for age, sex, hypertension, hyperlipidaemia, smoking

**Model 2 - adjusted for treatment with aspirin, statin, beta-blocker or ACE inhibitor

Table 33 MINAP - Risk in South Asian compared to White patients, stratified by diabetes, of all-cause mortality at one year

When examining survival within sex, analyses revealed similar prognoses between ethnic groups in men and women. Prognosis was also the same in South Asian compared to White patients with diabetes in those with and without hypertension. South Asian patients that smoked or had high cholesterol also appeared to have a similar prognosis to their White counterparts with these risk factors.

8.7.6.2 Disease severity

Stratified analyses by troponin ≥ 0.1 suggested a better prognosis in South Asian compared to White patients with troponin < 0.1 (HR 0.75 (95% CI 0.60-0.94), $p=0.049$ for two-tailed test for interaction with those with high troponin).

8.7.6.3 Social environment

Stratifying by distance from patient home to hospital and teaching status of hospital revealed similar prognoses between ethnic groups. South Asian patients in less deprived areas had a worse prognosis than White patients in less deprived areas (HR 2.34 (95% CI 1.21-4.56); $p=0.025$ for two-tailed test for interaction with more deprived areas).

8.7.6.4 Clinical management

Stratified analyses by coronary angiography and pharmacological treatment revealed similar prognoses between ethnic groups. There was a worse prognosis in South Asian patients compared to White patients amongst those selected for in-patient angiography (HR 1.32 (95% CI 1.04-1.66)).

		HR (95%CI)	P for interaction
Risk factors			
Age	Over 65	0.66 (0.58-0.75)	0.132
	Under 65	0.83 (0.63-1.08)	
Sex	Men	0.91 (0.78-1.05)	0.865
	Women	0.93 (0.76-1.14)	
Smoking	Yes	0.78 (0.62-0.99)	0.057
	No	1.04 (0.87-1.25)	
Hypertension	Yes	0.95 (0.81-1.11)	0.303
	No	0.83 (0.68-1.02)	
Hyperlipidaemia	Yes	0.98 (0.79-1.20)	0.581
	No	0.91 (0.77-1.06)	
Diabetes	Yes	0.75 (0.63-0.88)	0.766
	No	0.78 (0.64-0.95)	
Disease severity			
Troponin ≥ 0.1	Yes	0.99 (0.84,1.16)	0.049
	No	0.75 (0.60,0.94)	
Social environment			
Deprivation score (quartiles)	Most deprived	0.72 (0.47,1.11)	0.025
	Least deprived	2.34 (1.21,4.56)	
Distance from hospital	Far (≥ 7.6 km)	0.61 (0.23,1.63)	0.243
	Near (< 7.6 km)	1.12 (0.84,1.49)	
Teaching hospital	No	0.88 (0.76,1.01)	0.151
	Yes	1.06 (0.86,1.31)	
Clinical management			
Treatment	0-1 drugs	1.03 (0.86,1.23)	0.215
	2-4 drugs	0.93 (0.80,1.09)	
In-patient angiogram done	No	0.85 (0.72,1.01)	0.003
	Yes	1.32 (1.04,1.66)	

Table 34 MINAP - Risk in South Asian compared to White patients, stratified by risk factors, markers of disease severity, social environment and clinical management, of age-adjusted all-cause mortality at one year

8.8 Discussion

South Asian and White patients differed when presenting with acute coronary syndromes. The former were younger, more likely to be men, more likely to be diabetic and were more likely to live in more deprived areas. However, South Asian patients did not present with higher troponin levels than White patients, lived closer to hospitals, which themselves were more likely to be teaching hospitals and were not more likely to be under-treated. Survival in South Asian patients was no worse than in White patients after adjustment of confounding factors and if anything may be marginally better. The increased coronary mortality of the South Asian population from census data is thus not due to a

worse case fatality in them compared to the White population following presentation with acute coronary syndromes.

8.8.1 Admission characteristics and prognosis by acute coronary syndrome type

Within all three ACS types (STEMI, NSTEMI, troponin-negative), South Asian patients compared to White patients had similar baseline characteristics (such as being younger and more likely to be diabetic), consistent with the admission findings for the whole ACS cohort. Both South Asian and White STEMI and NSTEMI patients were on more medication on arrival than troponin-negative ACS, suggesting that they were already perceived to be at-risk patients. South Asian patients with troponin-negative ACSs were on less medication on arrival than white patients with troponin-negative ACS, and this may reflect they were appropriately perceived to be low-risk patients (perhaps with atypical symptoms). Survival was similar in South Asian patients compared with White patients for each ACS type.

There were increased numbers of troponin-negative ACSs in South Asian patients and fewer NSTEMIs. However, even when excluding those with troponin-negative ACS admissions (who may not have genuine coronary disease), the prognosis in South Asian patients compared to White patients was no worse.

8.8.2 Diabetes

The prevalence of diabetes was markedly higher in South Asian compared to White patients and diabetes in South Asian and White patients was associated with a worse survival than those who did not have diabetes.

Though these findings are what would be expected, the findings of the exploratory stratified analyses differ from some of the literature in South Asian patients with diabetes. Firstly, South Asian patients with diabetes in MINAP had a better survival than White patients with diabetes. The better survival in South Asian patients with diabetes compared with White patients with diabetes contrasts with the higher incidence of coronary complications of diabetes amongst the South Asian population compared to White populations as presented in this thesis's systematic review of incident coronary disease (Section

3.6.1.2.2, the UK Prospective Diabetes Study 32¹²⁴ and Southall Diabetes Survey¹²⁵ studies), Hence, diabetes in the South Asian population may indeed lead to a higher incidence of coronary events but prognosis from those coronary events once they have become a patient is no worse than in White patients with diabetes presenting with coronary disease.

Secondly, MINAP did not find worse medical care in South Asian patients than in White patients, as cross-tabulation analyses of diabetes status and medication revealed better treatment in South Asian patients with diabetes. This better treatment may account for the better survival observed in South Asian patients with diabetes compared to White patients with diabetes following presentation with an acute coronary syndrome. Adjusting for medication usage rendered survival similar in South Asian patients compared to White patients in stratified analyses of diabetes status. Previous studies in primary care have shown that the proportion of South Asian patients with good diabetes control is lower than the general population as is the proportion receiving insulin.¹⁷⁴ This may partly explain the higher incidence of coronary disease in South Asian patients with diabetes, but the results in MINAP infer that if providing good care in secondary prevention results in improved survival, the incidence of coronary complications in South Asian patients with diabetes could in a similar way be reduced by good quality care in primary care. A review of the literature on ethnic differences in the prevalence of complications and mortality among patients with diabetes suggested that any differences could be due to differences in quality of diabetes care.¹⁷⁵

8.8.3 Other risk factors

South Asians patients were younger than White patients, and adjusting for age for the whole cohort rendered the markedly better crude survival in South Asian patients closer to unity. Stratifying on age did not reveal a better prognosis in South Asian patients compared to White patients in either age group. However, it is likely that the younger age of presentation explains a large part of why survival in South Asian patients compared to White patients was no worse in the whole cohort.

8.8.4 Disease severity

Baseline differences in the severity of disease may also be a factor in differing prognoses, and within those with a lower troponin, South Asian patients had a better prognosis compared to White patients. However, as noted above, the prognosis in South Asian compared to White patients for those with either STEMI or NSTEMI was no worse in South Asian patients compared with White patients. Adjustment of prognostic analyses within the whole cohort for troponin level did not change this, and suggests that the marginal survival advantage in South Asian patients in the whole cohort is not explained by lesser disease severity at presentation.

8.8.5 Social environment

Analyses stratified by deprivation suggested that South Asian patients had a worse prognosis than White patients in less deprived areas. Though survival in South Asian patients was marginally better than White patients at one year in the whole cohort, after adjusting for age and deprivation score, 95% confidence intervals were equally spaced around unity (0.73-1.28). I investigate and discuss this further in the next chapter, as much of this finding may be explained by residual confounding.

8.8.6 Clinical management

With regard to clinical management, South Asian patients had a worse prognosis compared to White patients with in-patient angiography (HR 1.32 (95% CI 1.04-1.66)). This result does not however take into account factors that may have driven clinicians to performing angiography as a result of adverse clinical features on presentation (sicker patients needing more urgent invasive investigation) and these data do not consider whether or not revascularisation was undertaken after angiography. It would be the actual process of revascularisation rather than the process of angiography itself that would have determined prognosis.

8.8.7 Limitations

The large numbers within MINAP provided considerable statistical power but this is potentially attenuated by the quality of those numbers. Analyses of MINAP in chapter 4 stood up to scrutiny in terms of data quality in spite of

missing data. The marginally better survival in South Asian patients in the whole cohort was a surprise, though a more conservative conclusion that the South Asian patient certainly does not have a worse prognosis than the White patient should be made in light of the incompleteness of data.

Some factors which are likely to play a role in determining prognosis (such as degree of angiographic coronary disease) were unavailable in MINAP and hence this limited the scope of the stratified prognostic analyses. Other variables not available include readmission to hospital and also clinical management as an out-patient following discharge. Angiography and revascularisation may have been performed at a later date as an out-patient. Such limitations could in the future be addressed by linkage of MINAP to NHS data sources such as Hospital Episode Statistics. Such linkages will themselves depend on the availability and quality of identifiers of variables such as ethnicity.

Length of follow-up was only one year within MINAP, and thus makes conclusions on long-term prognosis impossible. However, with time, longer-term follow-up in MINAP could be sought.

8.8.8 Implications

It may be that the younger age of South Asian patients with acute coronary syndromes explains the similar prognosis, and certainly from adjusting for age, the markedly better prognosis seen on crude prognostic analyses disappeared. Though these results are encouraging and perhaps demonstrates a wide uptake of appropriate, evidence-based treatment across demographic groups in a disease well-served by evidenced-based therapy, the results should not prevent further analyses of prognostic outcomes by ethnic groups following presentation with acute coronary syndrome.

Firstly, prognosis for non-fatal symptomatic outcomes may not be equitable by ethnicity - this thesis has already observed this for symptomatic outcomes from revascularisation for chronic angina. Secondly, the younger average age of South Asian patients, which may reflect the age distribution of the local population, combined with equitable survival to that of older White patients, will markedly

increase the number of cases of coronary heart disease among the South Asian population. Finally, the future burden of heart failure will thus increase disproportionately in the South Asian population if survival continues to improve. These results thus have clear implications for the allocation of healthcare resources in this population of acute coronary syndrome patients.

8.9 Conclusions

Survival following acute coronary syndromes was no worse in South Asian patients than White patients. Diabetes, although more common in South Asian patients, was not associated with a higher relative risk of death in South Asian patients compared to White patients, nor were any other risk factors, clinical management strategies and socio-environmental characteristics.

9 The contribution of incidence and prognosis to overall coronary death rates in South Asian and White populations

9.1 Summary of chapter

Background The systematic review of this thesis reported that South Asian populations have a higher incidence of fatal coronary disease but could not answer whether prognosis is worse in South Asian compared to White populations. The results of this thesis thus far have shown a higher incidence of fatal and non-fatal coronary disease in South Asian compared to White populations but that prognosis for serious clinical events is no worse in South Asian populations.

Methods The four new prospective studies of this thesis, one aetiologic (South Asian N=580 initially healthy), and three prognostic (N=2189 with suspected stable angina, N= 502 undergoing coronary angiography and N=3037 with acute coronary syndromes) were examined for mortality outcomes. Previous studies on incidence and prognosis included on my systematic review were meta-analysed with these four studies using a random effects model respectively.

Results In analysing seven studies, South Asian populations showed an overall higher risk of incident coronary events than White populations (fatal and non-fatal HR 1.47 (1.29–1.66)). Ten prognostic studies examining risk of death from coronary disease showed overall survival was better in South Asian than White populations (HR 0.80 (0.71-0.88)). This effect was not explained by risk factors, disease severity at presentation, clinical management nor social environment.

Conclusions Incidence of non-fatal and fatal coronary disease is higher in South Asian than White populations, but prognosis for risk of death is better once coronary disease is manifest. The dissociation between the aetiologic and prognostic findings suggests that public health initiatives to reduce disparities in mortality should focus on primary prevention.

9.2 Introduction

There is a higher cross-sectional coronary mortality in South Asian compared to White populations in the UK. Understanding the contribution of incidence and prognosis to this may allow interventions to prevent disease onset or its progression to be better targeted. From the systematic literature review, most studies reported that South Asian populations have a higher incidence of fatal coronary disease compared to White populations, though data on non-fatal events were few. When considering prognosis, of the studies retrieved, the results could not answer whether prognosis was worse in South Asian compared to White populations.

In its investigation into the higher cross-sectional coronary mortality in South Asian compared to White populations in the UK, this thesis has so far contributed in the following ways:

- There is a higher incidence of prognostically-significant angina in South Asian compared to White populations. South Asian populations also have a higher incidence of non-fatal myocardial infarction or coronary death than White populations (Chapter 5).
- Prognosis in terms of fatal events is no higher in South Asian compared to White populations either with angina (Chapters 6, 7) or after acute coronary syndromes (Chapter 8).

I now sought to examine my studies in the context of these previous studies. A higher case fatality (i.e. worse prognosis) in South Asian people might have been expected for two main reasons. First, South Asian populations have a higher prevalence of insulin resistance and diabetes mellitus than White European populations,¹⁷⁶ and the presence of diabetes among people with coronary disease is associated with higher survival.¹⁷⁷ Certain risk factors such as diabetes mellitus may result in poorer outcomes in South Asians with diabetes than in White people with diabetes.⁹³ Second, some,⁶¹ but not all^{57 62 169} studies, suggest

that underuse of medical treatments, more common among South Asian populations, is associated with the deprived areas they live in.²⁹

9.3 Research objective to be investigated

This chapter sought to investigate specific research objective 5.

To assess the contribution of incidence and prognosis to the higher coronary death rates in South Asian compared to White populations through meta-analysis of the four cohorts and previously reported studies.

9.4 Specific research questions

- i. What are the relative effects of South Asian ethnicity compared to White ethnicity in healthy populations (aetiologic effects) and in populations with already-manifest coronary disease (prognostic effects) from meta-analysing the four cohort studies of this thesis with those previously reported in the literature ?
- ii. What is the influence of biological risk factors, clinical management and socio-environmental characteristics on prognosis within the prognostic studies of this thesis?

9.5 Methods

For the meta-analysis, studies obtained by systematic review that examined incidence of fatal outcomes in South Asian compared to White populations were combined with the fatal outcomes found in Whitehall-II (aetiologic, healthy population cohort). This was repeated for studies examining non-fatal combined with fatal outcomes. For prognosis, studies obtained by systematic review that examined fatal outcomes in South Asian compared to White populations were combined with the fatal outcomes found in the Chest Pain Clinic Study, ACRE (coronary angiogram cohort) and MINAP (acute coronary syndrome cohort).

Stratified analyses on prognosis by biological risk factors, clinical management and socio-environmental characteristics were then conducted within the studies of this thesis. The style already utilised in the previous chapter was used, and extended across all three prognostic cohorts. As an example, to examine whether the severity of coronary disease at presentation influenced prognosis by ethnic

group, measures appropriate to the stage of disease at which the cohort recruited were used. Exercise electrocardiography and typicality of angina were used in the chest pain clinic cohort, severity of angina (by Canadian Cardiovascular Society score), angiographic disease and left ventricular function were used in the coronary angiogram cohort and troponin level was used in the acute coronary syndrome cohort.

All three studies had data on biological risk factors and medication. The three prognostic studies also included data on deprivation, though by different measures. The chest pain cohort used the Townsend score, the coronary angiogram (ACRE) cohort Carstairs, and the acute coronary syndrome (MINAP) cohort had data on Index of Multiple Deprivation 2000 (IMD) score (appendix 13.7). The acute coronary syndrome cohort also had data on the distance the patient lived from the hospital and receipt of in-patient coronary angiography.

9.6 Statistical analysis

In calculating incidence, a combined non-fatal outcome (non-fatal myocardial infarction and admission with angina) in Whitehall-II was used, as well as risk of coronary death. For prognostic analyses within Whitehall-II, risk of coronary death in those with typical angina at baseline was assessed. Risk of coronary death in the Chest Pain Clinic Study and ACRE were assessed and all-cause death in MINAP was assessed as cause-specific death was unavailable. Cox proportional hazards regression were performed, adjusted for age (as a continuous variable), sex, hypertension, blood cholesterol, smoking and diabetes in all cohorts. These analyses were then stratified in the prognostic studies by baseline factors (age above/below 65, sex, presence or absence of individual coronary risk factors, disease severity, clinical management factors and social environment) and formally examined as to whether a statistical difference existed between hazard ratios of each strata with the Bland-Altman two-tailed test of interaction.

Using the systematic review, relative risks, adjusted where available, were extracted from each study. In studies in which summary relative risk estimates were not given, crude data in the paper were examined to estimate unadjusted

odds ratios and confidence intervals. The authors of studies were approached to confirm relevant numerical data where necessary (Thanks to Sarah Wild and Colin Fischbacher).

Results of individual studies found on systematic review were combined with the studies of this thesis using the metan command¹⁷⁸ in Stata10 and calculated pooled odds ratios, weights, and 95% confidence intervals using a random effects model. Heterogeneity was examined using the I² statistic.¹⁵⁴

9.7 Results

9.7.1 *The studies of this thesis*

All hazard ratios are adjusted for age, sex, hypertension, blood cholesterol, ex/current smoker, diabetes.

- Whitehall-II:
 - Incidence for coronary death was higher in South Asian compared to White participants (adjusted HR 3.83 (95% CI 2.32-6.30)).
 - Incidence for non-fatal events (non-fatal myocardial infarction, angina) was higher in South Asian compared to White participants (adjusted HR 1.64 (95% CI 1.33–2.02)).
 - Prognosis for coronary death in those with typical angina at baseline was similar in South Asian compared to White participants (adjusted 2.07 (95% CI 0.61-6.97)).
- Chest Pain Clinic study
 - Prognosis for coronary death was similar in South Asian compared to White participants (adjusted HR 0.82 (95% CI 0.29-2.33)).
- ACRE
 - Prognosis for coronary death was similar in South Asian compared to White participants (adjusted HR 0.80 (95% CI 0.47-1.36)).
- MINAP
 - Prognosis for all-cause death was marginally better in South Asian compared to White participants (adjusted HR 0.83 (95% CI 0.71-0.97)).

9.7.2 *Meta-analysis of incidence studies*

9.7.2.1 Fatal events

The upper panel of figure 14 below focuses on coronary death rates amongst South Asian compared to that of White majority populations. Balarajan's data based on the 1981 census reveals a higher mortality in South Asian men and women compared to the whole population of England and Wales,⁸ as does Wild's study based on 1991 census.¹⁰ Whitehall-II and Forouhi et al¹²² represent the only prospective studies of healthy individuals for risk of coronary death in healthy individuals comparing South Asian and White populations, both showing a higher incident mortality in South Asian compared to White populations.

On meta-analysis, these studies reveal higher incident coronary mortality in South Asian compared to White populations (HR 1.43 (95% CI 1.39–1.46)).

9.7.2.2 Fatal and non-fatal events

The lower panel of figure 14 below focuses on non-fatal incidence coronary rates amongst South Asians compared to that of White majority populations. Both Fischbacher et al's¹²³ study and the UK Prospective Diabetes Study 32¹²⁴ examine incidence of non-fatal myocardial infarction combined with fatal myocardial infarction. Whitehall-II and Mather et al¹²⁵ are able to study non-fatal events alone.

Irrespective of whether or not non-fatal events are combined with fatal ones, all studies bar UKPDS32 reveal a higher incidence of coronary events in South Asian compared to White populations, confirmed on meta-analysis (HR 1.47 (95% CI 1.29–1.66)).

9.7.3 *Meta-analysis of prognostic studies*

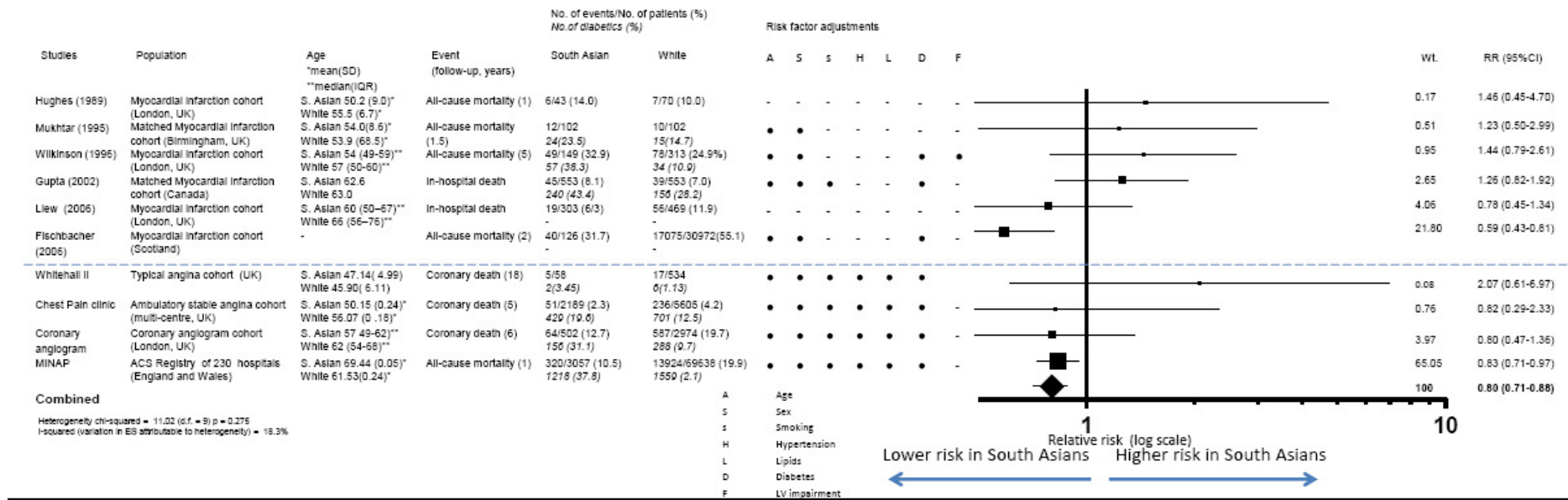
9.7.3.1 Previously published studies

The upper panel of figure 15 below focuses on the previously published studies retrieved on systematic literature review. On observation of the confidence intervals around the point estimates, prognosis for death seemed to not be worse in South Asian compared with White populations.

9.7.3.2 Studies from this thesis

The point estimates from the prognostic studies of this thesis (Chest Pain Clinic, ACRE and MINAP) suggested a trend towards a better prognosis in South Asian compared with White populations, especially with the more recent and larger studies. Prognosis in those with typical angina in Whitehall-II, a cohort not presenting to healthcare services, was similar in South Asian compared to White populations.

On meta-analysis of previously published studies with studies from this thesis, a better prognosis for death following presentation with coronary disease was observed for South Asian compared to White populations (HR 0.80 (0.71-0.88)).



The upper panel shows previously published studies; the bottom panel analyses from new studies from this thesis

Figure 15 Meta-analysis of prognostic studies of coronary disease in South Asian compared to White populations

9.7.4 *Ethnic comparisons of prognosis within strata of prognostic factors*

Whether South Asian participants of this thesis' studies had a worse prognosis than White participants in any of strata of prognostic factors is assessed in Table 35.

Table 35 Risk in South Asian compared to White participants, stratified by risk factors, markers of disease severity, social environment and clinical management, of age-adjusted all-cause mortality at one year in three prognostic cohorts

Study		Chest Pain Clinic				Coronary angiogram (ACRE)				Acute coronary syndrome (MINAP)			
		South Asian	White	p	HR (95%CI)	South Asian	White	p	HR (95%CI)	South Asian	White	p	HR (95%CI)
Page 1/2													
Whole study	Unadjusted	2189	5605		0.63 (0.39-1.02)	502	2974		0.66 (0.46-0.96)	3057	69638		0.53 (0.47-0.59)
	Age-adjusted				1.08 (0.66-1.76)				0.93 (0.64-1.36)				0.92 (0.82-1.04)
	*Adjusted				0.82 (0.29-2.33)				0.80 (0.47-1.36)				0.83 (0.71-0.97)
Risk factors													
Age	Over 65	270(12.3)	1602 (28.6)	<0.001	0.74 (0.33-1.64)	89 (17.7)	1159 (39.0)	<0.001	1.22 (0.69-2.15)	1118 (37.4)	41595 (60.3)	<0.001	0.66 (0.58-0.75)
	Under 65				0.99 (0.53-1.84)				1.08 (0.65-1.78)				0.83 (0.63-1.08)
Sex	Men	1209 (55.2)	2929 (52.3)	0.018	1.09 (0.61-1.92)	391 (77.9)	2112 (71.0)	0.002	0.78 (0.51-1.19)	2261 (74.3)	43746 (63.3)	<0.001	0.91 (0.78-1.05)
	Women				0.93 (0.45-1.91)				1.95 (0.80-4.74)				0.93 (0.76-1.14)
Smoking	Yes	355 (16.2%)	1607 (28.7)	<0.001	1.66 (0.71-3.92)	178 (47.2)	1937 (73.5%)	<0.001	0.88 (0.51-1.56)	1152 (47.7)	39,308 (71.7)	<0.001	0.78 (0.62-0.99)
	No				1.05 (0.57-1.91)				1.37 (0.69-2.73)				1.04 (0.87-1.25)
Hypertension	Yes	732 (33.4)	1892 (33.8)	0.791	1.16 (0.59-2.29)	191 (38.1)	889 (29.9)	<0.001	1.04 (0.58-1.87)	1493 (52.9)	29051 (45.2)	<0.001	0.95 (0.81-1.11)
	No				0.93 (0.45-1.91)				0.85 (0.51-1.40)				0.83 (0.68-1.02)
Hyperlipidaemia	Yes	366 (62.8)	1256 (64.5)	0.436	1.22 (0.39-3.79)	165 (44.4)	1012 (45.5)	0.691	0.64 (0.28-1.47)	1098 (41.5)	17868 (29.2)	<0.001	0.98 (0.79-1.20)
	No				0.70 (0.80-6.39)				1.69 (1.01-2.84)				0.91 (0.77-1.06)
Diabetic	Yes	428 (19.5)	372 (6.6)	<0.001	0.84 (0.34-2.06)	156 (31.1)	288 (9.7)	<0.001	0.90 (0.51-1.58)	1219 (43.8)	11417 (18.0)	<0.001	0.75 (0.63-0.88)
	No				0.95 (0.52-1.75)				0.64 (0.36-1.13)				0.78 (0.64-0.95)
Disease severity													
Angina symptoms	^ More	356 (16.3)	1481 (26.4)	<0.001	0.96 (0.44-2.07)	201 (54.3)	1076 (50.9)	0.217	1.65 (1.00-2.74)	-	-	-	-
	^^Less				1.26 (0.66-2.41)				1.07 (0.55-2.09)	-	-	-	-
Exercise ECG	Positive	182 (15.6)	668 (19.3)	0.017	1.33 (0.55-3.19)	-	-	-	-	-	-	-	-
	Negative				0.64 (0.18-2.31)	-	-	-	-	-	-	-	-
Coronary disease	>= 2 arteries	-	-	-	-	235 (47.2)	1339 (45.4)	0.452	0.97 (0.63-1.49)	-	-	-	-
	Normal-1 artery	-	-	-	-				0.61 (0.26-1.42)	-	-	-	-
Impaired left ventricular function	Yes	-	-	-	-	98 (23.6)	563 (23.3)	0.897	0.77 (0.43-1.38)	-	-	-	-
	No	-	-	-	-				0.88 (0.45-1.71)	-	-	-	-

Troponin >=0.1	Yes	-	-	-	-	-	-	-	-	1271 (52.3)	32267 (56.9)		0.99 (0.84-1.16)
	No	-	-	-	-	-	-	-	-				0.75 (0.60-0.94)
Social environment													
Deprivation score (lowest quartile vs highest)	Most deprived	242(49.9)	520 (18.6)	<0.001	0.93 (0.54-1.60)	650 (37.1)	787 (15.7)	<0.001	0.78 (0.31-1.95)	328 (48.4)	3341(24.1)	<0.001	0.72 (0.47-1.11)
	Least deprived				0.35 (0.05-2.53)				-(no events)				2.34 (1.21-4.56)
Distance from hospital	Far (≥7.6km)	-	-	-	-	-	-	-	-	95 (13.9)	7500 (51.1)	<0.001	0.61 (0.23-1.63)
	Near(<7.6km)	-	-	-	-	-	-	-	-				1.12 (0.84-1.49)
Clinical management													
Secondary prevention drugs	0-1 drugs (fewer)	1,785(81.5)	4,278(76.3)	<0.001	1.23 (0.48-3.18)	221 (44.0)	1288 (43.1)	0.765	0.86 (0.43-1.72)	617 (20.3)	17739(25.8)	<0.001	1.03 (0.86-1.23)
	2-4 drugs				0.97 (0.44-2.15)				1.04 (0.64-1.70)				0.93 (0.80-1.09)
Teaching Hospital	No	-	-	-	-	-	-	-	-	2010(66.2)	55890(81.2)		0.88 (0.76-1.01)
	Yes	-	-	-	-	-	-	-	-			<0.001	1.06 (0.86-1.31)
In-patient angiogram done	No	-	-	-	-	-	-	-	-	1095 (44.6)	29076 (59.9)		0.85 (0.72-1.01)
	Yes	-	-	-	-	-	-	-	-			<0.001	1.32 (1.04-1.66)
Revascularisation done	No	-	-	-	-	355 (70.7)	19 64 (66.1)	0.040	0.99 (0.65-1.51)	-	-	-	-
	Yes	-	-	-	-				0.79 (0.34-1.84)	-	-	-	-
Page 2/2		South Asian	White	p	HR (95%CI)	South Asian	White	p	HR (95%CI)	South Asian	White	p	HR (95%CI)
Study		Chest Pain Clinic				Coronary angiogram (ACRE)				Acute coronary syndrome (MINAP)			

* adjusted for age, sex, hypertension, blood cholesterol, ex/current smoker, diabetes; Stratified HRs are age-adjusted

Figures are numbers (%). Percentages represent the proportion of those with this entry for this field out of total number available for the field

HR (95%CI) – Cox proportional hazards regression ratio (95% confidence interval). comparing South Asian and White participants for coronary death (all-cause in acute coronary syndrome cohort). A hazard ratio less than 1 represents a better prognosis in South Asians.

^ - typical symptoms in chest pain clinic, CCS 3-4 in coronary angiogram ^^ - atypical symptoms in chest pain clinic, CCS 1-2 in coronary angiogram.

Secondary prevention drugs - aspirin, statins, beta-blockers and ACE inhibitor

9.7.4.1 Diabetes

Diabetes was significantly more prevalent in South Asian compared to White participants in all three of our prognostic studies. When stratifying survival by diabetic status in each of our studies, survival was not worse in South Asian participants with diabetes compared to White participants with diabetes, and South Asian participants in the acute coronary syndrome cohort had a better survival compared to White participants irrespective of diabetic status.

Further adjusting the stratified analyses in diabetics for sex, smoking, hypertension and hyperlipidaemia, South Asian participants still demonstrated no worse a prognosis compared to White participants in the chest pain clinic and coronary angiogram cohorts, whilst South Asian participants with diabetes had a better survival in the acute coronary syndrome than White participants with diabetes (Table 36). When additionally adjusting for receipt of aspirin, statin, beta-blocker or ACE inhibitor, South Asian and White participants still had a similar survival in all cohorts irrespective of diabetic status.

			Age-adjusted	*Model 1	**Model 2
Chest Pain Clinic	Diabetic	Yes	0.84 (0.34-2.06)	0.87 (0.35-2.17)	0.88 (0.35-2.22)
		No	0.95 (0.52-1.75)	0.88 (0.48-1.61)	0.90 (0.49-1.64)
ACRE	Diabetic	Yes	0.90 (0.51-1.58)	0.75 (0.34-1.68)	0.80 (0.35-1.85)
		No	0.64 (0.36-1.13)	0.77 (0.37-1.59)	0.74 (0.36-1.53)
MINAP	Diabetic	Yes	0.75 (0.63-0.88)	0.77 (0.63-0.94)	0.81 (0.67-1.00)
		No	0.78 (0.64-0.95)	0.82 (0.65-1.04)	0.83 (0.65-1.05)

*Model 1 - adjusted for age, sex, hypertension, hyperlipidaemia, smoking

**Model 2 - adjusted for treatment with aspirin, statin, beta-blocker or ACE inhibitor

Table 36 Risk in South Asian compared to White participants, stratified by diabetes, of all-cause mortality at one year in the three prognostic cohorts

9.7.4.2 Other risk factors

South Asian participants were more likely to be men, yet sex did not confer different prognoses between the ethnic groups. South Asian participants were more likely to have been diagnosed hypertensive in the coronary angiogram and

acute coronary syndrome cohorts but prognosis was the same in South Asian compared to White participants in those with and without hypertension. South Asian participants that smoked or had high cholesterol appeared to have a similar prognosis to their White counterparts with these risk factors.

9.7.4.3 Disease severity

South Asian participants did not present with more severe disease than White participants as evidenced by fewer positive exercise electrocardiograms in the chest pain clinic cohort, an equivalent degree of coronary disease at angiography in ACRE and a lower prevalence of a troponin above 0.1 in MINAP. Similar analyses by severity of disease and receipt of treatment revealed similar prognoses between ethnic groups.

9.7.4.4 Social environment

South Asian participants were more likely to live in deprived areas in all three prospective studies, but were closer to the hospital and more likely to use a teaching hospital in the acute coronary syndrome cohort. The previous chapter has already shown that South Asian participants in less deprived areas had a worse prognosis compared to White participants in those areas for the acute coronary syndrome cohort ($p=0.025$ for two-tailed test for interaction with those in the more deprived areas). This was not observed in the chest pain clinic cohort (Bland-Altman two-tailed test of interaction¹⁵⁴ test $p=0.544$). Data on deprivation with respect to outcome in the coronary angiogram cohort were too scarce, preventing similar prognostic analyses.

Although caution is required in interpreting such subgroup analyses, I carried out further exploratory analyses. I compared the baseline features of those in the most deprived quintile of MINAP with the least deprived quintile in each ethnic group (Table 37). In more deprived areas, patients were younger, smoking and diabetes were more prevalent and patients were closer to hospitals. These were more likely to be teaching hospitals, and patients in more deprived areas were more likely to get more secondary prevention drugs. There were no consistent differences in hypertension and high cholesterol between less and more deprived areas. These patterns were apparent in both ethnic groups, and

consistent with previously reported patterns in deprived areas.¹⁷⁹ Examining the overall mortality of the cohort, those in more deprived areas had a worse prognosis than those in less deprived areas (age-adjusted HR 1.35, 95% CI 1.12-1.52). Hence, the measure of deprivation appeared valid.

Ethnic group		South Asian		p	White		p
		Most deprived	Least deprived		Most deprived	Least deprived	
Risk factors							
Age	Over 65	133 (40.55)	195 (59.5)	0.061	1,655 (50.0)	2,043 (57.7)	<0.001
Sex	Men	254 (78.2)	65 (85.5)	0.151	2,222 (68.9)	2,533 (71.7)	<0.001
Smoking	Yes	146 (53.3)	23 (37.7)	0.028	2,374 (82.32)	2,003 (69.4)	<0.001
Hypertension	Yes	121 (41.6)	24 (34.3)	0.264	1,192 (38.9)	1,318 (39.9)	0.408
Hyperlipidaemia	Yes	75 (27.2)	19 (29.7)	0.685	752 (25.6)	770 (75.3)	0.744
Diabetic	Yes	121 (39.7)	21 (28.8)	0.084	431 (14.0)	375 (11.5)	0.002
Social environment							
Distance from hospital	Far (≥ 7.6 km)	21 (6.4)	26 (34.2)	<0.001	949 (28.4)	2,312 (65.3)	<0.001
Clinical management							
Secondary prevention drugs	0-1 drugs (fewer)	41 (12.5)	21 (27.6)	0.001	524 (15.7)	648 (18.3)	0.004
Teaching Hospital	No	222 (67.7)	57 (75.0)	0.214	2,600 (77.8)	2,883 (81.4)	<0.001
In-patient angiogram done	No	102 (38.2)	22 (36.7)	0.825	1,370 (56.4)	1,314 (51.1)	<0.001

Table 37 MINAP - Admission characteristics comparing those in the most deprived quintile with the least deprived quintile, in South Asian and White participants

		Age-adjusted	*Model 1	**Model 2	***Model 3
Deprivation score quartile	Most deprived	0.72 (0.47-1.11)	0.85 (0.52-1.39)	0.89 (0.54-1.46)	0.96 (0.56-1.66)
	Least deprived	2.34 (1.21-4.56)	1.72 (0.76-3.93)	1.64 (0.72-3.74)	2.18 (0.86-5.51)

HRs (95% CI) comparing South Asian vs White participants

*Model 1 - adjusted for age, smoking, diabetes, hypertension, hyperlipidaemia

**Model 2 - adjusted for age, smoking, diabetes, hypertension, hyperlipidaemia, secondary prevention medication

***Model 3 - adjusted for age, smoking, diabetes, hypertension, hyperlipidaemia, secondary prevention medication, use of angiography, distance to hospital and type of hospital

Table 38 MINAP - Effect of deprivation on all-cause mortality at one-year comparing South Asian and White participants

Adjustment for risk factors, secondary prevention medication, use of angiography, distance to hospital and type of hospital did not significantly alter the point estimates of worse prognosis seen in South Asian participants in less deprived areas compared to White participants in those areas, though confidence intervals were wider (Table 38).

9.7.4.5 Clinical management

South Asian participants were more likely to undergo in-patient coronary angiography than White participants following acute coronary syndromes, though received revascularisation less in the chest pain cohort. South Asian participants were on fewer secondary prevention drugs at chest pain clinics, equivalent treatment at angiography, and more treatment following acute coronary syndromes. Stratified analyses by these clinical management types revealed similar prognoses between ethnic groups, though in the acute coronary syndrome cohort, South Asian participants who underwent in-patient angiography had a worse prognosis compared to White participants who underwent the procedure (HR 1.32 (1.04-1.66)).

9.8 Discussion

9.8.1 Objective addressed

By meta-analysing the results of the four studies of this thesis with eleven previously published studies, I demonstrated a higher incidence of both fatal and non-fatal coronary disease in South Asian compared to White populations but a better prognosis for death following presentation with coronary disease in South Asian compared to White populations. Thus, the higher cross-sectional coronary

mortality in South Asian compared to White populations¹⁰ is more likely to be explained by the higher incidence of fatal and non-fatal coronary disease in South Asian populations than a higher case fatality compared to White populations.

9.8.2 Incidence

I have added new incidence data from Whitehall-II and shown a higher incidence of both fatal and non-fatal coronary disease in South Asian compared to White populations. There are few healthy population studies on the incidence of non-fatal events in South Asian compared to White populations, and none on angina. Whitehall-II demonstrates for the first time the higher incidence of non-fatal events in South Asian compared to White populations.

9.8.3 Prognosis and factors affecting it

The higher incidence of coronary disease in South Asian compared to White populations was in contrast to the lack of adverse prognostic consequences, as prognosis for death was in fact better in South Asian populations.

9.8.3.1 Risk factors

Biologically, South Asian and White populations differ when presenting with coronary disease. They tend to be younger, and more likely to be diabetic across the spectrum of clinical presentations of coronary disease. Age however did not, both on adjusted and stratified analyses, explain the better prognosis in South Asian compared to White populations. Stratifying on diabetes revealed that diabetes was not more likely to result in adverse outcomes in South Asian populations, a surprise considering that glycaemic control is reportedly poorer among South Asian people¹⁷⁴ and that a higher risk of diabetes complications are seen in this minority ethnic group compared to White people with diabetes.^{93 175}

9.8.3.2 Disease severity

Differences in the severity of disease at presentation might contribute to ethnic differences in prognosis but no evidence of this was found across a range of markers of disease severity such as degree of angiographic coronary disease and troponin level. A lower case fatality after hospitalisation for acute coronary syndromes might occur if South Asian populations had a higher incidence than

White patients of death from myocardial infarction before reaching hospital. The work by Fischbaker et al¹²³ however suggests this is not the case, as 21 of the 126 first episodes of myocardial infarction recorded were sudden deaths in the community among South Asian populations (16.7%) in comparison to 9672 out of 30978 (31.2%) for non South Asian populations.

9.8.3.3 Clinical management

In patients with coronary disease, access to clinical management strategies will be a factor in determining prognosis. A priori, one might have expected South Asian patients to be under-managed for coronary disease and for this to be associated with a worse prognosis. The lack of evidence on underuse of both secondary prevention management and specialist investigation and treatment among South Asian patients in the prognostic studies of this thesis contrasts with previous literature reporting that South Asian patients are under-managed for coronary disease²⁹ This may reflect that care in minority ethnic groups is improving, especially in the context of their predominantly inner-city locations near major centres of cardiac care. South Asian patients may also have quicker access to emergency treatment because of the proximity of their inner-city residences to hospitals, though distance to hospital in our analyses again could not account for the prognostic difference, nor did stratifying on use of angiography. The TIMI phase II trial showed comparable 1-year mortality rates in the White, Black, and Hispanic patients,¹⁸⁰ demonstrating the efficacy of appropriate, evidence-based treatment across demographic groups in a clinical trial setting.

I examined further whether the relative size of the South Asian ethnic group in a neighbourhood influenced the care hospitals provide, by excluding hospitals which reported <5% South Asian patients in the acute coronary syndrome cohort. I hypothesised that hospitals in areas of high South Asian populations may be more accustomed to treating this minority ethnic group in the same way that hospitals treating fewer cardiovascular cases are less likely to apply evidence-based processes of appropriate care.¹⁸¹ However, this did not alter the results.

9.8.3.4 Social environment

Analyses stratified by deprivation suggested that South Asian populations had a worse prognosis than White populations in less deprived areas in MINAP, with a similar suggestion from the point estimates in the chest pain clinic cohort. The results from these exploratory analyses may be explained by unmeasured confounders which could not be adjusted for. For instance, South Asian people in less deprived areas may be more socially isolated from family and communities compared to those in inner cities where the relative size of the South Asian ethnic group within the neighbourhood is higher. The measurement of deprivation may not take into account the increased social advantages to South Asian people of living in tight-knit, ethnic-dense inner city areas and the impact of local healthcare services specifically designed to serve those communities. However, associations between social network size and cardiovascular risk factors such as waist circumference, blood pressure and lipids have been previously examined in White and South Asian populations and no relationship found.¹⁸²

There are however published studies that have suggested increased deprivation is not always linked to worse ill-health. It has been previously reported that more deprived South Asian patients with heart failure have better all-cause mortality outcomes than less deprived White patients.¹⁸³ South Asian patients with heart failure were taking both ACE inhibitor and β blockers more commonly at presentation in this study and the results may therefore suggest the possibility of disease modification by pharmacological treatments known to improve outcome in heart failure. Again, this study conducted stratified analyses similar to those in MINAP – their findings were not biased by better survival of South Asian patients with preserved left ventricular function, more common in South Asian patients. Rather, survival was better for South Asian patients than White populations with moderate left ventricular systolic dysfunction on echocardiography. Thus, in this study as in MINAP, differing disease severity at presentation could not explain differences in prognosis between South Asian and White populations.

Whilst it is increasingly recognised that the social deprivation of areas influences the aetiology and prognosis of coronary disease,¹⁰⁵ large contemporary prognostic studies with detailed and comparable data on deprivation are lacking. For hospitals serving socially deprived communities it is important to understand the interaction of social deprivation with ethnicity. This is crucial in interpreting hospital league tables of outcomes (for which a dataset like MINAP is a crucial tool) and in meeting key policy objectives to improve the health of the worst-off in society.

Ethnic minority populations tend to be concentrated in areas of social deprivation as I have found in my cohorts, but as Figure 16 illustrates this is not a simple, or inevitable relationship. In London, boroughs like Camden (the 7th most deprived borough in London with Bangladeshis constituting 61% of the South Asian population) and Tower Hamlets (the most deprived borough in London, with Bangladeshis constituting 91% of South Asian population), are far more deprived than Harrow, one of the least deprived boroughs in London yet containing a high proportion of South Asian people. Furthermore, Indians make up 74% of the large South Asian population in Harrow. Hence, Indians appear superficially to be more affluent than Bangladeshis. Thus, if Indians live in less deprived areas than Bangladeshis, investigating the overall relationship between the South Asian group and deprivation will require differences between South Asian peoples to be taken into account. It may also be the case that if more Indians live in rich areas than in poor areas, then the increased risk of mortality for the South Asian group living in the least deprived areas could reflect the increased mortality risk of the Indian population living in rich areas compared to the (rich) White majority – in contrast, for the most deprived areas, it is plausible that Bangladeshis have a better all cause mortality compared to poor White people living in those deprived areas. Thus, the influence of social environment requires appreciation of the heterogeneity of the South Asian population, and this requires richer data.

In this thesis, the surprising data of the influence of deprivation on outcomes by ethnic groups needs further work to fully confirm these findings, and to take into

account the effect of unmeasured, residual confounders within these populations. More advanced analyses using multi-level level (hierarchical) regression models to investigate the extent to which individual and area deprivation and ethnicity may interact in their effects on prognosis of coronary disease would thus be a next step.

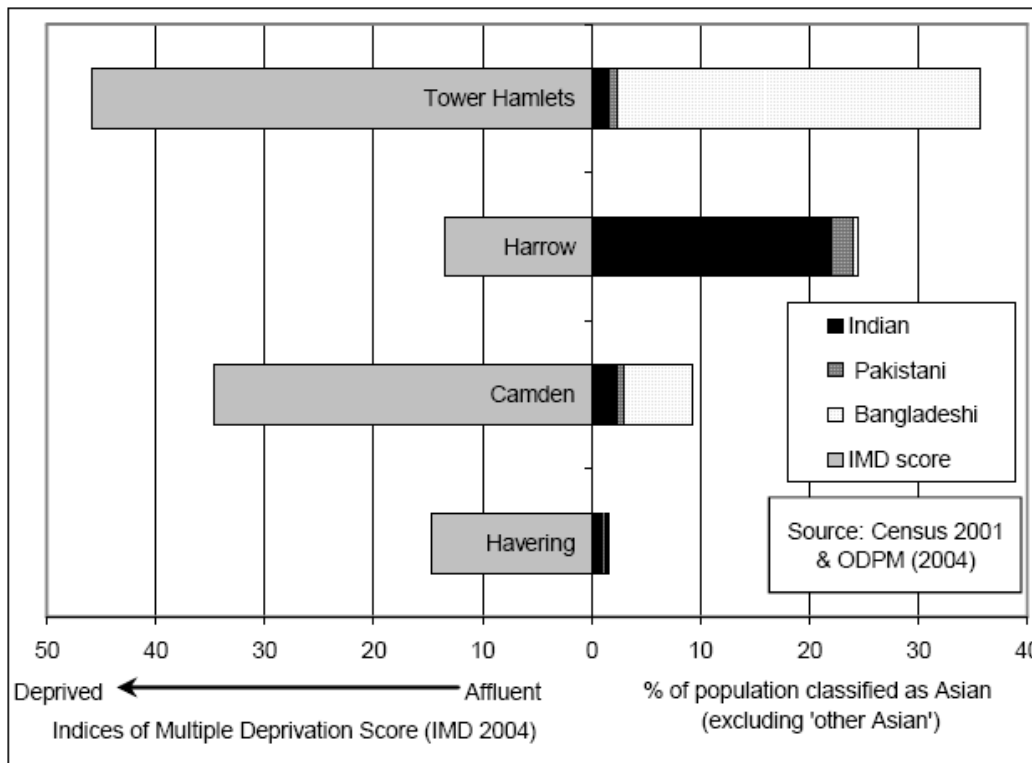


Figure 16 Proportion of population classified as Indian, Pakistani or Bangladeshi at the 2001 Census and Indices of Multiple Deprivation Score 2004, by selected London boroughs

9.8.3.5 Symptomatic prognosis

Though prognosis for death (case fatality) appears better in South Asian compared to White populations from this meta-analysis, symptomatic prognosis and improvement in quality of life may differ by ethnicity. Analyses within ACRE in chapter 7 showed that South Asian patients were less likely to have improved angina than White patients six years after undergoing coronary revascularisation. The use of a symptomatic outcome adds to the overall picture of prognosis of coronary disease, as whilst prognosis for fatal events is no worse in South Asian compared with White populations, prognosis for non-fatal

symptomatic may not be equitable by ethnicity. The earlier age of presentation and the high rates of diabetes in South Asian populations will continue to cause increased morbidity following presentation with coronary disease.

9.8.4 Limitations

Interpretation of the summary estimates requires caution. This meta-analysis has important limitations:

- The studies were heterogeneous in their choice of populations and methods, and access to the raw individual participant data from previously published studies was not available to allow a more accurate meta-analysis to be conducted. The I^2 was particularly high for the incidence studies at 47.6% (An I^2 higher than 50% is deemed to be large enough to question whether combining studies is valid), and thus this should be considered when applying the findings in other settings.
- The studies by Wild and Balarajan included in the incidence analysis were mortality studies and thus strictly not true incidence (first coronary event) studies – however, death can be regarded as an incident event and these studies were age-adjusted. The data presented by these two large studies thus adds to the overall picture of incidence.
- The vast majority of participants studied for prognosis were those with myocardial infarction rather than angina, of which a large proportion were from MINAP. However, in both the chest pain clinic and coronary angiogram cohorts, there was no indication that prognosis was any worse in South Asian than in White participants. Combining patients with myocardial infarction and angina arguably contributes to increased heterogeneity – however, the focus of attention was on the examination of case fatality following presentation with coronary disease between ethnic groups, and hence the interest lies in comparison of longitudinal outcomes irrespective of the actual clinical phenotype at presentation. Thus, combining patients with differing clinical phenotypes remains of

value to the overall picture of prognosis of coronary disease between ethnic groups.

- Some studies had follow-up data on all-cause death, and others data on coronary death.
 - However, a high proportion of early deaths following an ACS are likely to be cardiac in cause - from the PRAIS UK registry (Prospective Registry of Acute Ischaemic Syndromes in the UK), the proportion of cardiovascular deaths was 92% in the first six months.¹⁸⁴
- Many of the studies on systematic review did not adjust for confounding factors such as diabetes. Having access to individual participant data from previously published studies could have in part reduced this limitation, though this would have depended on whether data on factors such as diabetes were collected.

9.8.5 *Implications*

9.8.5.1 Public Health

The dissociation between the aetiologic and prognostic findings suggests that public health efforts to reduce ethnic disparities in mortality need to improve on primary prevention, as provision of healthcare to those with manifest coronary disease appears to be equitable between South Asian and White patients. By providing appropriate care to all, inequity of outcomes for manifest coronary disease may not result.

9.8.5.2 Clinical

It is conceivable however that the symptomatic prognosis and improvement in quality of life may differ by ethnicity beyond the study of case fatality. Whilst it is reassuring that prognosis in terms of case fatality seems no worse in South Asian patients, continuing monitoring of prognosis is necessary in the light of the higher incidence of coronary disease, the earlier age of presentation and continuing high rates of diabetes in South Asian populations.

9.8.5.3 Research

The analyses stratified by deprivation suggesting that South Asian patients had a worse prognosis than White patients in less deprived areas in MINAP was counter to what would have been expected, and thus to ensure the correct answer to this question is arrived at, richer individual and service data inputted into such clinical registries and studies is required.

9.9 Conclusion

In contrast to the higher incidence of coronary disease in South Asian compared to White populations, once coronary disease is manifest, their prognosis in terms of future risk of death may be better. Public health efforts to reduce ethnic disparities in mortality need a heightened focus on primary prevention whilst ensuring that equitable management of manifest coronary disease continues to result in equitable prognosis between ethnic groups.

10 Discussion

10.1 Overall findings

The index finding underlying this thesis is the higher coronary mortality in South Asian compared to White populations in the UK. The aim of the thesis was to investigate the relative contributions of incidence and prognosis of coronary disease to these higher mortality rates observed in South Asian compared to White populations. Overall, this thesis found that these increased coronary mortality rates in South Asian populations are due to their higher incidence of fatal and non-fatal coronary disease, as the prognosis in South Asian populations of manifest coronary disease is not worse than in White populations.

As coronary disease is an aggregation of differing phenotypes such as angina and myocardial infarction, the thesis sought to separate these phenotypes and examine their incidence and prognosis. It then sought to further disaggregate angina by nature of symptoms, which varies by ethnic group, and myocardial infarction by severity, using biomarker-based diagnoses. As prognosis can be measured by both coronary events (such as death/myocardial infarction) but also future quality of life, the receipt and impact on improving angina symptoms of management strategies for chronic coronary disease was examined between South Asian and White populations. This is of importance as receipt and efficacy of management strategies for chronic coronary disease may differ between South Asian and White populations.

My specific objectives were as follows, and answered thus:

- | |
|---|
| (i) To determine the incidence and prognosis of angina in healthy South Asian and White populations |
|---|

There was a higher cumulative incidence of typical angina and exertional chest pain in South Asian compared to White populations using a detailed characterisation of symptoms of stable angina using the Rose questionnaire at

seven time-points over 18 year follow-up. There was not a higher incidence of non-exertional chest pain in South Asian compared to White populations. In both South Asian and White populations, typical angina and exertional chest pain at baseline were associated with increased rates of future coronary events when compared to those with no chest pain, but those with non-exertional chest pain did not have a worse prognosis compared to those with no chest pain. South Asian populations had a worse long-term prognosis than White populations within all types of chest pain though South Asian populations with no chest pain at baseline were not at more long-term risk than White populations with no chest pain at baseline.

(ii) To determine in those presenting with incident chest pain whether differences exist in the description of symptoms between South Asian and White populations, and the impact symptom descriptors have on prognosis and receipt of management strategies for chronic coronary disease

Although atypical chest pain was more common in South Asian than White populations within a chest pain clinic, typical angina compared to atypical chest pain was as likely to be associated with a worse prognosis in South Asian as in White populations. Although South Asian populations attending chest pain clinics did report a marked excess of atypical symptoms, the rate of subsequent adverse coronary outcomes in this group was similar in White and South Asian populations. However South Asian populations were less likely to receive coronary angiography and revascularisation than White populations in both those with typical angina and atypical chest pain.

(iii) To determine impact on symptomatic prognostic outcomes (change in angina severity) in South Asian and White populations from management strategies for chronic angina

South Asian populations were less likely to experience long-term improvement in angina following coronary revascularisation when compared to White populations, despite a similar prognosis for adverse clinical events such as

myocardial infarction and death, even after having taken into account appropriateness for revascularisation and differences in clinical characteristics.

(iv) To compare fatal prognostic outcomes of acute coronary syndromes in South Asian and White populations and assess factors underlying prognosis

Survival in South Asian populations was no worse than White populations at one year, even after adjustment of confounding factors. Factors such as diabetes, more prevalent in South Asian populations, nor any other risk factors, clinical management strategies and socio-economic characteristics did not appear to confer a worse prognosis in South Asian compared to White populations.

(v) To assess the contribution of incidence and prognosis to the higher coronary death rates in South Asian compared to White populations through meta-analysis of new and previously reported studies

By meta-analysing the results of my own studies with eleven previously published studies found on systematic review, the results reveal that incidence of coronary disease was higher in South Asian compared to White populations yet prognosis was better in South Asian populations. Thus, the higher coronary mortality in South Asian compared to White populations is likely to be explained by the higher incidence of coronary disease in South Asian populations rather than worse survival from coronary disease.

10.2 Implications

10.2.1 Aetiology and primary prevention within primary care

The relatively small number of South Asian civil servants in the Whitehall-II cohort, with their relatively low prevalence of diabetes, did not allow aetiological questions to be reliably addressed (why the higher incidence?). Clearly, a priority of future research is to unravel why South Asian populations have more diabetes than White populations.

The Whitehall-II cohort revealed a higher incidence of angina in South Asian compared to White people. The measurement of this angina through the Rose

questionnaire allowed the discrimination of prognostically-important chest pain from non-exertional chest pain that was associated with a lower rate of adverse events. Therefore, the use of the Rose questionnaire to assess the early presentation of chest pain was found to have prognostic validity in South Asian as well as in White populations, and may allow its use in early detection of angina to target clinical management to prevent progression to more adverse outcomes.

10.2.2 Secondary prevention within hospital care

By managing true angina well (such as in a chest pain clinic), equitable outcomes may result irrespective of the ethnic group. Whitehall-II revealed a worse prognosis in South Asian compared to White people in those with typical angina. This contrasted with the finding from the Chest Pain Clinic study which showed that typical angina did not predict a worse outcome in South Asian compared to White people. Whitehall-II was a purely observational cohort, and thus it is conceivable that those South Asian people with typical angina went undiagnosed and hence unmanaged (unlike in the chest pain clinic cohort, whose participants were within a healthcare setting).

South Asian populations may continue to suffer increased morbidity following presentation with acute coronary disease on account of their higher rates of diabetes and this disease's ensuing complications. The coronary angiogram cohort showed that though the prognosis in those with angina in terms of subsequent events such as myocardial infarction and death was not worse in South Asian compared to White populations, South Asian patients were less likely to experience long-term improvement in angina following coronary revascularisation when compared to White patients. As the relief of angina determines return to work and perceived health status,⁴⁸ research on functional outcomes is of importance. As coronary mortality rates fall, morbidity in the form of angina becomes a more common clinical problem.

10.2.3 Further research

Few studies have collected data on chest pain symptom descriptors by ethnic groups, and none have examined their prospective validity. The increased

prevalence of atypical pain in South Asian people may be a reason why the improvement in angina in South Asian patients following revascularisation is poorer than in White patients. If ACRE had had information on typicality of pain, this would have aided interpretation of the analyses.

Using registry data to answer epidemiological questions has considerable cost-saving potential. That survival in South Asian patients following presentation with acute coronary syndromes was better than White patients at one year, even after adjustment of confounding factors may be a vindication of care in previously under-managed minority ethnic groups. This will encourage doctors and public health professionals that inequalities can be successfully addressed. However, to be able to use routinely-collected clinical data in research will require careful data quality checking and the usage of inbuilt entry/range checks.

10.2.4 Public health

The combination of higher incidence and similar prognosis in South Asian compared to White populations of coronary disease, coupled with the general aging of the whole UK population, will lead to an increase in the size of the prevalent pool of South Asian people with coronary disease. Thus, though coronary mortality rates may continue to drop, the total burden of coronary heart disease in South Asian populations is likely to increase. Hence, disaggregation of cross-sectional coronary mortality rates into incidence and prognosis, and by differing clinical presentations such as angina and myocardial infarction, is essential for the complete understanding of the epidemiology of coronary disease in different ethnic groups.

This thesis demonstrates that the health of South Asian populations in some respects - such as with regard to one-year case fatality after presentation with an acute coronary syndrome - is not worse than the majority White population. Such results should serve to stimulate further research into discovering more about the aspects of service provision that are responsible for these improvements in ethnic disparities. Not collecting any ethnicity data at all (the case in countries such as France) would mean that quantification of ethnic

disparities and hence instigation of measures to alleviate them and hence measurement of their improvement would not be possible at all.

10.3 Limitations

10.3.1 Definition and validation of ethnicity

Ethnic inequalities in public health continue to be highlighted and hence analyses of any data concerning ethnic groups remain of vital importance though need due caution and careful validation. As the main exposure of interest to this thesis was ethnicity, the comparability of measures of ethnicity within the four cohorts was of importance. However, the four cohorts defined ethnicity in differing ways. Ethnicity in Whitehall-II was defined according to the Office for National Statistics 1991 census types. In the Chest Pain Clinic Cohort, the doctor ascribed ethnicity as “Asian”, “White”, “Black” or “other” during the consultation. In the coronary angiogram cohort, self-assigned ethnicity, based on the national 1991 census classification, was obtained by questionnaire on the day of index coronary angiography. In the acute coronary syndrome cohort, the patient's ethnic group was classified by the coder into the groups Caucasian, Asian, Black, Oriental and other.

Though the four studies used differing methodology to define ethnicity, analyses on the ethnicity variable of each cohort confirmed validity of the measures in each cohort. Thus, though due care should be taken in the usage of the ethnicity variable in epidemiology, this work shows the importance of collecting data on ethnicity. A future gold standard for measuring ethnicity would use a self-assessed measure and include information on country of birth, religion and nationality of the participant and their parents to take into account the heterogeneity within the South Asian population as well as the differences that exist between a first-generation migrant and their progeny.

10.3.2 Heterogeneity of South Asians and whites

Cardiovascular risk within South Asian peoples is heterogeneous. For instance, Bangladeshis are shorter, are less obese and have a lower mean blood pressure than other South Asian peoples yet their risk of developing cardiovascular disease and diabetes is the highest of all the South Asian ethnic groups.^{17 116}

Beyond biological differences, differences in the individual reasons for migration (e.g., economic, educational, political) and differences in baseline literacy and skills will result in further heterogeneity. Demobbed soldiers will be different from ship's cooks who will be different from doctors or others from professional and mercantile backgrounds. This will also influence the future socio-economic and educational/professional status of their children. There is increasing evidence that those of the lowest socio-economic status, those of Pakistani and Bangladeshi origin, have the highest rates of coronary disease.^{20 185}

The majority of published literature in ethnicity and health has aggregated migrants from the different geographical, religious and linguistic backgrounds from the sub-continent as South Asian. Studies are increasingly disaggregating this ethnic group into the different nationalities, cultures and religions represented within it. Although in ACRE and Whitehall-II there were data on the breakdown of the studies' South Asian populations into Indians, Bangladeshis, Pakistani and Sri Lankan, there were too few numbers for analysis.

Equally, as discussed in section 1.3.2, these analyses only apply to White populations based mostly in England and Wales. The comparisons cannot be applied to Scotland and Ireland, to migrants from those countries to England and Wales, and to White migrants from Southern and Eastern Europe.

10.3.3 Definition and validation of chest pain and angina

Angina is a clinical constellation of symptoms rendering quantitative measurement difficult. Acute coronary syndromes can be measured in terms of biomarkers such as troponin - stable angina does not have a comparable blood test to measure it. Thus, it is difficult to compare cases of angina enrolled in one study with those in another, and indeed I have used three different measures of angina in the three cohorts. The advantage to the use of differing definitions of angina is in allowing differing questions to be asked. For instance, using the four-level CCS score in ACRE allowed severity calculation of a change in angina, while the Rose questionnaire has only two levels of severity. However, using the Chest Pain Clinic study's symptom score within ACRE to determine whether the pain was typical or atypical would have aided in determining why angina was

improving less in some compared to others. The ACRE study assumed all CCS angina was in fact typical angina which may not have been the case. The Chest Pain Clinic study might have been enhanced if data were available on the findings of subsequent coronary angiography if it took place, though from ACRE, there was little correlation between number of diseased coronary vessels and CCS score. This is not unreasonable, as one single severely stenosed coronary artery is likely to be highly symptomatic.

Though different case definitions for angina were used in Whitehall-II, Chest Pain Clinic Study and ACRE, there was some consistency in the results. For example, typical pain had a poorer outcome than atypical, be it pain defined by the Rose questionnaire or by the symptom score formulated from chest pain descriptors in the Chest Pain Clinic Study. However, within the atypical type of chest pain, they may still be patients with coronary disease who go on to develop adverse coronary outcomes. This is applicable to both ethnic groups, though considering those with a confirmed myocardial infarction, chest pain is still more likely to be atypical in nature in South Asian compared to White patients.^{40 45 46} Typical symptoms thus represent a filter for patients with suspected angina for further investigation, and that which can be improved by coronary disease management strategies.

Poor communication due to language difficulties have long been offered as an important factor relating to the health outcomes and experiences of health care for members of the South Asian community.¹⁸⁶ However, throughout the analyses of this thesis, the measures of chest pain used had equal cross-sectional and prognostic validity in South Asian and in White populations. The ethnographic qualitative study of 59 clinic consultations performed by colleagues at Newham University Hospital also showed how the chest pain classification and diagnosis were reached,¹⁵⁹ and there was little evidence that this negotiation was patterned by ethnicity. None of the South Asian patients in this study relied on translators. It may be that the major differences between South Asian patients who are not fluent in English and White will be longer

consultations than White patients¹⁸⁷ and increased dissatisfaction with medical care¹⁸⁸ rather than an adverse prognosis.

10.3.4 Data quality and validity

The cohorts for study in this thesis, selected on account of the coverage they provide across the different stages of the natural history of coronary disease, used very different methodologies. I sought to examine the quality and validity of this data throughout this thesis. In chapter 4, I assessed recruitment of baseline data through to data on follow-up and found that data, though variable in its completeness between the studies chosen for this thesis, was of good quality.

Validity of specific variables essential to prognostic analyses was assessed in cross-sectional and prospective analyses within all four cohorts. When examining angina for example, in Whitehall-II there was an increasing prevalence of hypertension and higher cholesterol levels with more typical chest pain and trends towards more metabolic syndrome and higher body mass index. In the Chest Pain Clinic study, typical symptoms strongly predicted a positive exercise ECG result, and both the cardiologist summary and the symptom score of typical symptoms were predictive of a diagnosis of angina across sex and ethnicity. In ACRE, the CCS variable, calculated from a patient questionnaire, correlated with South Asian patients having a higher prevalence of primary care doctor-diagnosed angina at follow-up. Increasing angina as measured by CCS at baseline was associated with worsening patterns in other baseline clinical measures and higher rates of prospective all-cause mortality.

Hence, though data across the four cohorts varied in definitions and completeness, a range of checks on data quality and validity ensured any conclusions made from the results of the analyses were not biased.

10.4 Future work

10.4.1 Improving the measure of angina

Until standardised case definitions for angina are agreed, prevalence and prognostic assessments will remain variable and contradictory. Case definitions

of angina rely on the presence of one or more findings in three domains. These domains are represented in the figure below.

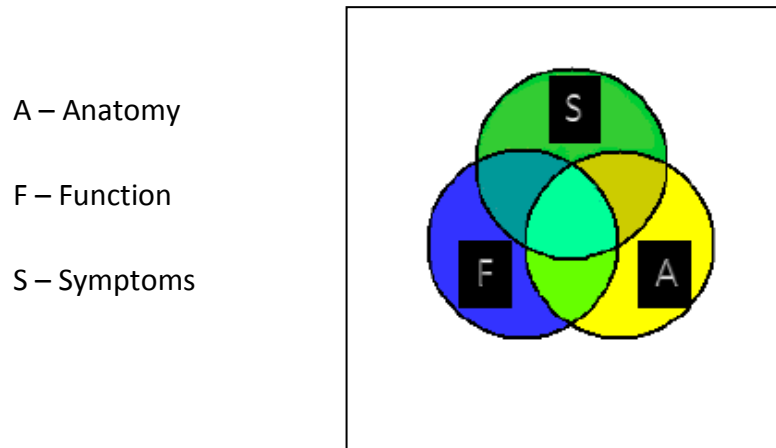


Figure 17 Differing angina phenotypes: anatomy, symptoms and function domains

- Anatomy of coronary arteries' lesions may be data from coronary angiography (both invasive and computerised tomography).
- Function in terms of ischaemia may be data from exercise ECG, stress echocardiography, myocardial perfusion imaging and magnetic resonance imaging.
- Symptoms may be data from the Rose angina questionnaire, symptom descriptors, CCS classification and nitrate use.

Finding an instrument to measure angina will require the definition of the angina phenotype in the first instance in terms of symptoms, anatomy and functional findings. An atheromatous plaque causing coronary vessel narrowing visualised on angiography and ischaemic changes on exercise ECG may not in itself cause ischaemic symptoms for example and thus span the A and F cells. Syndrome X, with its anginal symptoms and positive exercise test but normal coronary anatomy would span the F and S cells.

Differing phenotypes of angina may be built up using a composite of measures and the use of these will be dictated by the questions asked of the proposed

research. It is possible that multiple phenotypes underlying angina will result. Different combinations here will give different syndromes, and there may ethnic differences in any of the seven cells of the Venn diagram above.

10.4.2 Improving the quality of the data and statistical methodology

Throughout this thesis, I assessed both data quality and validity through techniques available to me. To further improve the data, more advanced statistical methodology could be employed.

10.4.2.1 Propensity scores

Propensity scores can be used to reduce bias in observational studies. The lack of randomisation in such studies can complicate prognostic analyses as these comparisons may be biased due to prognostically important baseline differences among patients, often as a result of unobserved treatment selection biases. This would bias for example the comparison of patients with typical and atypical pain within the chest pain clinic. Within ACRE, an observational study of invasive procedures, such studies are more prone to bias because patients who are candidates for the procedure often differ in immeasurable ways from patients who are not. Doctors may also be more risk averse in selecting those needing further invasive investigation, performing interventions on lower-risk patients despite greater clinical benefit to higher-risk patients (such as reduced prescription of statins in elderly patients with a higher future probability of death).^{189 190} The propensity score for an individual is defined as the probability of being treated conditionally on (or only on the basis of) the individual's covariate values and was originally proposed as a method for producing a balance of many covariates between two groups.^{191 192}

However, propensity-based matching have the same limitations as multivariable risk adjustment model methods if unmeasured variables that may determine allocation to one exposed group compared to another are not measured. They also cannot overcome initial selection bias.¹⁹³

10.4.2.2 Multiple Imputation of Baseline Data

Imputation is a procedure used for entering a value for a specific data item where the response is missing or unusable. It uses the principle that missing data

can range from being missing completely at random (where no other information in the database can predict reasons for data missingness) to being not missing at random, where a systematic pattern of missingness is found (e.g., one of the centres of a multi-centre study may not have a sphygmomanometer and thus no recordings of blood pressure were taken at that centre). The technique relies on the capacity of the database to predict associations between exposure and missingness, and requires that every variable used in the statistical model takes account of imputation, not just those that predict missingness.

The technique has been used and described in large observational studies in cardiovascular disease. The success of this technique depends on the wealth of covariate data available within the dataset. The Cardiovascular Health Study, a population-based study designed to identify risk factors for cardiovascular disease in individuals aged 65 or more years in the US, has reported on this technique.¹⁹⁴ It is a relevant example to this thesis as there existed two separate cohorts within this study (which were enrolled in different years) with differences in the data collected, in particular differing substantially in their numbers of African American participants. The richness and slight redundancy of the Cardiovascular Health Study data set allowed the researchers to impute groups of similar and highly correlated variables together – they gave the example of heart rate, measured at four different times. Multiple Imputation has also been used in Whitehall-II to assess the association between persistent economic difficulties and serious coronary events.¹⁹⁵

10.4.3 Linkage of databases

10.4.3.1 Linking secondary care data with primary care data

The three prognostic cohorts examined within this thesis have all recruited participants in the secondary care setting, at different points along the natural history of coronary disease. However, no information was available in any of the cohorts before and after (aside from outcomes) on other healthcare data. Linkage with data from primary care sources such as the General Practice

Research Databaseⁿ (GPRD) may augment secondary care data sets and provide more information on the patient journey along the natural history of coronary disease - such as information on earlier events (e.g. onset of hypertension) - that will provide more explanatory data for investigating the aetiology of events such as angina and myocardial infarction. The GPRD is a computerised database of anonymised longitudinal medical records from primary care that can be linked with other healthcare data. Currently data are available on around 13 million patients from around 488 primary care practices throughout the UK. By linking MINAP data to the GPRD, such a resource would be able to identify the extent and prognostic impact of missed opportunities for preventive care earlier in the patient journey.

The influence of primary care on variation in prognosis is also of vital importance. Within MINAP, no data were available on healthcare between admission and follow-up for vital status at one year. Prognostic analyses thus cannot take into account the care received in primary care after an admission with an acute coronary syndrome and thus its influence on outcomes. This is commonly the case for hospital-based follow-up studies, as secondary prevention is deemed to be the remit of primary care.

The GPRD currently does not record ethnicity at the individual patient level, but other primary care research databases like QRESEARCH do.^o QRESEARCH is a database derived from the anonymised health records of over 11 million patients from 574 general practices using the EMIS clinical computer system. The practices are spread throughout the UK and include data from patients who are currently registered with the practices as well as historical patients who may have died or left. Thus, multiple databases may be linked to ensure the availability of the necessary data fields for a research hypothesis.

ⁿ <http://www.gprd.com>

^o <http://www.qresearch.org>

10.4.3.2 Linking secondary care data with other secondary care data

Linkage of secondary care databases and studies with data sources such as Hospital Episode Statistics (HES) will allow the addition of information such as cause-specific future admission to databases such as MINAP. HES is the national statistical data warehouse for England of the care provided by NHS hospitals and for NHS hospital patients treated elsewhere. The two main clinical classifications currently used in HES are the International Classification of Diseases, Tenth Revision from which descriptions of the conditions treated or investigated can be obtained and the Office of Population, Censuses and Surveys: Classification of Interventions and Procedures, 4th Revision which records details of procedures or interventions performed.

10.4.4 The influence of genetics

Differences in genetic susceptibility may be responsible for part of the variation of coronary heart disease rates between ethnic groups. In twin studies, the relative hazard of death from premature coronary heart disease (age less than 55) when one's twin died of coronary heart disease is eight times higher in men and 15 times higher in women, even after taking into account other risk factors for coronary heart disease.¹⁹⁶ Similar findings of familial aggregation have been reported in North-Eastern Indian origin South Asian people in Mauritius, where a study has reported a 7.4-fold increased prevalence of coronary disease in siblings of individuals with myocardial infarction.¹⁹⁷

Detailed investigation into the causes of the increased incidence of coronary disease observed in South Asian populations was beyond the remit of this thesis, but the increased prevalence of the metabolic syndrome and diabetes mellitus in this population is the most widely-held explanation.^{198 199} Though much of this excess is thought to be due to environmental factors, genetic factors may play a role in determining the level of such risk factors. An inherited susceptibility to type 2 diabetes may derive from multiple genes of individual modest effect,²⁰⁰ and a component of insulin resistance, more prevalent in South Asian populations,²⁰¹ may be inherited.²⁰² The thrifty gene hypothesis proposes that conditions of food scarcity increased evolutionary selection pressure for efficient metabolism, which then disadvantages those who become exposed to the

modern obesogenic environment, the supposed combination facing the migrant from South Asia.²⁰³ Genes and pathways involved in the insulin resistance metabolic syndrome may underlie this.

The recent advances in the understanding of the human genome have opened up possibilities for new biological insights, new clinical insights, and new clinical applications. Genome-wide association studies have for example found an association between myocardial infarction and a common sequence variant on chromosome 9p21.²⁰⁴ A genome-wide association study for insulin resistance and related phenotypes in 2684 Indian Asian people, with further testing in 11955 individuals of Indian Asian or European ancestry, found associations of the allele rs12970134 (near the Melanocortin 4 receptor MC4R, a human gene near which common genetic variation is associated with risk of adiposity and insulin resistance^p) with waist circumference and independently with insulin resistance.²⁰⁵

Such future work in genetics will help to unravel the interaction of genes with the environment, and may play a role in explaining the dissociation between the higher incidence of coronary disease in South Asian compared to White populations and the similar prognosis between the two ethnic groups. Such future work should also be designed to allow investigations on whether differences exist between South Asian peoples and thus whether the heterogeneity of this group is predominately socio-economic and behavioural or biological.

10.4.5 South Asians in South Asia

In South Asia today, an epidemiological transition is taking place against a background of economic globalisation that has greatly increased the size of the urban poor and middle classes, at the same time leaving many millions to continue living on the land at subsistence level. There is an emerging double burden of disease in the countries of South Asia, characterised by a combination

^p Homozygotes for the risk allele of rs12970134 have approximately two cm increased waist circumference.

of pandemic infectious disease and high rates of coronary disease. Though coronary risk factors tend to be concentrated in those of higher social classes,²⁰⁶ the poor in India are increasingly affected. Higher levels of tobacco consumption are associated with low levels of education and income²⁰⁷ and both urban slums in Delhi and rural south India have a high prevalence of diabetes and dyslipidaemia. The high prevalence of coronary risk factors such as smoking, high blood pressure and overweight in areas of rural India are also of concern.²⁰⁸

The answers to research questions surrounding ethnic differences in coronary health may thus increasingly come from the sub-continent. Regional endeavours such as registry data collection are already providing answers on treatment outcomes.²⁰⁹ CREATE is such an endeavour which, in a study design similar to MINAP, recruits eligible patients with suspected acute coronary syndrome in 89 centres from 10 regions and 50 cities in India. Many of the data fields are common to MINAP and comparisons can be made to CREATE. Time from symptom onset to presentation at hospital is typically longer in India than in the UK for example, the delay in presentation being due to a lack of symptom awareness, longer distances travelled to reach hospital and problems of transportation (only 5.4% of patients are brought to hospital in an ambulance, with the large majority using public transport (buses) and hired vehicles (taxis, autorickshaws).²¹⁰ In addition, older people and women have been observed to present disproportionately late, irrespective of whether their symptoms were typical or atypical. Thus, there is much potential for the reciprocal exchange of ideas as well as collaborative work between such registries.

10.4.6 Generational effects

My data mostly concern 'first-generation' migrants from South Asia. It is unlikely that a large proportion of the South Asian people in my cohorts were born in the UK, as even the oldest second-generation South Asian people are only now in 2009 beginning to enter their 40s.

However, it is a pertinent question to ask whether the sons and daughters of first-generation South Asian migrants will be at equal risk. Decreasing mortality with increasing duration of residence in the new host country was observed for

migrants from South Asia in a study in Australia,¹⁵⁵ perhaps due to cardio-protective behavioural practices in the Australia. However, studies in the UK have presented opposite results to the Australian work, with increasing cardiovascular risk with length of residence among South Asian migrants.²¹¹

The interaction of behavioural practices and socio-economic patterns awaits further elucidation. The coronary risk of a group of educated and affluent second-generation South Asian people may more resemble that of a similarly educated and affluent White group, as opposed to a less educated group and less affluent group of second-generation South Asian people. It is here that perhaps the heterogeneity of the South Asian group may become increasingly important in the future. It is interesting that apart from Indian people, minority ethnic groups (including Pakistani/Bangladeshis) are found to be more likely than White majority groups to engage in poor dietary behaviours in a study of adolescent and parental lifestyles, with those born in the UK and girls being more susceptible.²¹² Thus, some South Asian peoples may inherit (more so through their behaviour than their genes) the diseases of their parents, whilst others – like the offspring of some professional Indian classes – acquire the disease profile of the majority White population.

Beyond socio-economic mechanisms, the influence of biology may continue to adversely affect the children of South Asian migrants. South Asian populations have a smaller superficial subcutaneous adipose tissue compartment than White populations and a theory has been proposed that babies born to mothers of South Asian descent are smaller and have less peripheral fat, and that during subsequent growth and development immersed in the richer diet of the developed world, this primary compartment reaches its capacity for fat storage rapidly and the deep subcutaneous and visceral compartments become more prominent, with adverse consequences for risks of diabetes and coronary disease.²¹³ Early evidence of ethnic differences in coronary risk has also been presented in a cross sectional comparison of British South Asian and White children, with ethnic differences being present even in these children aged 8 to 11 years – an increased tendency to insulin resistance was observed in South

Asian children, and the authors inferred an increased sensitivity to adiposity as a result.⁵¹

The finding that second-generation minority ethnic groups in England continue to report as poor a general health as their parents, unaffected by changes in health behaviours,²¹⁴ suggests that continuing investigation into ethnic inequalities in health will be needed in the progeny of first-generation migrants.

10.4.7 Ethnic inequalities in other diseases

In a study in the UK of increasing cardiovascular risk with length of residence among South Asian migrants,²¹¹ increased cancer mortality of South Asian migrants was also shown to increase with duration of residence in England and Wales. Increasing adoption of the detrimental aspects of the developed world lifestyle is resulting in a shift of epidemiological patterns of cancers in South Asian people living in the developed world towards that of the majority population. With increased time since migration and increasing life expectancy amongst ethnic minorities, disease patterns will start to resemble that of the majority population. This was highlighted over ten years ago.²¹⁵

The heterogeneity of South Asian people becomes particularly important when comparing behavioural practices that may in turn determine a shift in future epidemiological disease patterns. 43% of Bangladeshi men smoke compared to the national average of 27%.²¹⁶ Bangladeshis have also been found to tend to rely on willpower rather than health service interventions, resulting in poor quit rates²¹⁷ whilst ethnic minority patients were significantly less likely to receive advice on smoking cessation in one study.²¹⁸ Much of the UK Bangladeshi community are classified as having low socioeconomic status, high rates of unemployment and low levels of formal female employment,²¹⁹ and with higher smoking rates being found in inner-city ethnic minority communities,²²⁰ the finding that those in higher social classes have higher quit rates²²¹ is a further source of inequity. If lung cancer mortality reflects smoking habits of populations 20-30 years previously as has been proposed,¹¹ the likely progression from contemporary behavioural changes to future incidence and mortality data is all too predictable.

11 Conclusions

A systematic review of the literature revealed incidence of fatal coronary disease to be higher in South Asian compared to White populations, with few studies available on non-fatal incidence. When considering prognosis, the literature was unable to answer whether prognosis was worse in South Asian compared to White populations.

South Asian populations had a higher incidence of typical angina over long-term follow-up compared to White populations, but not a higher incidence of non-exertional chest pain. Typical angina was predictive of coronary death and non-fatal myocardial infarction on long-term follow-up, but non-exertional chest pain was not, in both South Asian and White populations.

South Asian populations with typical chest pain, though at increased risk of adverse coronary outcomes compared with those who presented with atypical pain, had lower rates of coronary angiography and revascularisation compared with White populations with typical chest pain.

South Asian patients were less likely to have improved angina than White patients on long-term follow-up after undergoing coronary revascularisation, even after having taken into account appropriateness for revascularisation and differences in clinical characteristics. South Asian patients with chronic angina were not at increased risk of coronary death and non-fatal myocardial infarction.

Survival following acute coronary syndromes was not worse in South Asian compared with White patients and this was not explained by risk factors, clinical management strategies or socio-environmental factors.

On meta-analysing the studies of this thesis with previously published literature retrieved on systematic review, there was a higher incidence of coronary disease in South Asian compared to White populations but once coronary disease is manifest, their prognosis was better.

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13 Appendices

13.1 Census 2001 - Ethnicity in England and Wales

In the 2001 census, ethnicity categories were coded as follows:

White British Irish Any other White background
Mixed White and Black Caribbean White and Black African White and Asian Any other mixed background
Asian or Asian British Indian Pakistani Bangladeshi Any other Asian background
Black or Black British Caribbean African Any other Black background
Other ethnic groups Chinese Any other ethnic group

Results on ethnicity and religion from the 2001 census revealed that 87.5 per cent of the population of England and Wales (seven out of eight people) gave their ethnic group as White British. The highest proportions describing themselves as White British are in the North East, Wales and the South West (all over 95 per cent).

	Total population		Minority ethnic population	
	Count	%	Count	%
White	54153898	92.1		n/a
Mixed	677117	1.2		14.6
Asian or Asian British				
Indian	1053411	1.8		22.7
Pakistani	747285	1.3		16.1
Bangladeshi	283063	0.5		6.1
Other Asian	247664	0.4		5.3
Black or Black British				
Black Caribbean	565876	1.0		12.2
Black African	485277	0.8		10.5
Black Other	97585	0.2		2.1
Chinese	247403	0.4		5.3
Other	230615	0.4		5.0
<i>All minority ethnic population</i>	<i>4635296</i>	<i>7.9</i>		<i>100</i>
All population	58789194	100		n/a

Eighty-seven per cent of the population of England and 96 per cent of the population of Wales gave their ethnic origin as White British. White Irish people make up 1.2 per cent of the population of England and Wales as a whole, with the highest proportion in the London borough of Brent (6.9 per cent of the population). The largest proportions of White Other (that is, not White British or White Irish) people are in central London, particularly the borough of Kensington and Chelsea (25.3 per cent).

London had the highest proportion of people from minority ethnic groups apart from more who identified themselves as of Pakistani origin, of whom there was a higher proportion in Yorkshire and the Humber (2.9 per cent) and the West Midlands (2.9 per cent). Two per cent of the population of England and Wales were Indian, with Leicester having the highest proportion (25.7 per cent). Bangladeshis formed 0.5 per cent of the population of England and Wales, with the highest proportion in the London borough of Tower Hamlets (33.4 per cent).

The largest proportions of people of Mixed origin were in London, with the exception of Nottingham, where two per cent of people were Mixed White and Black Caribbean.

The 1991 census ethnicity categories were:

White British Irish Any other White background
Asian or Asian British Indian Pakistani Bangladeshi Any other Asian background
Black or Black British Caribbean African Any other Black background
Other ethnic groups Chinese Any other ethnic group

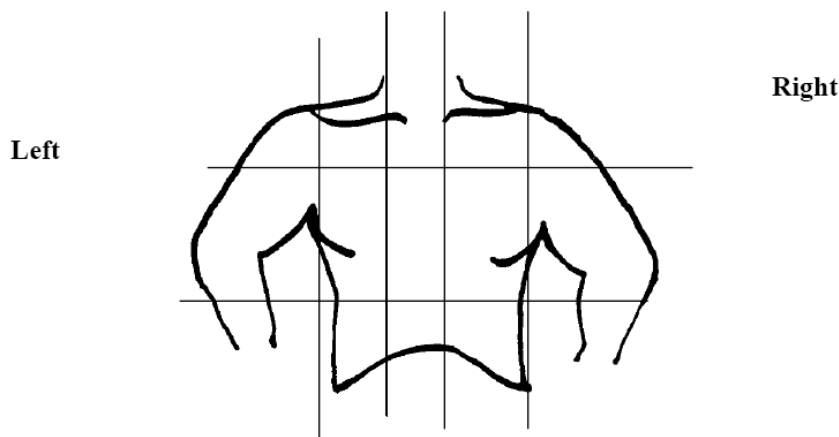
13.2 International Classification of diseases 2007 version- Ischaemic heart disease

I20	Angina pectoris
I20.0	Unstable angina
I20.1	Angina pectoris with documented spasm
I20.8	Other forms of angina pectoris
I20.9	Angina pectoris, unspecified
I21	Acute myocardial infarction
I21.0	Acute transmural myocardial infarction of anterior wall
I21.1	Acute transmural myocardial infarction of inferior wall
I21.2	Acute transmural myocardial infarction of other sites
I21.3	Acute transmural myocardial infarction of unspecified site
I21.4	Acute subendocardial myocardial infarction
I21.9	Acute myocardial infarction, unspecified
I22	Subsequent myocardial infarction
I22.0	Subsequent myocardial infarction of anterior wall
I22.1	Subsequent myocardial infarction of inferior wall
I22.8	Subsequent myocardial infarction of other sites
I22.9	Subsequent myocardial infarction of unspecified site
I23	Certain current complications following acute myocardial infarction
I23.0	Haemopericardium as current complication following acute myocardial infarction
I23.1	Atrial septal defect as current complication following acute myocardial infarction
I23.2	Ventricular septal defect as current complication following acute myocardial infarction
I23.3	Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction

I23.4	Rupture of chordae tendineae as current complication following acute myocardial infarction
I23.5	Rupture of papillary muscle as current complication following acute myocardial infarction
I23.6	Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction
I23.8	Other current complications following acute myocardial infarction
I24	Other acute ischaemic heart diseases
I24.0	Coronary thrombosis not resulting in myocardial infarction
I24.1	Dressler's syndrome
I24.8	Other forms of acute ischaemic heart disease
I24.9	Acute ischaemic heart disease, unspecified
I25	Chronic ischaemic heart disease
I25.0	Atherosclerotic cardiovascular disease, so described
I25.1	Atherosclerotic heart disease
I25.2	Old myocardial infarction
I25.3	Aneurysm of heart
I25.4	Coronary artery aneurysm
I25.5	Ischaemic cardiomyopathy
I25.6	Silent myocardial ischaemia
I25.8	Other forms of chronic ischaemic heart disease
I25.9	Chronic ischaemic heart disease, unspecified

13.3 Rose angina questionnaire

1. Have you ever had any pain or discomfort in your chest? Yes No
- a) Do you get this pain or discomfort when you walk uphill or in a hurry? Yes No
- b) Do you get it when you walk at an ordinary pace on the level? Yes No
- c) When you get any pain or discomfort in your chest, what do you do?
 Stop Slow down Continue at the same pace
- d) Does it go away when you stand still? Yes No
- e) How soon? in 10 minutes or less More than 10 minutes
- f) Where do you get this pain or discomfort? Mark the place(s) with an X on the diagram^a



^a In the Rose angina questionnaire, angina is defined as being present in subjects who answer as follows: Q1: yes; Q1a or Q1b: yes; Q1c: stop or slow down; Q1d: relieved; Q1e: 10 minutes or less; Q1f: either (a) sternum (upper or middle or lower) or (b) left anterior chest and left arm

13.4 Incidence of coronary disease MEDLINE literature search strategy

1. MEDLINE; exp CORONARY DISEASE/; 148892 results.
2. MEDLINE; "coronary disease\$.af; 122799 results.
3. MEDLINE; "coronary heart disease\$.af; 30935 results.
4. MEDLINE; coronary\$.af; 308926 results.
5. MEDLINE; exp MYOCARDIAL INFARCTION/; 119450 results.
6. MEDLINE; "myocardial infarction\$.af; 149432 results.
7. MEDLINE; exp MYOCARDIAL ISCHEMIA/; 286602 results.
8. MEDLINE; exp CARDIOVASCULAR DISEASES/; 1471574 results.
9. MEDLINE; 2 OR 3 OR 4 OR 6 OR 8; 1542777 results.
10. MEDLINE; exp INCIDENCE/; 119216 results.
11. MEDLINE; Incidence.af; 422668 results.
12. MEDLINE; 9 and (10 or 11); 72317 results.
13. MEDLINE; exp ASIAN CONTINENTAL ANCESTRY GROUP/; 18210 results.
14. MEDLINE; exp INDIA/eh (eh=Ethnology); 2540 results.
15. MEDLINE; india\$.ti,ab; 56482 results.
16. MEDLINE; exp SRI LANKA/eh (eh=Ethnology); 86 results.
17. MEDLINE; "sri lanka\$.ti,ab; 2497 results.
18. MEDLINE; exp BANGLADESH/eh (eh=Ethnology); 324 results.
19. MEDLINE; "bangladesh\$.ti,ab; 4610 results.
20. MEDLINE; exp PAKISTAN/eh (eh=Ethnology); 618 results.
21. MEDLINE; "pakistan\$.ti,ab; 6191 results.
22. MEDLINE; exp EUROPE/eh (eh=Ethnology); 7364 results.
23. MEDLINE; exp EUROPEAN CONTINENTAL ANCESTRY GROUP/; 35109 results.
24. MEDLINE; european\$.ti,ab; 73839 results.
25. MEDLINE; White\$.ti,ab; 166506 results.
26. MEDLINE; 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21; 86227 results.
27. MEDLINE; 22 OR 23 OR 24 OR 25; 264106 results.
28. MEDLINE; 12 and 26 and 27; 137 results.

13.5 Prognosis of coronary disease MEDLINE literature search strategy

1. MEDLINE; exp CORONARY DISEASE/; 148892 results.
2. MEDLINE; "coronary disease\$".af; 122799 results.
3. MEDLINE; "coronary heart disease\$".af; 30935 results.
4. MEDLINE; coronary\$.af; 308926 results.
5. MEDLINE; exp MYOCARDIAL INFARCTION/; 119450 results.
6. MEDLINE; "myocardial infarction\$".af; 149432 results.
7. MEDLINE; exp MYOCARDIAL ISCHEMIA/; 286602 results.
8. MEDLINE; exp CARDIOVASCULAR DISEASES/; 1471574 results.
9. MEDLINE; ("coronary disease\$".af) OR ("coronary heart disease\$".af) OR (coronary\$.af) OR ("myocardial infarction\$".af) OR (exp CARDIOVASCULAR DISEASES/); 1542777 results.
10. MEDLINE; (exp CORONARY DISEASE/) OR ("coronary disease\$".af) OR ("coronary heart disease\$".af) OR (coronary\$.af) OR (exp MYOCARDIAL INFARCTION/) OR ("myocardial infarction\$".af) OR (exp MYOCARDIAL ISCHEMIA/) OR (exp CARDIOVASCULAR DISEASES/) OR (("coronary disease\$".af) OR ("coronary heart disease\$".af) OR (coronary\$.af) OR ("myocardial infarction\$".af) OR (exp CARDIOVASCULAR DISEASES/)); 192810 results.
11. MEDLINE; (exp CORONARY DISEASE/) OR ("coronary disease\$".af) OR ("coronary heart disease\$".af) OR (coronary\$.af) OR (exp MYOCARDIAL INFARCTION/) OR ("myocardial infarction\$".af) OR (exp MYOCARDIAL ISCHEMIA/) OR (exp CARDIOVASCULAR DISEASES/) OR (("coronary disease\$".af) OR ("coronary heart disease\$".af) OR (coronary\$.af) OR ("myocardial infarction\$".af) OR (exp CARDIOVASCULAR DISEASES/)); 237093 results.
12. MEDLINE; (exp CORONARY DISEASE/) OR ("coronary disease\$".af) OR ("coronary heart disease\$".af) OR (coronary\$.af) OR (exp MYOCARDIAL INFARCTION/) OR ("myocardial infarction\$".af) OR (exp MYOCARDIAL ISCHEMIA/) OR (exp CARDIOVASCULAR DISEASES/) OR (("coronary disease\$".af) OR ("coronary heart disease\$".af) OR (coronary\$.af) OR ("myocardial infarction\$".af) OR (exp CARDIOVASCULAR DISEASES/)); 63612 results.
13. MEDLINE; exp ASIAN CONTINENTAL ANCESTRY GROUP/; 18210 results.
14. MEDLINE; exp INDIA/eh; 2540 results.
15. MEDLINE; india\$.ti,ab; 56482 results.
16. MEDLINE; exp SRI LANKA/eh; 86 results.

17. MEDLINE; "sri lanka\$.ti,ab; 2497 results.
18. MEDLINE; exp BANGLADESH/eh; 324 results.
19. MEDLINE; "bangladesh\$.ti,ab; 4610 results.
20. MEDLINE; exp PAKISTAN/eh; 618 results.
21. MEDLINE; "pakistan\$.ti,ab; 6191 results.
22. MEDLINE; exp EUROPE/eh; 7364 results.
23. MEDLINE; exp EUROPEAN CONTINENTAL ANCESTRY GROUP/; 35109 results.
24. MEDLINE; european\$.ti,ab; 73839 results.
25. MEDLINE; White\$.ti,ab; 166506 results.
26. MEDLINE; (exp ASIAN CONTINENTAL ANCESTRY GROUP/) OR (exp INDIA/eh) OR (india\$.ti,ab) OR (exp SRI LANKA/eh) OR ("sri lanka\$.ti,ab) OR (exp BANGLADESH/eh) OR ("bangladesh\$.ti,ab) OR (exp PAKISTAN/eh) OR ("pakistan\$.ti,ab); 86227 results.
27. MEDLINE; (exp EUROPE/eh) OR (exp EUROPEAN CONTINENTAL ANCESTRY GROUP/) OR (european\$.ti,ab) OR (White\$.ti,ab); 264106 results.
28. MEDLINE; ((exp CORONARY DISEASE/) OR ("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR (exp MYOCARDIAL INFARCTION/) OR ("myocardial infarction\$.af) OR (exp MYOCARDIAL ISCHEMIA/) OR (exp CARDIOVASCULAR DISEASES/) OR (("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR ("myocardial infarction\$.af) OR (exp CARDIOVASCULAR DISEASES/))) AND ((exp ASIAN CONTINENTAL ANCESTRY GROUP/) OR (exp INDIA/eh) OR (india\$.ti,ab) OR (exp SRI LANKA/eh) OR ("sri lanka\$.ti,ab) OR (exp BANGLADESH/eh) OR ("bangladesh\$.ti,ab) OR (exp PAKISTAN/eh) OR ("pakistan\$.ti,ab)) AND ((exp EUROPE/eh) OR (exp EUROPEAN CONTINENTAL ANCESTRY GROUP/) OR (european\$.ti,ab) OR (White\$.ti,ab)); 98 results.
29. MEDLINE; ((exp CORONARY DISEASE/) OR ("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR (exp MYOCARDIAL INFARCTION/) OR ("myocardial infarction\$.af) OR (exp MYOCARDIAL ISCHEMIA/) OR (exp CARDIOVASCULAR DISEASES/) OR (("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR ("myocardial infarction\$.af) OR (exp CARDIOVASCULAR DISEASES/))) AND ((exp ASIAN CONTINENTAL ANCESTRY GROUP/) OR (exp INDIA/eh) OR (india\$.ti,ab) OR (exp SRI LANKA/eh) OR ("sri lanka\$.ti,ab) OR (exp BANGLADESH/eh) OR ("bangladesh\$.ti,ab) OR (exp PAKISTAN/eh) OR ("pakistan\$.ti,ab)) AND ((exp EUROPE/eh) OR (exp EUROPEAN CONTINENTAL ANCESTRY GROUP/) OR (european\$.ti,ab) OR (White\$.ti,ab)); 253 results.
30. MEDLINE; ((exp CORONARY DISEASE/) OR ("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR (exp MYOCARDIAL INFARCTION/) OR ("myocardial infarction\$.af) OR (exp MYOCARDIAL

ISCHEMIA/) OR (exp CARDIOVASCULAR DISEASES/) OR (("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR ("myocardial infarction\$.af) OR (exp CARDIOVASCULAR DISEASES/))) AND ((exp ASIAN CONTINENTAL ANCESTRY GROUP/) OR (exp INDIA/eh) OR (india\$.ti,ab) OR (exp SRI LANKA/eh) OR ("sri lanka\$.ti,ab) OR (exp BANGLADESH/eh) OR ("bangladesh\$.ti,ab) OR (exp PAKISTAN/eh) OR ("pakistan\$.ti,ab)) AND ((exp EUROPE/eh) OR (exp EUROPEAN CONTINENTAL ANCESTRY GROUP/) OR (european\$.ti,ab) OR (White\$.ti,ab)); 316 results.

31. MEDLINE; exp PROGNOSIS/; 639740 results.

32. MEDLINE; prognosis.af; 356881 results.

33. MEDLINE; (exp CORONARY DISEASE/) OR ("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR (exp MYOCARDIAL INFARCTION/) OR ("myocardial infarction\$.af) OR ("myocardial infarction\$.af) OR (exp CARDIOVASCULAR DISEASES/) OR ("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR ("myocardial infarction\$.af) OR (exp CARDIOVASCULAR DISEASES/)); 1560108 results.

34. MEDLINE; ((exp CORONARY DISEASE/) OR ("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR (exp MYOCARDIAL INFARCTION/) OR ("myocardial infarction\$.af) OR ("myocardial infarction\$.af) OR (exp CARDIOVASCULAR DISEASES/) OR ("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR ("myocardial infarction\$.af) OR (exp CARDIOVASCULAR DISEASES/))) AND ((exp PROGNOSIS/) OR (prognosis.af)); 136554 results.

35. MEDLINE; (((exp CORONARY DISEASE/) OR ("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR (exp MYOCARDIAL INFARCTION/) OR ("myocardial infarction\$.af) OR ("myocardial infarction\$.af) OR (exp CARDIOVASCULAR DISEASES/) OR ("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR ("myocardial infarction\$.af) OR (exp CARDIOVASCULAR DISEASES/))) AND ((exp PROGNOSIS/) OR (prognosis.af))) AND ((exp ASIAN CONTINENTAL ANCESTRY GROUP/) OR (exp INDIA/eh) OR (india\$.ti,ab) OR (exp SRI LANKA/eh) OR ("sri lanka\$.ti,ab) OR (exp BANGLADESH/eh) OR ("bangladesh\$.ti,ab) OR (exp PAKISTAN/eh) OR ("pakistan\$.ti,ab)) AND ((exp EUROPE/eh) OR (exp EUROPEAN CONTINENTAL ANCESTRY GROUP/) OR (european\$.ti,ab) OR (White\$.ti,ab)); 59 results.

36. MEDLINE; ((exp CORONARY DISEASE/) OR ("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR (exp MYOCARDIAL INFARCTION/) OR ("myocardial infarction\$.af) OR ("myocardial infarction\$.af) OR (exp CARDIOVASCULAR DISEASES/) OR ("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR ("myocardial infarction\$.af) OR (exp CARDIOVASCULAR DISEASES/))) AND ((exp PROGNOSIS/) OR (prognosis.af)); 138044 results.

37. MEDLINE; (((exp CORONARY DISEASE/) OR ("coronary disease\$.af) OR ("coronary heart disease\$.af) OR

(coronary\$.af) OR (exp MYOCARDIAL INFARCTION/) OR ("myocardial infarction\$.af) OR ("myocardial infarction\$.af) OR (exp CARDIOVASCULAR DISEASES/) OR (("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR ("myocardial infarction\$.af) OR (exp CARDIOVASCULAR DISEASES/))) AND ((exp PROGNOSIS/) OR (prognosis.af))) AND ((exp ASIAN CONTINENTAL ANCESTRY GROUP/) OR (exp INDIA/eh) OR (india\$.ti,ab) OR (exp SRI LANKA/eh) OR ("sri lanka\$.ti,ab) OR (exp BANGLADESH/eh) OR ("bangladesh\$.ti,ab) OR (exp PAKISTAN/eh) OR ("pakistan\$.ti,ab)) AND ((exp EUROPE/eh) OR (exp EUROPEAN CONTINENTAL ANCESTRY GROUP/) OR (european\$.ti,ab) OR (White\$.ti,ab)); 59 results.

38. MEDLINE; exp FOLLOW-UP STUDIES/; 378507 results.

39. MEDLINE; follow-up.af; 642761 results.

40. MEDLINE; exp TREATMENT OUTCOME/; 365669 results.

41. MEDLINE; (disease AND outcome).af; 206093 results.

42. MEDLINE; ((exp CORONARY DISEASE/) OR ("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR (exp MYOCARDIAL INFARCTION/) OR ("myocardial infarction\$.af) OR ("myocardial infarction\$.af) OR (exp CARDIOVASCULAR DISEASES/) OR (("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR ("myocardial infarction\$.af) OR (exp CARDIOVASCULAR DISEASES/))) AND ((exp PROGNOSIS/) OR (prognosis.af) OR (exp FOLLOW-UP STUDIES/) OR (follow-up.af) OR (exp TREATMENT OUTCOME/) OR ((disease AND outcome).af)); 237774 results.

43. MEDLINE; (((exp CORONARY DISEASE/) OR ("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR (exp MYOCARDIAL INFARCTION/) OR ("myocardial infarction\$.af) OR ("myocardial infarction\$.af) OR (exp CARDIOVASCULAR DISEASES/) OR (("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR ("myocardial infarction\$.af) OR (exp CARDIOVASCULAR DISEASES/))) AND ((exp PROGNOSIS/) OR (prognosis.af) OR (exp FOLLOW-UP STUDIES/) OR (follow-up.af) OR (exp TREATMENT OUTCOME/) OR ((disease AND outcome).af))) AND ((exp ASIAN CONTINENTAL ANCESTRY GROUP/) OR (exp INDIA/eh) OR (india\$.ti,ab) OR (exp SRI LANKA/eh) OR ("sri lanka\$.ti,ab) OR (exp BANGLADESH/eh) OR ("bangladesh\$.ti,ab) OR (exp PAKISTAN/eh) OR ("pakistan\$.ti,ab)) AND ((exp EUROPE/eh) OR (exp EUROPEAN CONTINENTAL ANCESTRY GROUP/) OR (european\$.ti,ab) OR (White\$.ti,ab)); 133 results.

44. MEDLINE; (((exp CORONARY DISEASE/) OR ("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR (exp MYOCARDIAL INFARCTION/) OR ("myocardial infarction\$.af) OR ("myocardial infarction\$.af) OR (exp CARDIOVASCULAR DISEASES/) OR (("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR ("myocardial infarction\$.af) OR (exp CARDIOVASCULAR DISEASES/))) AND ((exp PROGNOSIS/) OR (prognosis.af) OR (exp FOLLOW-UP STUDIES/) OR (follow-up.af) OR (exp TREATMENT OUTCOME/) OR ((disease AND outcome).af))) AND ((exp ASIAN CONTINENTAL ANCESTRY GROUP/) OR (exp

INDIA/eh) OR (india\$.ti,ab) OR (exp SRI LANKA/eh) OR ("sri lanka\$.ti,ab) OR (exp BANGLADESH/eh) OR ("bangladesh\$.ti,ab) OR (exp PAKISTAN/eh) OR ("pakistan\$.ti,ab)) AND ((exp EUROPE/eh) OR (exp EUROPEAN CONTINENTAL ANCESTRY GROUP/) OR (european\$.ti,ab) OR (White\$.ti,ab))) NOT (((exp CORONARY DISEASE/) OR ("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR (exp MYOCARDIAL INFARCTION/) OR ("myocardial infarction\$.af) OR ("myocardial infarction\$.af) OR (exp CARDIOVASCULAR DISEASES/) OR ("coronary disease\$.af) OR ("coronary heart disease\$.af) OR (coronary\$.af) OR ("myocardial infarction\$.af) OR (exp CARDIOVASCULAR DISEASES/))) AND ((exp PROGNOSIS/) OR (prognosis.af))) AND ((exp ASIAN CONTINENTAL ANCESTRY GROUP/) OR (exp INDIA/eh) OR (india\$.ti,ab) OR (exp SRI LANKA/eh) OR ("sri lanka\$.ti,ab) OR (exp BANGLADESH/eh) OR ("bangladesh\$.ti,ab) OR (exp PAKISTAN/eh) OR ("pakistan\$.ti,ab)) AND ((exp EUROPE/eh) OR (exp EUROPEAN CONTINENTAL ANCESTRY GROUP/) OR (european\$.ti,ab) OR (White\$.ti,ab))); 74 results.

13.6 Search Strategies for prognosis in MEDLINE in Ovid Syntax and the PubMed translation

For prognosis, the following data are shown: the single term with the highest sensitivity while keeping specificity at 50%; the single term with the highest specificity while keeping the sensitivity at 50%; the single term with the least (minimal) absolute difference between sensitivity and specificity; and then the same data for multiple terms (the single term strategy may be shown again if it performs at least as well as multiple terms). In the second column of the table the search strategies are shown in Ovid syntax followed by the PubMed translation. In the third column of the table: sens = sensitivity; spec = specificity; prec = precision; acc = accuracy.

Prognosis		
Strategy type	Ovid Strategy	Sens / spec / prec / acc (%)
	PubMed Translation	
1 term high sensitivity	exp epidemiologic studies	65 / 79 / 1 / 79
	epidemiologic studies(MeSH term)	
1 term high specificity	exp epidemiologic studies	65 / 79 / 1 / 79
	epidemiologic studies(MeSH term)	
1 term min difference	exp epidemiologic studies	65 / 79 / 1 / 79
	epidemiologic studies(MeSH term)	
2 or more terms high sensitivity	incidence.sh. OR exp mortality OR follow-up studies.sh. OR prognos:.tw. OR predict:.tw. OR course:.tw.	90 / 80 / 2 / 80
	incidence(MeSH:noexp) OR	

	mortality(MeSH Terms) OR follow up studies(MeSH:noexp) OR prognos*(Text Word) OR predict*(Text Word) OR course*(Text Word)	
2 or more terms high specificity	prognos:.tw. OR first episode.tw. OR cohort.tw.	52 / 94 / 3 / 94
	prognos*(Title/Abstract) OR (first(Title/Abstract) AND episode(Title/Abstract)) OR cohort(Title/Abstract)	
2 or more terms min difference	prognosis.sh. OR diagnosed.tw. OR cohort:.mp. OR predictor:.tw. OR death.tw. OR exp models, statistical	83 / 84 / 2 / 84
	prognosis(MeSH:noexp) OR diagnosed(Title/Abstract) OR cohort*(Title/Abstract) OR cohort effect(MeSH Term) OR cohort studies(MeSH:noexp) OR predictor*(Title/Abstract) OR death(Title/Abstract) OR "models, statistical"(MeSH Term)	

With thanks to Bridget Cole, Trust Librarian, Sir Thomas Browne Library,
Norfolk & Norwich University Hospitals NHS Foundation Trust

13.7 Deprivation scores

13.7.1 Indices of Multiple Deprivation

The Indices of Multiple Deprivation are measures of deprivation for every area in England. The Index consists of 33 indicators of need which have been statistically condensed into six themes with some given more importance or weight than others:

- Income deprivation (two and a half times the importance of the lowest).
- Employment deprivation (two and a half times the importance of the lowest).
- Health deprivation/disability (one and a half times the importance of the lowest).
- Education/skills and training deprivation (one and a half times the importance of the lowest).
- Housing deprivation (joint lowest importance).
- Geographical access to services (joint lowest importance).

Indices of Multiple Deprivation are based on a range of administrative data and have the advantage that as they are not based solely on census results they can be updated more than once every ten years. The indices combine these indicators into a single deprivation score for each small area in England. This allows each area to be ranked relative to one another according to their level of deprivation. In 2000, they were measured at a ward level which may not take into account heterogeneity within that area. IMD 2004 and 2007 used the smaller Lower Super Output Area level, of which there are 32,482 in the country.

13.7.2 Carstairs

Carstairs scores are an unweighted combination of four census variables: unemployment, overcrowding, car ownership and low social class (Social Class IV and V). The definitions used by the Office for National Statistics for the 2001 scores are shown below:

Unemployment	Overcrowding	Car ownership	Low Social Class
Unemployed males 16 and over as a proportion of all economically active males aged 16 and over.	Persons in households with one or more persons per room as a proportion of all residents in households.	Residents in households with no car as a proportion of all residents in households.	Residents in households with an economically active head of household in Social Class IV or V approximated from NS-SEC (see Table 3) as a proportion of all residents in households.

Each variable is standardised (z-scored) to avoid the score being unduly influenced by a high or low value for any one variable and to put each variable on the same scale, centred around zero. This is done for each variable by subtracting the mean of the observations for all wards in England and Wales from the value of that variable for each ward and dividing by the standard deviation for that variable. The resulting values for each variable are summed to give a single score for that ward. The scores can be either positive (more deprived) or negative (less deprived).

13.7.3 Townsend

The Townsend Score is derived from the following census variables:

- Unemployment - the percentage of economically active residents aged 16-59/64 who are unemployed.
- Car ownership - the percentage of private households who do not possess a car.
- Home ownership - the percentage of private households not owner occupied.
- Overcrowding- the percentage of private households with more than one person per room.

The Townsend Score is a summation of the standardised scores (z scores) for each variable (scores higher than zero indicate higher levels of material deprivation).

13.8 Terminology for description of people

In the general description of persons who may be relevant to this work, I have used the terms people and populations.

When specifically discussing those within the studies of this thesis, I used the term participants when referring to the healthy population of Whitehall-II and to those in Chest Pain Clinic study, who have yet to be diagnosed with disease. For those participating in ACRE and MINAP, I have used the term patient. For general discussion of these participants, I continue to use the terms people and populations.

Towards the end, I discuss all people – whether describing those in general or those in the studies of this thesis - as part of populations or as patients rather than as participants of studies.

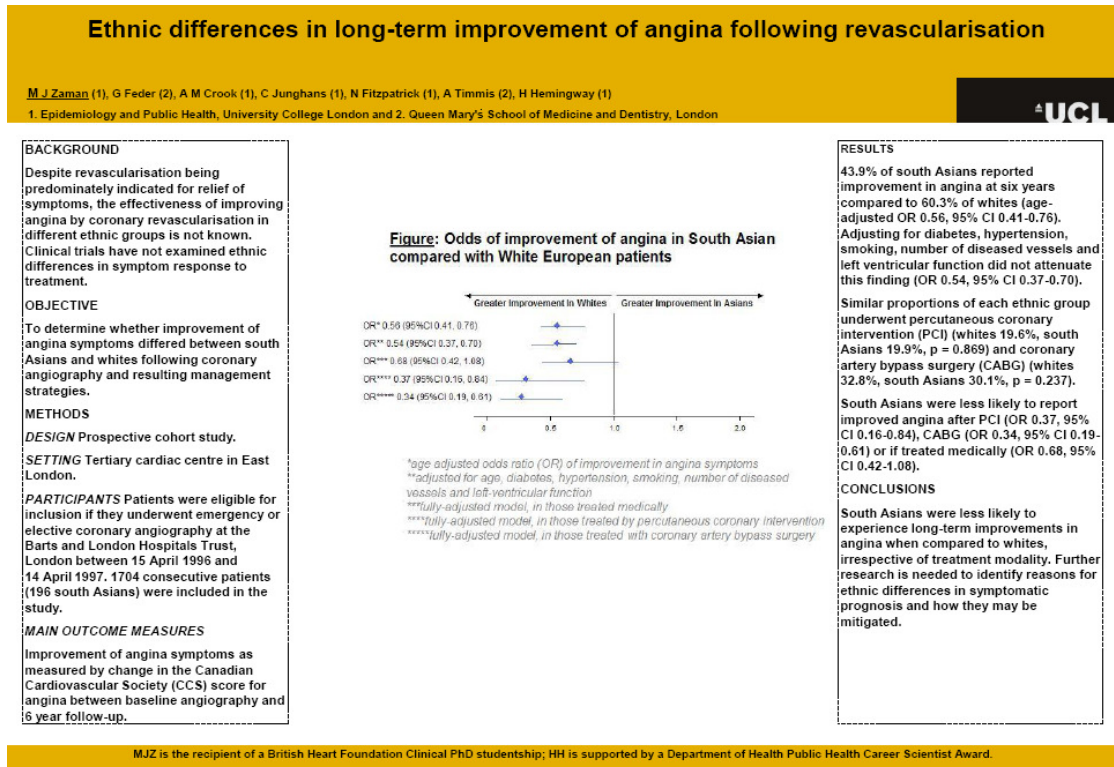
13.9 Fonts

The text is written in Cambria, the figures/tables in Calibri

14 Abstracts

14.1 ACRE

Zaman MJ, Feder G, Crook AM, Junghans C, Fitzpatrick N, Timmis A, Hemingway H. Ethnic differences in long-term improvement of angina following revascularization. *World Congress of Cardiology 2006*, Barcelona, Spain



14.2 Chest pain clinic

Zaman MJ, Junghans C, Sekhri N, Chen R, Feder G, Timmis A, Hemingway H. Stable Angina Histories - Do Sex And Ethnic Differences Matter?- A Prospective Study In 7794 Ambulatory Patients. *AHA Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke* 2007, Washington DC, USA

STABLE ANGINA HISTORIES - DO SEX AND ETHNIC DIFFERENCES MATTER? - A PROGNOSTIC STUDY IN 7794 AMBULATORY PATIENTS

M. J. Zaman (1), C. Junghans (1), N. Sekhri (2), R. Chen (1), G. Feder (3), A. Timmis (3), H. Hemingway (1)
 1. University College London, 2. Newham University Hospital, London and 3. Queen Mary's School of Medicine and Dentistry, London

BACKGROUND
 Descriptors of stable angina pectoris were derived largely in white men and their diagnostic and prognostic validity in women and ethnic minorities is unknown. It is widely perceived that the descriptors of angina are non-typical in women and in South Asians. Both women and South Asian patients are less likely to undergo invasive management of coronary disease than men and whites.

OBJECTIVE
 To determine the extent of sex and ethnic differences in the diagnostic and prognostic value of detailed components of a patient's history of chest pain, and whether differences can account for inequalities in management.

METHODS
DESIGN Prospective cohort study.
SETTING 6 Rapid access chest pain clinics (RACPC) in the UK
PARTICIPANTS Prospective, multi-centre cohort study of consecutive patients attending 6 rapid access chest pain clinics in the UK (2676 white women, 2929 white men, 980 South Asian women, 1209 South Asian men).
EXPOSURE Patients with three or more typical descriptors* (location, duration, quality and provocation) were defined as having typical cardiac chest pain.
OUTCOMES Death due to coronary disease or admission with acute coronary syndrome over mean follow-up of 5 years and receipt of angiography and revascularization over 3 years.

Table 1

	Women			Men		
	South Asian (n=980)	white (n=2676)	p	South Asian (n=1209)	white (n=2929)	p
Pain						
Typical	388 (39.4%)	1243 (46.5%)		482 (40.7%)	1509 (51.5%)	
Non-typical	594 (60.6%)	1433 (53.5%)	<0.001	717 (59.3%)	1420 (48.5%)	<0.001

SEX

ETHNICITY

Table 2

			Outcome		
			Coronary outcome	Angiography	Revasc
Pain	Typical	South Asians vs. whites	0.97 (0.74, 1.27)	0.52 (0.42, 0.64)	0.39 (0.29, 0.53)
		Women vs. men	0.89 (0.71, 1.11)	0.54 (0.46, 0.64)	0.28 (0.22, 0.37)
Non-typical	South Asians vs. whites		1.13 (0.79, 1.60)	0.62 (0.45, 0.85)	0.51 (0.37, 1.02)
		Women vs. men	0.60 (0.43, 0.82)	0.56 (0.43, 0.74)	0.29 (0.17, 0.48)

Hazard ratios with 95% confidence intervals adjusted for age, sex or ethnicity, diabetes, smoking and hypertension

RESULTS
 South Asians of both sexes were more likely to report non-typical chest pain compared to whites (table 1). Typical symptoms predicted angina diagnosis across both sexes and ethnic groups. Probability of sustaining the coronary outcome was similar by ethnic group in both those with typical and non-typical pain [KM curves]. Women with non-typical pain were less likely to suffer the coronary outcome than men with non-typical pain.

South Asians and women with both typical [HR 0.39 (95% CI 0.29, 0.53) and HR 0.28 (95% CI 0.22, 0.37) respectively] and non-typical pain were less likely to receive angiography and revascularisation than whites and men respectively [table 2].

CONCLUSIONS
 Though both South Asian women and men attending chest pain clinic had an excess of non-typical chest pain, there were no ethnic or sex differences in the diagnostic or prognostic validity of anginal symptom classification. These findings suggest that sex and ethnic differences in symptom descriptors do not account for inequalities in healthcare.

* Typical descriptors were taken to be pain that was of a constricting quality, located centrally or on the left-side of the chest, lasted more than seconds and up to 15 minutes and was provoked by exercise.

M.J.Z is the recipient of a British Heart Foundation Clinical PhD studentship.

14.3 Systematic review and meta-analysis

Zaman MJ, Chen R, Timmis A, Marmot M, Hemingway H. Increased cardiovascular mortality in minority ethnic groups: a result of increased incidence or case fatality? Four new studies and a meta-analysis in South Asians. *AHA Epidemiology* 2008, Colorado Springs

Increased coronary heart disease mortality in South Asians: a result of increased incidence or case fatality? A systematic review and meta-analysis of cohort studies.

MJ Zaman (1), R Chen (1), G Feder (2), A Timmis (2), M Marmot (1), H Hemingway (1)

1. University College London, 2. Barts and the London School of Medicine and Dentistry, United Kingdom

INTRODUCTION

Coronary heart disease death rates among South Asians in high income countries are higher than those of the white majority population. The relative contribution of incidence and case fatality to the high coronary mortality rates observed in South Asians is not known.

OBJECTIVES

We aimed to investigate whether South Asians suffer an increased incidence of coronary disease as well as an increased case fatality when presenting with coronary disease by systematically reviewing the literature and meta-analysing the results with our own studies on aetiology and prognosis of coronary disease across a spectrum of presentations of coronary disease.

METHODS

Our own four studies comprised of three prognostic cohorts - the ACRE (Appropriateness of Coronary Revascularisation) angiographic cohort of stable coronary disease, the chest pain clinic (CPC) incident angina cohort, the Myocardial Infarction National Audit Project (MINAP) of acute coronary syndrome patients, and one aetiological - the Whitehall II study of civil servants. We thus contributed 14244 events in MINAP, 651 events in ACRE and 287 events in CPC, Whitehall II contributing 101 events. A systematic literature review was carried out using MEDLINE 1966-2007 and citations from references. We calculated pooled odds ratios, and 95% confidence intervals using a random effects model. The summary estimates used in the meta-analysis were those adjusted for as many baseline coronary disease risk factors as given. We examined coronary death endpoints wherever possible, though accepted all-cause deaths in acute coronary syndrome cohorts.

Study ID	no. of events	no. of patients	ES (95% CI)	% Weight
Forouhi 2006	94/787	106/1420	3.75 (2.27, 6.10)	16.30
Whitehall II	80/9184	215/77	1.88 (1.21, 2.94)	85.70
INCIDENCE (I-squared 62.3%, p=0.070)			2.02 (1.23, 3.31)	100.00
Hughes 1990	2950	2923	2.17 (0.97, 4.80)	0.11
Chest pain clinic (angina)	236/6895	512/189	0.82 (0.29, 2.61)	0.41
Wilkinson 1996	325/3	23/149	1.44 (0.79, 2.61)	0.51
Cajka 2001	38/53	45/53	1.26 (0.82, 1.92)	1.42
ACRE (coronary angiogram)	56/72974	64/502	0.80 (0.47, 1.38)	2.13
Liew 2003	56/689	19/303	0.78 (0.45, 1.34)	2.17
Fitzhaker 2006	296/721306	49/105	0.59 (0.43, 0.81)	11.08
MINAP (acute coronary)	13024/4216	320/223	0.83 (0.73, 0.95)	34.85
Mak 2003	2942/7102	503/224	0.81 (0.72, 0.91)	46.72
PROGNOSIS (I-squared 30.5%, p=0.174)			0.81 (0.74, 0.87)	100.00

Hazard ratios with 95% confidence intervals

RESULTS

Aetiological studies examining the incidence of coronary disease in healthy populations found that South Asians had higher rates of incident coronary events (pooled OR 2.02, 95% CI 1.23-3.31). For prognosis, survival after presentation with coronary disease was better in South Asians (pooled OR 0.81 95% CI 0.74-0.87).

SUMMARY OF CONCLUSIONS

In contrast to the higher incidence of coronary disease in South Asians compared to whites, once coronary disease is manifest, their prognosis is better.

The dissociation between the aetiological and prognostic findings has implications for the understanding of disease progression, and suggests that public health efforts to reduce disparities in mortality should focus on primary prevention rather than provision of healthcare to those with disease.

MJSZ is the recipient of a British Heart Foundation Clinical PhD studentship

14.4 The Whitehall-II study

Zaman MJ, Shipley M, Stafford M, Brunner E, Marmot M, Timmis AD, Hemingway H. The incidence, character and prognosis of angina in South Asian and European populations. *EuroPrevent* 2008, Paris, France

The incidence, character and prognosis of angina in South Asian and European populations – the Whitehall II study, UK

M.J Zaman (1), M Shipley (1), M Stafford (1), E Brunner (1), M G Marmot (1), A D Timmis (2), H Hemingway (1)
1. University College London, 2. Barts and The London Hospitals, London



BACKGROUND

The explanation for higher coronary death rates in South Asians compared to white populations may be the result of a higher incidence of disease in South Asians. Most new onset coronary disease is non-fatal, but incident rates of angina are as yet unknown in South Asians. The diagnosis of angina is perceived to be more difficult in South Asians as they are often labelled as having 'atypical' pain when presenting with ischaemia, and the utility of the Rose questionnaire [RQ] for angina in South Asian populations has been questioned.

PURPOSE

We sought to determine the cumulative incidence of angina in South Asians compared to whites in the Whitehall II cohort study of British civil servants. Furthermore, we examined the prognosis of differing forms of chest pain by ethnicity.

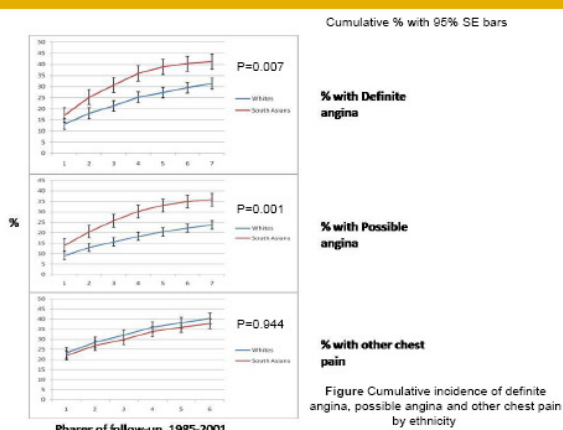
METHODS

DESIGN Prospective cohort study.

SETTING London civil service offices and community follow-up.

PARTICIPANTS Prospective, multi-centre cohort study of all non-industrial civil servants aged 35–55 years who worked in the London offices of 20 civil service departments. The cohort consisted of 9195 whites and 560 South Asians.

OUTCOMES Chest pain was categorised as 'definite' angina, 'possible' angina and 'other' [non-Rose-possible] using the RQ. The outcome was a measure of coronary death and non-fatal myocardial infarction (NFMi) at phase 7 [2003-2004].



RESULTS

There were no differences in the prevalence of all three categories of chest pain at baseline between South Asians and whites. With follow-up, there was a higher cumulative incidence of definite [41.2% vs 31.3%, $z=2.71$, $p=0.007$] and possible angina [35.9% vs 23.7%, $z=3.28$, $p=0.007$] amongst South Asians compared to whites. On the contrary, South Asians did not demonstrate a higher cumulative incidence of other types of chest pain. [42.8% vs 43.1%, $z=0.07$, $p=0.944$]

In both ethnic groups, angina that was definite or possible predicted likelihood of coronary outcomes when compared to those with no chest pain [fully-adjusted HR 2.94 (1.59,5.43) in South Asians with definite angina]. Other chest pain did not predict coronary outcomes in either ethnic group pain [fully-adjusted HR 0.85 (0.40,1.82) in South Asians with other chest pain].

CONCLUSIONS

South Asians demonstrated a higher cumulative incidence of angina of a cardiac nature than whites. This angina, as ascertained by the Rose questionnaire, was predictive of coronary events. Our findings demonstrate that South Asians have a genuinely increased incidence of prognostically-significant angina, and that the Rose questionnaire can be used in South Asians to predict prognosis.

Chest pain [at phases 1,2 or 3]	Outcome – non-fatal myocardial infarction or coronary death – compared to those with no chest pain	Age and sex-adjusted	Adjusted for age, sex, hypertension, blood cholesterol, ex/current smoker, overweight, diabetes, living alone, family history and grade at work
Definite angina	Whites	2.38 (1.90,2.98)	2.06 (1.64,2.59)
	South Asians	3.15 (1.78,5.57)	2.94 (1.59,5.43)
Possible angina	Whites	2.95 (2.34,3.72)	2.45 (1.93,3.10)
	South Asians	3.26 (1.84,5.76)	2.83 (1.54,5.21)
Other chest pain	Whites	0.75 (0.57,0.98)	0.81 (0.62,1.06)
	South Asians	0.89 (0.44,1.81)	0.85 (0.40,1.82)

MJZ is the recipient of a British Heart Foundation Clinical PhD studentship

15 Papers

15.1 Prognosis of incident typical and non-typical angina

CMAJ

RESEARCH

Presentation of stable angina pectoris among women and South Asian people

M. Justin Zaman MBBS MSc, Cornelia Junghans PhD, Neha Sekhri MBBS, Ruoling Chen MD PhD, Gene S. Feder MD, Adam D. Timmis MBBChir MD, Harry Hemingway MBBChir

See related commentary by Diercks and Miller, page 631

ABSTRACT

Background: There is speculation that women and South Asian people are more likely than men and white people to report atypical angina and that they are less likely to undergo invasive management of angina. We sought to determine whether atypical symptoms of angina pectoris in women and South Asians impacted clinically important outcomes and clinical management.

Methods: We prospectively identified 2189 South Asian people and 5605 white people with recent-onset chest pain at 6 chest-pain clinics in the United Kingdom. We documented hospital admissions for acute coronary syndromes, coronary deaths as well as coronary angiography and revascularization procedures.

Results: Atypical chest pain was reported by more women than men (56.5% vs 54.5%, $p < 0.054$) and by more South Asian patients than white patients (59.9% vs 52.5%, $p < 0.001$). Typical symptoms were associated with coronary death or acute coronary syndromes among women (hazard ratio [HR] 2.30, 95% CI 1.70–3.11, $p < 0.001$) but not among men (HR 1.23, 95% CI 0.96–1.57, $p = 0.10$). Typical symptoms were associated with coronary outcomes in both South Asian and white patients. Among those with typical symptoms, women (HR 0.76, 95% CI 0.63–0.92, $p = 0.004$) and South Asian patients (HR 0.52, 95% CI 0.41–0.67, $p < 0.001$) were less likely than men and white patients to receive angiography.

Interpretation: Compared to those with atypical chest pain, women and South Asian patients with typical pain had worse clinical outcomes. However, sex and ethnic background did not explain differences in the use of invasive procedures.

Une version française de ce résumé est disponible à l'adresse www.cmaj.ca/cgi/content/full/179/7/659/DC1

CMAJ 2008;179(7):659-67

stable angina pectoris is as high or higher in women compared with men. In addition, the prevalence of typical symptoms is higher among people of South Asian descent than among white people.³ Despite these findings, it is widely perceived that women,^{4,6} South Asian people⁷⁻⁹ and other ethnic minorities with suspected ischemia are more likely than white men to report atypical features of pain.^{10,11} This has been attributed to vasospastic and microvascular angina in women¹² and to the higher prevalence of diabetes mellitus¹³ and socio-economic deprivation⁷ among South Asian people.

Both women^{14,15} and South Asian^{16,17} patients are less likely than men and white people in general to undergo invasive management of angina. It has been proposed that differences in how these patients describe their symptoms may contribute to inequalities in medical care,^{8,18} because the diagnostic validity of symptoms plays an important role in deciding appropriate clinical management.¹⁹ However, it is not known if the distinction between typical and atypical symptoms of chronic stable angina pectoris has similar prognostic value for subsequent coronary events in women and men of white and South Asian ethnic backgrounds.

We sought to determine whether the description of angina pain as typical or atypical is associated with coronary outcomes. We also investigated whether differences in how patients report their symptoms is related to the clinical management of angina.

Methods

Population

We recruited 11 082 consecutive patients with recent onset chest pain from 6 rapid-access chest-pain clinics in the United Kingdom from Jan. 2, 1996, to Dec. 31, 2002. These ambulatory care clinics are run by cardiology teams and accept same-day referrals from family physicians of patients with recent-onset chest pain suspected to be stable angina pectoris. These clinics do not accept referrals of patients who have previously been suspected to have coronary disease, who have received a diagnosis of coronary disease, or who received a diagnosis of acute coronary syndromes on the day of the visit.

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The description of symptoms, articulated by patients and recorded by doctors, remains a cornerstone of diagnosis. History-taking is central to the diagnosis of chronic stable angina pectoris, yet "textbook" descriptions have been largely derived and validated among white men.¹ A meta-analysis that included almost 25 000 people from 31 countries² found that the prevalence of typical symptoms of

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15.2 Symptomatic outcomes following coronary angiography in patients with chronic stable angina

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Ethnic differences in long-term improvement of angina following revascularization or medical management: a comparison between south Asians and white Europeans

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ABSTRACT

Background It is not known whether there are disparities in morbidity outcomes between south Asians and whites with established coronary disease.

Methods Six-year prospective cohort study to determine whether improvement of angina symptoms differs between 196 south Asians and 1508 whites following revascularization or medical management.

Results 43.9% of south Asians reported improvement in angina at 6 years compared with 60.3% of whites (age-adjusted OR 0.56, 95% CI 0.41–0.76, adjusted for diabetes, hypertension, smoking, number of diseased vessels, left ventricular function and social class OR 0.59, 95% CI 0.41–0.85). Similar proportions of whites and south Asians underwent percutaneous coronary intervention (PCI) (19.6% versus 19.9%) and coronary artery bypass surgery (CABG) (32.8% versus 30.1%). South Asians were less likely to report improved angina after PCI (OR 0.19, 95% CI 0.06–0.56) or CABG (OR 0.36, 95% CI 0.17–0.74). There was less evidence of ethnic differences in angina improvement when treatment was medical (OR 0.87, 95% CI 0.48–1.57).

Conclusion South Asians were less likely to experience long-term improvements in angina than whites after receipt of revascularization. Further research is needed to identify why these ethnic groups differ in symptomatic prognosis following revascularization for coronary disease and how these differences may be mitigated.

Keywords ethnicity, prognosis, South Asian, stable angina

Background

The cardiovascular mortality^{1–3} of south Asians are often worse than those of the majority population. This may be explained in most part by a higher incidence of cardiovascular disease, as survival among south Asians following myocardial infarction or coronary revascularization appears no worse.^{4–6} However, little is known about the ethnic differences in morbidity outcomes among people with established coronary disease as studies on cardiovascular outcomes following coronary revascularization have tended to focus on mortality and hospitalized clinical events rather than chronic symptoms, despite revascularization being undertaken primarily for symptomatic relief of angina.⁷

Angina is the most prevalent symptomatic manifestation of coronary disease,⁸ a significant burden in primary care,⁹

and has considerable economic implications.¹⁰ The Health Survey for England on minority health reported that morbidity due to angina pectoris may be higher in some minority ethnic populations such as south Asians, a group comprising those of Indian, Pakistani, Bangladeshi and Sri Lankan origin.¹¹ Age-standardized risk ratios for angina were higher for Pakistani men relative to men in the general

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16 Prizes

16.1 Best Poster (Clinical Science), UCL Cardiovascular Science Day 2006

Ethnic differences in long-term improvement of angina following revascularisation

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BACKGROUND

Despite revascularisation being predominately indicated for relief of symptoms, the effectiveness of improving angina by coronary revascularisation in different ethnic groups is not known. Clinical trials have not examined ethnic differences in symptom response to treatment.

OBJECTIVE

To determine whether improvement of angina symptoms differed between south Asians and whites following coronary angiography and resulting management strategies.

METHODS

DESIGN Prospective cohort study.

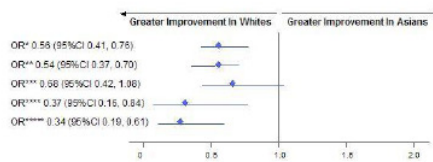
SETTING Tertiary cardiac centre in East London.

PARTICIPANTS Patients were eligible for inclusion if they underwent emergency or elective coronary angiography at the Barts and London Hospitals Trust, London between 15 April 1996 and 14 April 1997. 1704 consecutive patients (196 south Asians) were included in the study.

MAIN OUTCOME MEASURES

Improvement of angina symptoms as measured by change in the Canadian Cardiovascular Society (CCS) score for angina between baseline angiography and 6 year follow-up.

Figure: Odds of improvement of angina in South Asian compared with White European patients



*age adjusted odds ratio (OR) of improvement in angina symptoms

**adjusted for age, diabetes, hypertension, smoking, number of diseased vessels and left ventricular function

***fully-adjusted model, in those treated medically

****fully-adjusted model, in those treated by percutaneous coronary intervention

*****fully-adjusted model, in those treated with coronary artery bypass surgery

RESULTS

43.9% of south Asians reported improvement in angina at six years compared to 60.3% of whites (age-adjusted OR 0.56, 95% CI 0.41-0.76). Adjusting for diabetes, hypertension, smoking, number of diseased vessels and left ventricular function did not attenuate this finding (OR 0.54, 95% CI 0.37-0.70).

Similar proportions of each ethnic group underwent percutaneous coronary intervention (PCI) (whites 19.6%, south Asians 19.9%, $p = 0.869$) and coronary artery bypass surgery (CABG) (whites 32.8%, south Asians 30.1%, $p = 0.237$).

South Asians were less likely to report improved angina after PCI (OR 0.37, 95% CI 0.16-0.84), CABG (OR 0.34, 95% CI 0.19-0.61) or if treated medically (OR 0.68, 95% CI 0.42-1.08).

CONCLUSIONS

South Asians were less likely to experience long-term improvements in angina when compared to whites, irrespective of treatment modality. Further research is needed to identify reasons for ethnic differences in symptomatic prognosis and how they may be mitigated.

**16.2 British Junior Cardiologist's Association-Cordis International
Research Awards Finalist 2006**



Ethnic differences in long-term improvement of angina following revascularisation

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16.3 Royal Society of Medicine Cardiology Section's President's Medal finalist 2008



The power of speech

Dr Justin Zaman BSc MBBS MRCP MSc

British Heart Foundation Clinical PhD Research Fellow, University College London
Specialist Registrar in Cardiology, East of England Deanery [Norfolk and Norwich University Hospital]

17 Invited talks

17.1 MINAP conference, Royal College of Physicians 27 March 2007

The slide features a light blue background with a pattern of overlapping squares in various shades of blue and white. A dark blue horizontal bar is positioned in the middle, containing the title text in white. In the top right corner, there is a black rectangular box with the UCL logo in white. The speaker's name and credentials are listed in the bottom left, and their affiliation is provided in smaller text at the bottom center.

MINAP conference, Royal College of Physicians 27 March 2007

UCL

Asians disadvantaged in terms of management and outcomes – fact or fiction?

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**17.2 South Asian Health Foundation conference on management of
Coronary Heart Disease in South Asians, Royal College of
Physicians 1st December 2008**

Presentation of CHD in south Asians: typical or atypical?

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