RISK STRATIFICATION OF CORONARY HEART DISEASE IN UK SOUTH ASIANS

A thesis submitted for the degree of

DOCTOR OF PHILOSOPHY

by

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Date of Submission:

April 2007

ACKNOWLEDGMENT

I would like to express my sincere appreciation to a number of individuals who have helped me tremendously through this process.

I would first like to thank my supervisor, Dr. Peter R Jackson, for his continuous support and encouragement. I am also grateful for his confidence in me to bring this idea to fruition. Without his dedication to this work, I would have been unable to implement it.

I acknowledge and thank the Golestan University of Medical Sciences and Iranian Ministry of Health and Medical Education for their financial support without which these studies would have never been conducted.

I would also like to acknowledge the involvement of Dr. John Skinner & Dr. Charles Price (collaborators at Sheffield West Primary Care Trust) for their help in the Patients' acceptance project.

I also acknowledge and thank the UK Archive, University of Essex for providing access to the Health Survey for England 1998, 1999, and 2003 datasets.

Also, I am grateful to Mrs. Derinda Colley, Mrs. Anne Lee, Ms Vicky Rowberry, and Mr Steve Parkin for the administrative, secretarial, and computer support.

I am also grateful to my friend and fellow student Dr Charles Beck (former PhD candidate) for his advice and support during my study.

I would especially like to thank my wife and our parents and family for their tireless encouragement, support, and prayers as I have pursued this degree. Their guidance and advice was a definite source of inspiration.

Finally, thank you to my beloved kids (Carameh, Fatemeh, and Ali) who had patience during my study that I spent less time with them.

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Summary of this thesis

It is clear that South Asians living in the West have substantially greater relative (coronary heart disease) CHD mortality and morbidity than the general population. Despite this current risk functions based on classical risk factors alone underestimate risk in non-diabetic South Asians. After reviewing the available literature for longitudinal studies exploring the relationship between South Asian ethnicity, as an independent factor, and CHD an adjustment factor suitable for use with the paper-based risk prediction functions was derived. The exploration of possible explanations for the excess risk identified dysglycaemia as one possible explain.

Adding 10 years to age, although crude and based on the single prospective study, provides adequate sensitivity and specificity to take into account an "ethnicity factor" accounting for average excess risk in individual UK South Asians. Using this adjustment it was shown that more South Asian men and women, living in the UK, are

candidates to receive lipid-lowering therapy for primary and secondary prevention than their Caucasian counterparts. Although the evidence base for a CVD risk estimation procedure in South Asians is slight it is better that they have their risk estimated, albeit with less precision, than be excluded. The present work provides a properly researched evidence base. Moreover, it provides its own very simple, but in practice acceptable, adjustment for currently used paper risk estimation tools.

Acceptance of antihypertensives as a primary prevention treatment was looked at in the South Asians community. South Asians are at least equally accepting of treatment as Caucasians when given information about the personal impact of CVD and the effect and tolerability of antihypertensive treatment. With South Asians having a greater need and at least equal acceptance of preventive therapy, they should receive more such treatment. Current evidence suggests that this is not the case and targeted intervention may be needed.

Further research is still required in many areas such as risk factors, risk estimation and recalibration, lifestyle intervention, and efficacy of preventive drug therapy in ethnic minorities. Because this population is at high risk, the benefits of appropriate research will also be high.

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS THESIS

Peer reviewed publications

Aarabi, M. and P. R. Jackson, 2004: Coronary risk in South Asians: role of ethnicity and blood sugar. *Eur J Cardiovasc Prev Rehabil*, **11**, 389-93.

Aarabi, M. and P. R. Jackson, 2005: Predicting coronary risk in UK South Asians: an adjustment method for Framingham-based tools. *Eur J Cardiovasc Prev Rehabil*, **12**, 46-51.

Aarabi M. Jackson P R. Prevention of coronary heart disease in South Asian and Caucasian in UK. *Eur J Cardiovasc Prev Rehabil*. (In press- A).

Aarabi M. Skinner J, Price C., Jackson P R. Patients' acceptance of antihypertensive therapy to prevent cardiovascular disease: a comparison between South Asians and Caucasians in the UK. *Eur J Cardiovasc Prev Rehabil*. (In press- in review process)

Presentations at peer reviewed conferences

Aarabi, M. and PR Jackson. Coronary Heart Disease in South Asian people: a systematic review of longitudinal studies. National Conference of Health, Culture, and Diversity. 12-13 September 2002, Sheffield,UK.

Aarabi, M. Skinner J, Price C, and Jackson PR. Minimal clinically important differences (MCID) for antihypertensive treatment in South Asians and Caucasians. The 16th Scientific Meeting of the European Society of Hypertension (ESH); 12-15 June 2006, Madrid, Spain.

Attendance to the related workshops and conferences

International fellow, the World Heart Federation Council of Epidemiology and Prevention, 37th Ten Day International Teaching Seminar on Cardiovascular Disease Epidemiology and Prevention Aug. – Sep. 2004, Beijing, China.

A Workshop of Experts on Cardiovascular Risk Prediction and A Workshop of Experts on Metabolic Syndrome. The South Asian Health Foundation (UK); July 6th 2006, Botanical Gardens, Birmingham.

CHD in South Asians: A Workshop of Experts to Identify Research Needs and Promote Good Practice. The South Asian Health Foundation (UK); December 19th 2005, BMA House, Tavistock Square, London.

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LIST IF ABBREVIATIONS

Abbreviation	Definition
ATP	Adult Treatment Panel
BMI	Body mass index
BNF	British national formulary
BP	Blood pressure
CABG	Coronary artery bypass grafting
CHD	Coronary heart disease
CI	Confidence interval
CRP	C-reactive protein
DALYs	Disability adjusted life years
DBP	Diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
DRCG	The Diverse Population Collaborative Group
ECG	Electrocardiogram
FBG	Fasting blood glucose
HbA1C	Glycated haemoglobin
HDL	High density lipoprotein
HPS	Heart protection study
HSE	Health Survey for England
IQR	Interquartile range
JBS-2	Joint British Societies
LDL	Low density lipoprotein
MCID	Minimal clinically important difference
MI	Myocardial infarction
NCEP	National Cholesterol Education Program

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Abbreviation	Definition
NNT	Number needed to treat
NSF-CHD	National Service Framework for coronary heart disease
OR	Odds ratio
PAI-1	Plasminogen activator inhibitor-1
PCT	Primary care trust
RBC	Red blood cell
RCT	Randomized clinical trial
ROC curve	receiver-operating characteristic curve
RPSGB	Royal Pharmaceutical Society of Great Britain
SBP	Systolic blood pressure
SD	Standard deviation
SHARE	Study of Health Assessment and Risk in Ethnic groups
SPSS	Statistical package for social sciences
TC	Total cholesterol
UK	United Kingdome
UKPDS	United Kingdome prospective diabetic study
US	United States of America
WHF	World heart federation
WHO	World health organization

CHAPTER 1

BACKGROUND OF THE PRESENT RESEARCH

1.1 INTRODUCTION

Over the 20th century, most countries in the world have experienced great transition in social structures, economics, politics, education, and home environment. This has resulted in a shift from agricultural and rural societies to industrial and urban societies in the first 3 quarters of the 20th century, with a further shift in the last quarter to information-based societies. These social and economic transitions have resulted in major changes in population demography, industrial structure, income levels, expenditure patterns, education levels, family structures, eating habits, and physical activity (Yusuf *et al.*, 2001). Along with these changes cardiovascular risk factors and disease rates have markedly increased. One in three deaths across the world is now due to heart disease and stroke, and this figure is rising rapidly. In absolute number this is 17 million deaths a year, six times more than due to HIV\AIDS related deaths, and this Cardiovascular (CVD) epidemic is not limited to industrialised countries (WHF, 2001). CVD is a major contributor to the global burden of disease among the non-communicable diseases. Coronary heart disease (CHD) is likely to be the most common cause of disability adjusted life years (DALYs) loss in 2020 as compared with its fifth position in 1990 (Murray & Lopez, 1996).

In the United Kingdom (UK) diseases of the heart and circulatory system are the main cause of death, accounting for over 235,000 deaths in 2000. More than one person in three (39%) die from CVD. The main forms of CVD are coronary heart disease and stroke. About half of deaths from CVD are from CHD and about a quarter are from stroke and the other quarter die from other CVDs such as heart failure, rheumatic heart disease, hypertensive disease, and other circulatory system disease (BHF, 2006). CHD itself is the most common cause of death in the UK.

One in four men and one in six women die from the disease. CHD caused around 125,000 deaths in the UK in 2000, and was the most common cause of premature death in the UK with just under 45,000 premature deaths. Premature death is a death which occurs prior to that which is expected of the person in relation to developmental, physiological, psychological, and socio-cultural expectations or before the average age of death within a given population. Twenty four percent of premature deaths in men and 14% of premature deaths in women were from CHD (Petersen & Rayner, 2002).

South Asian migrants are at increased risk of cardiovascular disease. This susceptibility is well demonstrated in places as diverse as the UK, South Africa, the Caribbean, Singapore, the United States (US), and Canada. Even within India people moving from rural areas to large cities are at increased risk (McKeigue & Sevak, 1994). Based on British research there is a virtual consensus that the proportionate excess risk of CHD in South Asians, as compared with the population of England and Wales, is greater than 40 per cent (McKeigue, 1989; McKeigue & Sevak, 1994; Shaukat & de Bono, 1994; Enas *et al.*, 1992). Moreover the 1999 Health Survey for England shows Pakistani and Bangladeshi men had prevalence rates of CVD about 60% to 70% higher than men in the general population, and the picture was similar for women (Erens & Primatesta, 1999; Erens *et al.*, 2001). CVD is the primary cause of mortality among Asian Indians in the US. They appear to be at higher risk of heart disease compared with other ethnic groups (nearly three times the rate was seen in South Asian physicians living in the US compared with the Framingham offspring study) (Ivey *et al.*, 2002) . South Asians, in Canada, had a greater prevalence of cardiovascular

disease compared with Canadians of European or Chinese descent; 11%, 5%, and 2%, respectively, P = 0.0004 (Anand *et al.*, 2000).

The latest estimate of the ethnic minority population in Great Britain from the 2001 census shows that approximately half was made up of the three groups originating from the Indian subcontinent - the Indian, Pakistani, and Bangladeshi populations. These represent 1,916,000 South Asians of a total 4,039,000 minority population (Haskey & Scott, 2001).

Because cardiovascular disease has become the number one killer worldwide since the end of the 20th century, widespread deployment of affordable preventive strategies is essential for both developed and developing countries. However this is not possible without exact knowledge of the nature of the disease, its risk factors, and how it may be prevented in the different susceptible populations (Murray & Lopez, 1996). Diabetes and insulin resistance, characterised by glucose intolerance, raised plasma insulin, increased triglycerides, decreased high density lipoprotein (HDL) cholesterol, and central obesity, are more prevalent in UK South Asians than European whites. These are proposed as the underlying factors in high rates of coronary heart disease among South Asians worldwide and have been related to lack of exercise and obesity (Shaukat & de Bono, 1994).

1.1.1 What are risk factors?

A risk factor is a characteristic which predisposes the individual to the development or progression of a particular disease. Risk factors are defined on the basis of epidemiological studies but a distinction must be made between characteristics which are simply associated with CHD and those which actually cause it. For causation to be established the following criteria must be fulfilled (Hennekens & Buring, 1987):

- Having a strong, temporal correlation between the existence of the characteristic and the incidence of CHD
- This correlation must be consistent, dose responsive and predictive
- There must be a plausible mechanism of action by which the risk factor can exert its influence
- The association must be reversible and modification of the risk factor should alter the incidence of the disease which is a very restricted criterion only for modifiable risk factors.

There are a large number of characteristics which have been identified as risk factors for CHD (Wong *et al.*, 1991; Grundy, 1997; O'Connor *et al.*, 1989; Levy *et al.*, 1996; Wald & Hackshow, 1996; Schwartz *et al.*, 1992). A small number of these function are known as independent risk factors, exerting their influence independent of the presence of any other risk factor. In contrast, many others are secondary risk factors that require the presence of other risk factors to have a positive correlation with CHD. In the clinical setting risk factors are divided into those which can be modified, either by lifestyle changes or therapeutic intervention, and those which are not modifiable, Table 1.1.

It is important to grasp that CHD risk factors do not generally occur in isolation but tend to cluster in an individual (Kannel, 1990). This is significant because when risk factors co-exist they tend to interact such that their combined effect is much greater than would be expected from the sum of their individual influence. Furthermore in the list of non-modifiable CHD risk factors age, as well as having its own direct influence, has a major impact on some of the other main risk factors (Frost *et al.*, 1996).

Table 1.1 Risk factors for coronary heart disease

Modifiable	**Non-modifiable**
Cigarette smoking	Age
Raised blood pressure, LDL cholesterol, triglyceride	Male gender
Low HDL cholesterol	Family history of CHD
Diabetes mellitus	Personal history of CHD
Diet, Obesity, and excessive alcohol consumption	
Lack of exercise	
Poverty	

Blood pressure rises with age due to the reduced elasticity of the arterial system. The average total cholesterol concentration in older people is higher than in middle aged people. In addition, insulin resistance increases with age and the prevalence of the metabolic syndrome and diabetes increases (Fink *et al.*, 1983).

Importantly the influence of risk factors was investigated mainly in the White population and there is no certainty that conventional risk factors can be applied in different ethnic groups like South Asians.

1.1.2 Definition of South Asian and Caucasian

South Asian:
A person whose ancestry is in the countries of the Indian sub-continent, including India, Pakistan, Bangladesh, and Sri Lanka (in terms of racial classifications, most people in this group probably fit best into Caucasian or Caucasoid but this is confusing and is not recommended). This label is usually assigned, for individuals rarely identify with it (Bhopal, 2004).

Caucasian:
An Indo-European. This is Blumenbach's 18th century term for the white race of mankind, which he derived from the people who lived in the Caucasus. This term is usually used synonymously with Caucasoid, European, or White. Alone among terms derived from traditional racial classification, Caucasian remains popular in both science and everyday language (Bhopal, 2004).

1.1.3 What is "South Asia"?

South Asia is a part of Asia and the term came into use after World War II as a way of grouping the newly independent countries of the British Indian Empire (WWW.Wikipedia.org). South Asia occupies most of the Indian subcontinent. This region is commonly taken as including the countries of India, Pakistan, Bangladesh, Nepal, Sri Lanka, Bhutan, the Maldives, and Tibet. Afghanistan is variably included in Central Asia or South Asia. For the location of these countries, view the South Asia Map.

Just over one fifth of all the people in the world live in this region. India alone has a population of just over one billion and is the second most populous country in the world after China. Relative to other parts of Asia, South Asia is geographically isolated. On the west is the Oman Sea, to the east is the Bay of Bengal and to the south is the Indian Ocean which stretches from Africa to Southeast Asia to Australia.

When the British left South Asia, the country then known as India split along religious lines. India became mainly Hindu while Pakistan, which had geographic halves located on either side of India, became mainly Muslim (www.wikipedia.org). There is a difference between South Asian groups due to time since they migrated to the UK. Immigrants from India and Pakistan arrived in the UK mainly during the 1960s. Bangladeshi people came to Britain with the peak phase of migration during the 1980s and most of them come from rural area in North East Bangladesh.

1.1.4 Defining ethnicity

The concept of ethnicity contains notions of shared origins, culture and tradition. Ethnicity has a dynamic relationship to both the historical and contemporary experiences of social groups and is related to the living conditions of individuals (Nazroo, 1997). Central to the concept of ethnicity is that it is a reflection of the self-definition of individuals with particular cultural traditions. Despite the complexity of the concept of ethnicity some research on health and ethnicity has taken a crude approach to the allocation of individuals into ethnic groups. This has partly been a consequence of limitations of available data. For example country of birth is recorded on death certificates and in national census. As a result most of the published papers in this area have allocated ethnicity based on this record of

birth country which is inadequate. An approach that acknowledges the role of ethnicity in self-perception has been adopted since the 1991 census. It allows individuals to assign themselves into an ethnic group. Some investigators assign ethnicity according to country of family origin which is highly related to the perceived ethnicity (Nazroo, 1997). Senior and Bhopal argue that ethnicity implies one *or more* of three conditions:

(1) a common language or religious tradition;

(2) shared origins or social background; and

(3) shared culture and traditions that are distinctive, maintained between generations, and conducive to a sense of identity and group (Senior & Bhopal, 1994). It suggests that ethnicity, whatever else it may be, is inseparable from shared social experience or culture and avoids genetic or biological markers as a main reason for between ethnic variations. Despite this in many studies ethnicity is used as a means of identifying grouping belong to consist of geographically relatively homogenous.

1.1.5 CHD prevalence in South Asians

Rudat (1994) carried out a general health survey of a national sample of people from ethnic minorities mainly those in English inner city. Indians had a lower prevalence of self-reported heart disease than Pakistanis and Bangladeshis. A different sampling procedure was used for Whites and the results were therefore not directly comparable with South Asians.

Nazroo (1997) measured crude prevalence, and age and gender standardized prevalence rate of diagnosed heart attack or angina in a national sample in England and Wales. In this study, whereas Indian and African Asian groups combined had a lower prevalence ratio for diagnosed angina or heart attack than the white

population, Pakistani and Bangladeshis combined had a higher prevalence. Adjusted prevalence ratios accounting for standard of living were 0.67 in Indian and African Asians and 1.24 in Pakistanis and Bangladeshis (Nazroo, 1997).

Bhopal *et al.*, (1999) and McKeigue *et al.*, (1993) measured CHD prevalence based on the data from self-reports and electrocardiogram (ECG) evidence. Although there were no differences between South Asians and Europeans in self-reported CHD, based on ECG evidence there was a 37% excess of CHD in South Asians (Bhopal *et al.*, 1999). South Asians had more ischemic ECG abnormalities than Europeans (17% versus 12%, $P < 0.001$), with an excess of major Q waves (Minnesota codes 1-1 or 1-2) in younger South Asian men ($P = 0.01$ for the age-ethnicity interaction) (McKeigue *et al.*, 1993). Other researchers have shown that myocardial infarction develops 5-10 years earlier in South Asians than in other populations, and its occurrence in patients under 40 is 5 to 10-fold higher than general population (Chambers *et al.*, 1999; 2000; Obeid *et al.*, 1998).

Williams *et al.*, (1993) reported a higher prevalence rate of CHD in South Asian women compared to Whites based on self-reported heart disease and angina symptoms (Rose questionnaire) in Glasgow, $P < 0.05$. The differences when data from men and women were combined, were however not statistically significant. Admission rates with myocardial infarction among the South Asians were twofold higher despite being of younger age and less likely to smoke. In addition South Asians undergoing coronary artery bypass grafting (CABG) had almost twice the mortality of Caucasians (Zindrou *et al.*, 2001).

Similar findings were discovered for South Asian migrants to other Western countries. Findings from the SHARE study (Study of Health Assessment and Risk

in Ethnic groups) were that South Asians had a higher prevalence of established cardiovascular disease than Europeans and Chinese (10.7%, 5.4%, and 2.4% respectively, P = 0.0004) (Anand *et al.*, 2000). In addition, when the definition of cardiovascular disease was expanded to include silent myocardial infarction detected by electrocardiogram, South Asians had a greater burden of disease than Europeans and Chinese. Despite this finding Canadians of European origin had more atherosclerosis (mean of the maximum intimal medial thickness 0.75 [SD=0.16] mm) than South Asians (0.72 [SD=0.15] mm), P = 0.00098 (Anand *et al.*, 2000).

Headline prevalence rates are similar in some urbanised non-migrant South Asian communities. Mohan *et al.* (2001) reported a prevalence rate of 11% of coronary artery disease in native urban South Indian population. Elsewhere rates may be lower. Mendis and Ekanayake (1994) investigated prevalence of CHD in the Central province of Sri Lanka in a sample of 975 men aged 35-59 years. They estimated prevalence rates as 5.4% (95% CI, 40 to 71) and 3.2% (95% CI, 21 to 46) based on history of coronary heart disease and ECG changes respectively.

Prevalence data will underestimate incidence when the case fatality rate is high, as is the case in the UK (Enas *et al.*, 1996). Therefore the burden of CHD in South Asians may be even higher than that reflected by the prevalence data.

1.1.6 Mortality

The relative risk of CHD mortality in South Asians is 20-50% higher than Whites in Canada, South Africa, and UK. Studies of cross-sectional design based upon the UK Censuses of 1971, 1981, and 1991 have shown various excess in the standardised mortality ratio for South Asians. Marmot and colleagues (1984)

reported 15% excess deaths due to CHD in both men and women in the 1971 Census. Analysis of the 1981 Census suggested that the excess was greater, varying from 30 to 50% in different ethnic groups (McKeigue & Marmot, 1988; Balarajan *et al.*, 1984). Balarajan (1991) compared mortality from cardiovascular disease in 1970-1972 with that in 1978-1983. Over this time mortality from ischaemic heart disease increased in Indians, 6% in men and 13% in women. In contrast from 1971 to 1991 the national average standardised mortality ratios for ischaemic heart disease fell by 29% for men and by 17% for women within the ethnic minorities. Wild & McKeigue (1997) analysed the 1991 Census data and reported that standardised mortality ratios for ischaemic heart disease were highest for South Asian men and women compared with the general population. Caribbean immigrants showed a steeper decrease (38% for men and 40% for women) of mortality, and South Asian immigrants showed a shallower decline (20% for men and 7% for women) than White people.

Balarajan (1996) and Mckeigue *et al.* (1991) showed Indian, Bangladeshi, and Pakistani people born on the Indian subcontinent but living in England and Wales had a 40- 50% higher mortality from coronary heart disease than the population average. The excess risk of CHD in South Asians appears to be greater at younger ages. In the UK the relative risk of CHD mortality in South Asian men compared with White men is 3.3 between ages 20-29 but only 1.4 overall (Balarajan, 1991). This raises the possibility that risk might be greater in second generation immigrants.

Wilkinson *et al.* (1996) reported that six month mortality after acute MI was twofold higher in UK Indian Asians compared to Europeans, despite similar use of

thorombolysis, beta-blockers, and aspirin. They attributed this worse outcome to a higher prevalence of diabetes. The high mortality from all causes for South Asian immigrants could largely be explained by their high mortality from ischaemic heart disease.

1.2 CORONARY HEART DISEASE RISK FACTORS

These observed differences in morbidity and mortality between South Asians and Caucasians could be due to differences in conventional risk factors, due to differences in the hazard associated with a given risk factor or due to novel risk factors.

1.2.1 Lipid abnormalities

Lipid abnormalities may contribute to the high rate of CHD among South Asians. These abnormalities include low levels of high-density lipoprotein cholesterol, high levels of low-density lipoprotein (LDL), elevated triglyceride and lipoprotein (a) levels. Bohpal *et al*. reported that South Asian men and women had a lower HDL cholesterol concentration compared to Europeans, 95% CI for differences 1.1 to 2.3 mmol/l and 0.6 to 1.3 mmol/l respectively (Bohpal *et al.*, 1999). Bangladeshis had the highest concentration of triglycerides (2.04 mmol/l) and the lowest level of HDL cholesterol (0.97 mmol/l). South Asians, of both sexes, were more likely to have total cholesterol: HDL cholesterol ratio higher than 5.0 compared to Europeans, mean difference (Δ) 12.0% 95% CI: 6.7% to 17.9% (Bhopal *et al.*, 1999).

Anand *et al.* (2000) found South Asians living in Canada had the highest total cholesterol, LDL cholesterol, and triglyceride concentrations compared with Chinese and Europeans although there was no difference in the proportion of individuals receiving lipid lowering drug. In a study of 1150 subjects from seven

ethnic groups in Singapore, mean lipoprotein (a) levels among Asian Indians were double those of all other ethnic groups, with the exception of the Sudanese population (Sandholzer *et al.*, 1991).

1.2.2 High blood pressure

In a study of Glaswegian men Williams and colleagues found diastolic but not systolic blood pressure was higher among South Asians (predominantly Punjabi) than the general population, but this was not so for South Asian women (Williams *et al.*, 1993).

In contrast Bhopal *et al.* (1999) found hypertension to be less common in South Asians than Europeans. Within the South Asian community there were no significant differences in the prevalence of hypertension between ethnic groups but Bangladeshis had, if anything, the lowest. Reported hypertension or blood pressure > 160/95 mmHg were 14%, 9%, and 4% in Indians, Pakistanis, and Bangladeshis (P = 0.202). In the HSE 1999, mean systolic blood pressure was significantly lower in Pakistani and Bangladeshi men after age standardization, relative risks of having hypertension compared to the general population were 0.98 and 0.94 respectively, in contrast to the significantly higher mean in Indian men (Erens *et al.*, 2001).

Anand *et al.* (2000) reported no significant differences in mean systolic blood pressure between South Asians and Europeans in Canada, 118 and 119 mm Hg respectively (P = 0.90), although South Asians had higher diastolic blood pressure than Europeans, 79 and 73 mm Hg respectively, P = 0.006.

Figure 1.1 shows differences between the mean systolic (P < 0.0001) and diastolic (P < 0.001) blood pressures of those who developed CHD and those who did not

developed the disease in the longitudinal epidemiological study of coronary heart disease in a rural population of Kheda district, Gujarat, India (Trivedi *et al.*, 1996).

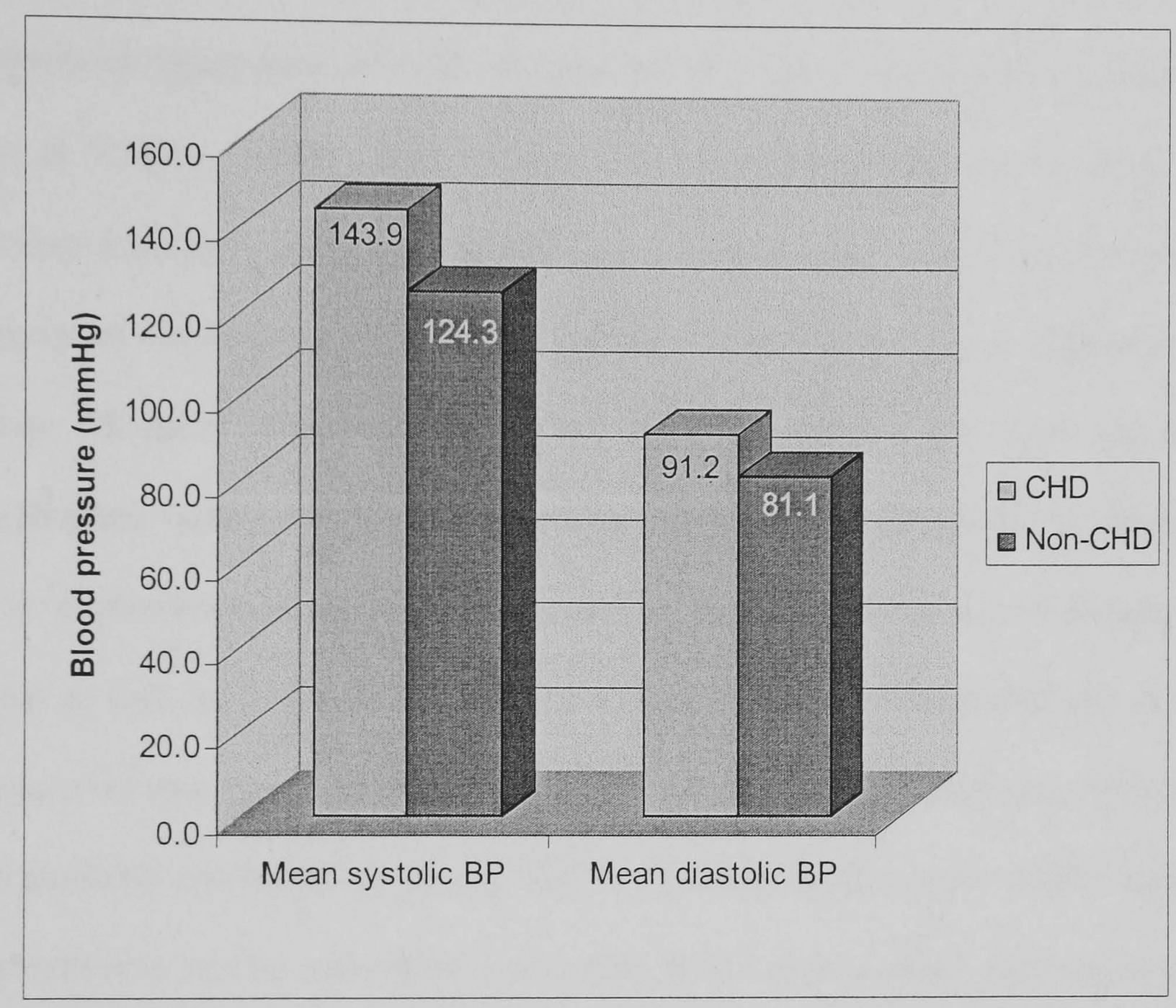

Figure 1.1 Mean systolic and diastolic blood pressure in CHD and non-CHD patients

Trivedi *et al.* (1996) reported a high degree of association between hypertension and CHD in an Indian population. As 8.1% of the hypertensive developed CHD, while only 1% of normotensives and 1.7% of those with borderline blood pressure subsequently suffered from CHD.

1.2.3 Metabolic syndrome

Insulin resistance, characterised by glucose intolerance, raised plasma insulin, and diabetes are more prevalent in UK Indian Asians than European whites (McKeigue *et al.*, 1993; Wild & McKeigue, 1997) and may form part of the metabolic

syndrome (more details on the metabolic syndrome provided in chapter 2). Certainly both diabetes and impaired glucose tolerance are associated with an increase risk of CHD. However other populations with a higher prevalence of diabetes such as Hispanic-Americans, African-Americans and Native Americans do not have higher rates of CHD showing that this cannot be the only explanation (Rao & Kakkar, 2001). The prevalence of myocardial infarction is lower in Mexican-American men, with or without diabetes, than in the corresponding category of non-Hispanic white men, but there is no similar ethnic difference in women. Hispanic Americans tended to have a lower prevalence of MI than non-Hispanic whites despite their greater prevalence of diabetes (Stern & Mitchell, 1995). Furthermore in the UK Afro-Caribbean migrants, prevalence of diabetes is almost as high as in South Asians but the lipid disturbances characteristic of the insulin resistance syndrome do not occur to the same extent (McKeigue, 1996) and their mortality and morbidity due to CHD is less than South Asians. Higher insulin concentrations can be associated with higher levels of potentially atherogenic and diabetogenic metabolic parameters. However, depending on ethnic origin, the mean levels of these parameters seems to differ, with the consequence that, even if they are elevated with increasing insulin levels, they may not reach values high enough to determine a substantial risk of disease.

The increased likelihood of developing diabetes in middle age in South Asians has been described by many authors and this diabetic tendency has been demonstrated for different subgroups living in diverse locations. In UK South Asians, diabetes is reported to be 3-6 times more common than in the White population (Mather & Keen, 1985). Pakistanis and Bangladeshis of both sexes are more than five times as likely as the general population to have diabetes, and in Indian men and women

this risk is three fold greater. In the Health Survey for England 1999 the observed prevalence of diabetes is higher in South Asians than in the general population. The age-standardised prevalence of diabetes was 3.3% in the general population compared to 10.6, 8.7, and 7.7% in Bangladeshi, Pakistani, and Indian groups respectively (Erens & Primatesta, 2001).

The Study of Health Assessment and Risk in Ethnic groups (Anand *et al.*, 2000) in Canada reported that non-diabetic South Asians were more likely to have impaired glucose tolerance (a 2-h glucose of 7.8 mmol/l or more and less than 11.1 mmol/l) than Chinese and Europeans (19%, 15%, and 12% respectively; overall P = 0.03). In addition their mean fasting blood glucose concentration (5.47 mmol/L) was higher than that in Chinese (5.19 mmol/L) or Europeans (5.13 mmol/L), overall P = 0.0001. After exclusion of people with diabetes at entry, the prevalence of newly diagnosed glucose intolerance (impaired glucose tolerance or new diabetes) was 28% (87 of 308) in South Asians *v* 20% (61 of 302) in Chinese, and 18% (55 of 305) in Europeans (overall P = 0.04) suggesting that incidence is also increased .

The age standardized prevalence of diabetes is similar in both genders living in urban areas in India, 11.9% and 12.5% respectively (Ramachandaran *et al.*, 2001). This is less than the prevalence for UK South Asians but more than of Caucasians. In addition the prevalence of impaired glucose tolerance is also high in both genders (14%).

1.2.4 Smoking

Several studies demonstrated a similar or lower prevalence of current smoking among South Asians compared to Whites (Trivedi *et al.*, 1996; Miller *et al.*, 1988). However there is heterogeneity in the rates of current smoking within UK South

Asian men according to origin with 50%, 33%, and 20% for Bangladeshis, Pakistanis, and Indians respectively (Nazroo, 1997). In another study, Bangladeshi men had the highest prevalence of current smoking, at 57%, compared to Indian and Pakistanis, $P < 0.001$, but overall South Asians had a similar current smoking pattern to that of Whites (Bhopal *et al.*, 1999). In the Health Survey for England 1999 risk ratios relative to the general population for current self-reported cigarette smoking were 1.57, 0.90, and 0.78 for Bangladeshi, Pakistani, and Indian men respectively (Erens *et al.*, 2001).

Tobacco use among Asian Indians living in the US appears to be lower than for other Asian Americans (Kuo & Porter, 1998). A survey of South Asians in Northern California showed only 12% of respondents had ever smoked. (Ivey *et al.*, 2002).

Pais et al reported current smoking of cigarettes or beedis (a local form of tobacco) as the most important predictor of acute MI in Indian men in Bangalore in India, with odds ratio 3.6, 95% CI 2.20 to 3.07 comparing smokers with non-smokers (Pais *et al.*, 1996).

1.2.5 Physical inactivity

South Asian men were less likely to take vigorous exercise than the general population in Glasgow (Williams *et al.*, 1993). In the HSE 1999, there was an ethnic gradient in participation in sports and recreational exercise among adults, with the highest level seen in the general population, followed by Indian, then Pakistani and finally Bangladeshi men and women (Erens *et al.*, 2001). In a sample of the Newcastle Heart Project Indians were the most physically active South Asians and Bangladeshis the least, 29.2% and 13.2% having weekly aerobic activity (a 30 minutes episode of at least moderate activity on most days of the

week) respectively. Moreover South Asians did less than half the physical activity done by European, 30% and 19% less in South Asian men and women respectively (Haynes *et al.*, 2002). This probably reflects the original rural lifestyle of South Asians in general rather than being specific to migrants. Fischbacher *et al.* (2004) carried out a systematic literature review of studies describing levels of physical activity and fitness in UK South Asians. All studies reported substantial lower levels of physical activity and fitness in Indian, Pakistani, and Bangladeshi ethnic groups compared to the general population or those defined as White or Europeans in the UK (Fischbacher *et al.*, 2004). In Gupta's study of Indian men in India, 83% of them had no leisure-time physical activity (Gupta & Sharma, 1994).

1.2.6 Alcohol consumption

Williams *et al.* (1993) demonstrated that alcohol use was uncommon in women and also in people practicing Islam among South Asians. Results of the Fourth National Survey of Ethnic Minorities showed very few of the almost entirely Muslim Pakistani and Bangladeshi respondents ever drank alcohol, whilst one in five Indians were regular drinkers (Nazroo, 1997). Another study showed that 17% of Indian men drank alcohol (Gupta & Sharma, 1994). Pais et *al.* (1996) reported more Indians with a first MI (44%) consumed alcohol than healthy Indians (31%). But this probably reflected the confounding effect of smoking as after adjustment for the effect of smoking, alcohol was no longer a risk factor (P = 0.22).

1.2.7 Diet

There is a dietary diversity amongst the UK South Asians ranging from strict vegetarian to meat and fish containing diets. South Asians ate meat, fruit, salad and vegetables more frequently than the general population in Glasgow (Williams *et al.*, 1993). Dietary patterns of South Asians in urban Glasgow show that traditional

South Asian rural diets are augmented with the high fat and high sugar foods of the majority culture, including crisps, confectionery and sweetened carbonated beverages (Anderson & Lean, 1995). Pais *et al.* (1996) classified individuals in a case-control study as being vegetarian or non-vegetarian. Vegetarianism appeared to have a protective effect against coronary heart disease (OR 0.55, 95% CI 0.35-0.85; P = 0.006), which remained significant after adjusting for smoking, blood glucose, HDL and LDL cholesterol, and triglycerides. However in the Gupta study, 25% and 35% of Indian men ate non-vegetarian and high fat diets respectively (Gupta & Sharma, 1994).

It is important to notice that dietary habits of second generation UK South Asians are changing to become more similar to those of the general UK population (Landman & Cruickshank, 2001).

1.2.8 Socio-economic situation

Socio-economic status varies between the South Asian communities. The Newcastle upon Tyne study showed Indians were most and Bangladeshis least educated (Bhopal *et al.*, 1999). Indians were most likely to be in social classes I, II, and III (70%) and Bangladeshis least (26%). Europeans and Indians had the highest median income and Bangladeshis the lowest. Indians were socio-economically advantaged compared with Pakistanis and Bangladeshis, based on the Townsend deprivation score derived from 1991 census data (Bhopal *et al.*, 2002).

However, an analysis by Marmot and colleagues based on the 1971 Census reported no relation between social class and coronary mortality in immigrants from the Indian subcontinent (Marmot *et al.*, 1984). McKeigue & Marmot (1988)

demonstrated that both relatively poor Bangladeshis, and more affluent Indians, in London were at similarly high risk of coronary mortality. In contrast Nazroo (1997) reported that self-reported CHD in South Asians, in a national cross-sectional survey in 1993-1994, was associated inversely with standard of living as measured by social class (according to the Registrar General's criteria), unemployment, and living in poor housing.

1.2.9 Other biological factors

While lipids and lipoprotein (a) in particular, appear to be specific risk factors among South Asians, other recent research has focused on abnormalities of vascular endothelial function among even healthy South Asian men and elevated serum homocysteine, among other metabolic abnormalities. In the studies of Chambers *et al.* (1999; 2000) and Obeid *et al.* (1998) homocysteine concentrations were higher in UK South Asians than European Whites. They also confirmed that homocysteine is a risk factor for CHD in South Asians. From these data it was possible to estimate that an elevated homocysteine concentration may contribute twice as many CHD deaths in UK South Asians as in Europeans (Chambers *et al.*, 1999; 2000).

The SHARE study in Canada demonstrated that South Asians' excess cardiovascular disease prevalence may be partially attributable to elevated levels of plasminogen activator inhibitor-1 (PAI-1) in addition to elevated lipoprotein (a) (Anands *et al.*, 2000). Also, a study in the UK found that elevated levels of C-reactive protein (CRP) were associated with risk factors for cardiovascular disease in Indian Asian men compared to Europeans (Chambers *et al.*, 2000).

1.2.10 CHD and CVD risk prediction tools for South Asians

In people with no history of CVD estimating the absolute risk of vascular event, mainly using the Framingham equation, is a strategy for primary prevention that provides an opportunity for taking appropriate action according to the level of risk (more details can be found at the introduction of chapter 3 of this thesis). The performance of the Framingham risk scores varies considerably between populations and evidence supporting the use of cardiovascular risk scores for primary prevention is scarce (Brindle *et al.*, 2006a) however this risk estimation and consequent prevention strategies are better than doing nothing. At the time of collecting background information there was no evidence for suggesting proper CHD or CVD risk estimation in South Asian group however two studies were found in updating attempt of the literature review. Cappuccio *et al.* (2002) suggested that primary care doctors should use a lower threshold of CHD risk when treating mild uncomplicated hypertension in South Asians. Brindle *et al.* (2006b) recalibrated the Framingham risk score and produced a web-based tool for estimating the 10-year risk of CHD and CVD in the UK south Asians as well as six other ethnic minorities.

1.3 CONCLUSION

Although the increased prevalence of the classical risk factor of diabetes may explain some of the increased cardiovascular disease in South Asians it is not clear whether novel risk factors or even ethnicity itself might contribute to the difference in risk. It is tempting to attribute increased CVD risk in South Asians to differences in a single established risk factor e.g. diabetes. However other metabolic differences have been demonstrated although the importance of these is as yet unknown.

1.4 AIMS OF THIS THESIS

The purpose of this thesis was to study several aspects of CHD in the UK South Asians. The problems were approached from the epidemiological and clinical angles.

The aims of the study were;

1. To explore qualitative and quantitative differences in the impact of established risk factors for CHD between South Asians and Caucasians in order to identify and quantify any additional independent "ethnic" risk factor.
2. To compare the level of dysglycaemia in non-diabetic South Asians and Caucasians in the UK population.
3. To develop a practical risk estimator tool for the South Asians.
4. To identify a method for adjusting the input to Framingham equations for use in South Asian individuals to accommodate their greater risk of CHD and apply this to the simple practical paper based tools.
5. To determine the prevalence of subjects eligible for primary and secondary prevention of CHD among the British South Asian population and to compare that with British Caucasians.
6. To explore the relationship between ethnicity and individual attitude to prescribed primary prevention drug.
7. To investigate prevalence, treatment, and control of hypertension in the UK South Asians using Health Survey for England 1998 and 1999 data.

CHAPTER 2

CORONARY RISK IN SOUTH ASIANS: ROLE OF DYSGLYCAEMIA

2.1 INTRODUCTION

A multitude of risk factors has been implicated in the development of coronary heart disease (CHD) (Tunstall-Pedoe *et al.*, 1997). The conventional risk factors are associated with the risk of coronary heart disease in South Asians but may not fully explain the excess burden of CHD in this group. Although believed at higher risk of CHD, surprisingly, South Asians have a lower prevalence of hypertension, hypercholesterolemia, obesity, and smoking when compared to Caucasians and additional risk factors may well be responsible. However, there is marked heterogeneity between groups within the South Asian population in terms of prevalence of risk factors, e.g. Bangladeshi smoke a lot and Indian smoke less (Erens *et al.,* 2001). Factors proposed to explain the higher CHD risk in South Asians include diabetes, raised plasma insulin, increased triglycerides, decreased high-density lipoprotein (HDL) cholesterol, and central obesity, all of which are more prevalent in UK South Asians. However it is not clear whether even these differences explain all of the increased risk of CHD in South Asians, an issue of some importance when attempting to predict CHD risk in individuals (Shaukat & de Bono, 1994). South Asians commonly develop the insulin resistance syndrome (metabolic syndrome) if they experience only moderate weight gain (Chandalia *et al.*, 1999). The metabolic syndrome described by Reaven and other researchers (Reaven & Chen, 1988; Reaven & Laws 1994; Garvey & Hermayer 1998; Gaudet *et al.*, 1998; Haffner *et al.*, 1999; Meigs *et al.*, 2000; Misra *et al.*, 1999) provides a pathophysiologic framework for investigating the increased cardiovascular risk and subsequent development of clinical events related to atherosclerosis. Although the components of the metabolic syndrome as originally described included obesity, hypertension, dyslipidemia, impaired glucose tolerance, and diabetes mellitus, it

has been assumed that insulin resistance is the central pathogenic basis for the syndrome, with hyperinsulinemia frequently used as its marker. The Adult Treatment Panel (ATP) III of the National Cholesterol Education Program (NCEP) recently proposed a definition for metabolic syndrome to aid identification of individuals at increased risk of both CHD and type 2 diabetes (NCEP-III, 2001). The definition incorporates thresholds for 5 easily measured variables linked to insulin resistance: waist circumference, plasma concentration of triglycerides, HDL cholesterol, fasting glucose, and blood pressure. The World Health Organization (WHO) definition (WHO, 1999) and the European Group for the Study of Insulin Resistance require glucose intolerance or insulin resistance as an essential component. Both WHO and NCEP definitions of the metabolic syndrome include widely accepted clusterings of risk factors for CVD, but neither of them recognises that the nature and contribution of each component may vary across ethnic groups.

The metabolic syndrome is a precursor of diabetes and a common pathogenic mechanism for the development of CHD (Stern, 1995; Wilson *et al.*, 1999). Insulin resistance generally rises with increasing body fat content, yet a broad range of insulin sensitivities exists at any given level of body fat. Most people with categorical obesity (body mass index [BMI] ≥ 30 kg/m^2) have postprandial hyperinsulinemia and relatively low insulin sensitivity (Bogardus *et al.*, 1985), but variation in insulin sensitivities exists even within this population (Abbasi *et al.*, 2002). Overweight people (BMI 25 to 29.9 kg/m^2) likewise exhibit a spectrum of insulin sensitivities, suggesting an inherited component to insulin resistance. South Asians tend to have more visceral adipose tissue, despite having low BMI (Banerji *et al.*, 1999; Chandalia *et al.*, 1999) and this may contribute to their high prevalence of insulin resistance, type 2 diabetes, and premature cardiovascular

disease (CVD). They have higher upper-body adiposity and higher visceral fat for a given BMI when compared with the Western population (Banerji *et al.*, 1999). A similar picture is also seen in Australian aboriginals, who have an epidemic proportion of glucose intolerance and have BMI values much lower than the obesity limits suggested by Western standards (Daniel *et al.*, 2002). South Asians and others who manifest insulin resistance when only mild-to-moderately overweight can be said to have primary insulin resistance. Even with primary insulin resistance, however, weight gain seems to enhance insulin resistance and metabolic syndrome (Grundy *et al.*, 2004). Thus, dissociation of obesity and primary insulin resistance as causes for the metabolic syndrome is difficult. This propensity for insulin resistance is seen particularly in South Asians who have migrated to other regions or who have moved into urban settings and become relatively affluent in their own countries. However, the prevalence of the metabolic syndrome and particularly diabetes is rising very rapidly even within the Indian subcontinent (Ramachandaran *et al.*, 1997). Tillin *et al.* analysed the datasets from the Brent and Southall studies and reported a significant association between the metabolic syndrome and prevalent CHD in South Asian men [NCEP definition, OR=2.1, (95% CI 1.5 to 3.1); WHO definition, OR=1.6 (95% CI 1.1 to 2.3)] (Tillin *et al.*, 2005).

Coronary risk prediction has evolved as a method of helping clinicians prioritize preventive measures in patients who do not yet have overt cardiovascular disease. The Framingham risk equation (Anderson *et al.*, 1991) and the clinical decision rules that have been derived from it are the mainstay of treatment decisions for CHD primary prevention. Some reviews also suggest that patients at low risk gain

nothing or may even be harmed by intervention. Risk assessment is essential to ensure that such patients are not exposed to unnecessary drug treatment.

There are three steps in the development of a clinical decision rule: deriving the rule, testing the rule, and assessing the impact of the rule on clinical behaviour (McGinn *et al.*, 2000). No studies have attempted to identify the common factors or characteristics that contribute to CVD in South Asians by following its development over a long period of time in a large number of participants who had not yet developed overt symptoms of CVD or suffered a heart attack or stroke. Consequently it is not possible to derive a primary rule, to test it or assess its impact in this ethnic group. Nor have there been studies investigating the validity of any Framingham-based risk or other established equation in South Asians. As a result current prediction models, that do not take into account the effect of ethnicity, will probably provide inaccurate risk estimation in South Asian people and hinder estimation of their prevention needs. An alternative way of dealing with this type of problem is to use an adjustment factor for the current prediction equations. Such an adjustment factor could be derived from longitudinal studies studying both South Asians and Caucasians recording risk factors and cardiovascular outcome measurements. This would allow estimation of a differential factor associated with ethnicity (South Asian) independent of currently used risk factors.

2.2 AIM AND OBJECTIVES

To explore qualitative and quantitative differences in the impact of established risk factors for CHD between South Asians and Caucasians in order to identify and quantitative any additional independent "ethnic" risk factor. My principal aim was to develop a practical risk estimator tool for the South Asians. When it became

evident that dysglycaemia might explain part of the higher risk in South Asians I also compared the level of dysglycaemia in non-diabetic South Asians and Caucasians in the UK population in order to explore a possible readily identifiable pathophysiologycal mechanism behind any such difference.

2.3 METHODS

2.3.1 Methods of review

Using the Centre for Review and Dissemination guidance (CRD Report 4, 2001) a search was performed for published papers up to March 2002 in MEDLINE, EMBASE, and citations from references. All longitudinal studies identifying both CHD and CVD events and putative risk factors in South Asian (Indian, Pakistani, and Bangladeshi) adults were sought. Inclusion and exclusion criteria for this search can be found in Table 2.1.

Table 2.1 Inclusion and exclusion criteria for searching longitudinal studies in South Asians

Selection criteria	Inclusion	Exclusion
Population	("South Asian" or Indian or Pakistani or Bangladeshis)	Others
Intervention /Diagnosis	("Coronary heart disease" or CHD or (CVD or "cardiovascular disease") and "risk factor"	Novel risk factors
Outcomes	CHD or CVD Mortality or Morbidity	
Comparisons	with Caucasian or non-migrant South Asians	
Study designs	("Cohort study" or "prospective study" or "longitudinal study" or "randomized clinical trial")	Other studies (e.g. qualitative)
Publication year	From 1966 – 2002	Before 1966
Language	English	Other language

The search of the MEDLINE and EMBASE led to 108 and 15 references. After reading of all abstracts, one cohort study (Heng *et al.*, 2000; Lee *et al.*, 2001) and four prospective population surveys (Khattar et al, 2000; Miller *et al.*, 1990; Trivedi *et al.*, 1996) were the only longitudinal studies identified.

2.4 RESULTS OF REVIEW

2.4.1 Prospective surveys

Trivedi *et al.* (1996) studied a cohort of 714 (429 male) participants in a rural population of Kheda district in Gujarat, India from 1987- 1992. A sample of 1460 was selected by the process of stratified random sampling from the voters' list aged 32-62 years. 549 (76.1%) of the subjects came from this sampling strategy and the other 172 (23.9%) were volunteers who were included after contacting local leaders. All subjects were examined in a clinic set up at a local hospital. The overall five-year incidence of CHD (myocardial infarction, angina pectoris, and sudden death) was 25.2 per thousand (95% CI: 15.0 to 39.1). Trends relating CHD incidence to family history, HDL cholesterol, and total cholesterol were in the expected direction but failed to reach statistical significance. The rate of CHD in men was about three times higher than in women. The systolic blood pressure in those who developed CHD was higher than in those who did not, mean difference 19.6 mmHg (95% CI: 18.3 to 20.0, $P < 0.001$). Hypertensives were 4.2 times more likely to develop CHD compared with people who had normal blood pressure. Rates of CHD were also higher in diabetics and smokers but again differences were not statistically significant. However, in what appears to be a post hoc subdivision according to the number of cigarettes smoked per day, the incidence of CHD among males smoking > 10 cigarettes was significantly higher than either non-smokers or smokers of < 10 cigarettes ($P = 0.002$) (Trivedi *et al.*, 1996).

Statistical analysis in this study was limited by its relatively small size and the low incidence of CHD. People in the lower socioeconomic strata were less likely to be included in this study. Volunteers formed almost a quarter of the sample which is a possible additional source of bias.

Miller *et al.* (1990) investigated the association between fasting serum lipoprotein concentrations and CHD in a population cohort including different ethnic groups in Trinidad. 960 men (321 Indian) aged 35 to 69 years and free of CHD between 1977 and 1986 were studied. Ethnicity was determined by grand parental origins. Indians had a higher rate of coronary events than Africans and men of mixed descent; RR=2.2 (95% CI: 1.3 to 3.6). The authors reported a curvilinear relation between HDL cholesterol concentration and age adjusted CHD risk with a 30% reduction in CHD per standard deviation increase in $\log_{10}$ HDL cholesterol ($P = 0.003$). Adjusted for other coronary risk factors the standardized hazard ratio for $\log_{10}$ HDL cholesterol was 0.73 ($P = 0.025$) with no difference between ethnic groups (Beckles *et al.*, 1986).

Khattar *et al.* (2000) reported an observational study of 688 hypertensive patients (106 South Asian) in England with a mean follow up of 9.2 years (Khattar *et al.*, 2000). All participants were originally referred for the management of hypertension based on a persistently raised clinic blood pressure. Patients with a secondary cause of hypertension were excluded. The prevalence of previous CVD at 7% was similar in both ethnic groups. The South Asians studied were on average younger, had significantly lower values of total cholesterol, and had the lowest 24 hour mean, daytime mean, and night time mean ambulatory systolic blood

pressures. Despite the lower prevalence of most classical risk factors South Asians suffered more than twice the coronary events than Caucasians, 2.86 *v* 1.32 events per 100 patient-years respectively, P = 0.002. South Asians had higher all cardiovascular event rates of 3.5 events/100 patients-years compared with 2.5 events/100 patients-years for Caucasians. This was only partially explained by their higher prevalence of diabetes (17% *v* 6%) even when adjusted for other risk factors. The estimated hazard ratio for the differences in race (South Asian: Caucasian) as predictor of time to a first cardiovascular event was RR=1.79, 95% CI: 1.16 to 3.66 (P = 0.008) (Khattar *et al.*, 2000). This study is limited by the retrospective collection of drug therapy information and lack of follow-up blood pressure data and may therefore have missed important differences in risk factor control during follow up. In addition as the study included both diabetic and non-diabetic patients it provides only a contaminated estimate of any ethnic factor in non-diabetic men.

The UK Prospective Diabetes Study (UKPDS) was a randomised controlled trial which showed that both intensive treatment of blood glucose and of blood pressure lowers the risk of diabetes-related complications in individuals newly diagnosed with Type 2 diabetes (Stevens *et al.*, 2001). The 4520 patients studied from 23 participating UKPDS hospitals included 432 Asian Indians. All patients aged 25-65 years had no recent history of myocardial infarction, angina or heart failure. The investigators fitted a model of the influence of baseline risk factors on the incidence of subsequent coronary heart disease using 29878 person-years of follow-up data. Significant factors in the final model were age, sex, ethnicity (Afro-Caribbean or not), smoking, HbA1c, systolic blood pressure, and total

cholesterol: HDL cholesterol ratio. A factor distinguishing Asian Indians from Caucasians was tested during model building but was not found to be significant, with a relative risk of CHD in Type II diabetes in Asian-Indians of 0.99 compared to Caucasians, with 95% confidence interval 0.66 to 1.32, P > 0.5 (personal communication & Stevens *et al.*, 2001).

2.4.2 Retrospective studies

The Singapore Cardiovascular Cohort Study linked individual risk factor information collected in three previous cross-sectional surveys to first CHD events identified from national registry databases (Heng *et al.*, 2000; Lee *et al.*, 2001). Record linkage with these registers was made possible by use of the National Registration Identity Card number which is a unique national registration identification number issued to all Singaporeans. The 2879 males (481 Indian) were followed for an average of 8.9 years. Indians had the highest incidence of ischemic heart disease; 10.6 per 1000 person-years (95% CI: 7.8 to 14.5) and 3.7 per 1000 person-years (95% CI: 2.3 to 6.2) in males and females respectively. Compared with Chinese and Malays Indian males had overall-adjusted hazard ratios for CHD of 3.1 (95% CI: 2.0 to 4.8) and 3.4 (95% CI: 1.9 to 3.3) respectively (Lee *at al.,* 2001). The numbers studied were insufficient to allow assessment of possible interaction between ethnic and independent risk factors. In a global univariate analysis adjusted only for age and ethnic group HDL cholesterol, triglyceride, BMI, hypertension and diabetes were associated with CHD whereas in a multivariate analysis only ethnic group, diagnosis of diabetes and hypertension remained significant (Table 2.2). As registry data were used to identify events issues of accuracy and completeness of the dataset for interpreting these findings are crucial.

Table 2.2 Predictors of coronary heart disease in South Asians

Study	Significant predictors of CHD in multivariate analysis
Singapore cardiovascular cohort Study (Heng *et al.*, 2000)	Ethnic group, Diagnosis of Diabetes and Hypertension
Observational follow up in hypertensive patients (Khattar *et al.*, 2000)	Ethnic groups, Diabetes Mellitus, Age, Sex, Previous History of cardiovascular disease,24 Hour mean systolic blood pressure
Prospective population survey in Trinidad (Miller *et al.*, 1990)	Log10 HDL Cholesterol (other risk factors not investigated)
Trivedi et al study (Trivedi *et al.*, 1996)	Hypertension *

* Univariate analysis

2.4.3 Understanding differences between study results

Despite the almost universal belief that South Asians are at higher risk of CHD only the studies of Khattar and colleagues (Khattar *et al.*, 2000) and the UKPDS group (Stevens *et al.*, 2001) investigated the role of ethnicity in risk independent of other risk factors. Even these two studies produced apparently discrepant results, only Khattar's suggesting a higher risk in South Asians when other risk factors had

been taken into account. This apparent contradiction might be explained by the populations studied. Khattar included mainly non-diabetic hypertensives whilst UKPDS investigated the management of patients with Type II diabetes. Exploration of whether this might explain the different results is warranted.

2.5 DYSGLYCAEMIA AND CARDIOVASCULAR DISEASE

The relation between blood glucose concentration and adverse clinical outcomes is still hotly debated especially whether any relationship is stepped or continuous. For microvascular complications, there appears to be a threshold in fasting glucose (6.1 mmol/l [110 mg/100]), post challenge glucose (11.1mmol/l [200 mg/100]), and HbA1c (7%) (Dagogo-Jack, 1995; Krolewski *et al.*, 1995; Warram *et al.*, 2000; Ohkubo *et al.*, 1995; Tanaka *et al.*, 1998; Shaw *et al.*, 1999) below which those are rarely seen. In contrast, a review and meta-regression analysis of 20 prospective studies, mainly in male Caucasians, concluded that the relation between glucose concentrations and cardiovascular disease is continuous and extends below the threshold for the diagnosis of diabetes (Coutinho *et al.*, 1999). Bjornholt & colleagues (1999) demonstrated that the highest quartile of non diabetic men ranked according to fasting glucose (> 4.8 mmol/l [86.5 mg/100]) had a significantly higher cardiovascular mortality at 22 years than those in the three lowest quartiles. The relative risk remained significant after adjustment for other risk factors, 1.4 (95% CI 1.0 to 1.8).

2.5.1 HbA1c and cardiovascular events in non-diabetics

In adults about 98% of the haemoglobin in the red blood cell (RBC) is haemoglobin A. About 7% of it consists of a type of haemoglobin (HbA1) that can combine strongly with glucose in a process called glycosylation. Once it occurs, it is not easily reversible. HbA1 is actually made up of three components

(haemoglobin A1a, A1b, and A1c. HbA1c is the component that most strongly combines glucose and makes up about 70% of HbA1. Blood glucose levels are a major determinant of HbA1c levels. Population studies in patients with diabetes have shown that HbA1c is highly correlated with preceding long term mean blood glucose (Koenig *et al.*, 1976; Svendsen *et al.*, 1982; DCCT, 1987). The amount of glycohaemoglobin depends on the amount of gloucose available in the bloodstream over the RBCs' 120-day lifespan. Therefore determination of its value reflects the average blood sugar level for the 100 to 120 day period before the test. HbA1c is of course an indirect measure of long-term glycaemia. In diabetic patients HbA1c may not accurately reflect diabetic control in situations in which red blood cell lifespan is reduced (Reynolds *et al.*, 2006). Whether this applies to non-diabetic populations remains unknown.

Two prospective studies in Caucasians investigated the relationship between HbA1c and future cardiovascular disease in non-diabetic subjects (Khaw *et al.*, 2001; Park *et al.*, 1996). In the Norfolk cohort (Khaw *et al.*, 2001), the effect of the HbA1c concentration on mortality was evident even at the lower end of the population distribution, and there was no apparent threshold effect: men with HbA1c concentrations above 5% had greater risk than the group with HbA1c < 5%. In this regard, glycated haemoglobin appears to resemble blood pressure and blood cholesterol concentration demonstrating a continuous relation with cardiovascular risk. A one percent increase in HbA1c is associated with a 28% ($P < 0.002$) increase in risk of death independent of age, blood pressure, serum cholesterol, body mass index, and smoking habits. This remained significant (relative risk 1.46, $P = 0.05$) after excluding men with known diabetes or a HbA1c concentration ≥7% (Khaw *et al.*, 2001) who could possibly have undiagnosed

diabetes. Park *et al.* (1996) reported that glycated haemoglobin, but not FBG or post-challenge plasma glucose, was significantly related to CVD and CHD mortality in women but not men. The age-adjusted relative hazard for those in the highest quintile of glycated haemoglobin (≥6.7%) compared with women in the lower levels was 2.4 for fatal CVD (95% CI 1.3 to 4.3, P = 0.005) and 2.4 for CHD (1.1 to 5.3, P = 0.024) (Park *et al.*, 1996).

Fasting blood glucose and HbA1c measuring different things; FBG measures blood glucose after fasting for 8 hours whereas HbA1c measures cumulative post-food sugars in blood. HbA1c is related to the development of microvascular disease (UKPDS-33, 1998; DCCG, 1993) in diabetes although there is evidence that it also associated, controversially, with macrovascular disease (Selvin *et al.*, 2004). For CHD patients with normal glucose tolerance and different extends of atherosclerotic disease, postload glycaemia and HbA1c level are not equally distributed but are significantly higher with cardiovascular risk according to a linear model (Sasso *et al.*, 2004). However HbA1c level were associated with an increased risk of cardiovascular mortality in CHD patients without diabetes (De Vegt *et al.*, 1999).

2.5.2 South Asians and dysglycaemia

Marked abnormalities of glucose metabolism are particularly common in South Asians with high rates of both impaired glucose tolerance and diabetes. Whilst these conditions are accepted as strong risk factors for CHD it is becoming increasingly evident that disturbances of glucose metabolism short of that needed for definition of glucose intolerance may also be associated with an increased risk. In 1991 McKeigue *et al.* (1991) reported the existence of an insulin resistance syndrome more prevalent in UK South Asians compared with Caucasians that was

characterized by higher concentrations of fasting insulin and an increased waist-hip ratio. The insulin resistance syndrome is a precursor of diabetes and may be a common pathogenic mechanism for developing coronary artery disease (Wilson *et al.*, 1999). This syndrome consists of hyperinsulinemia, atherogenic dyslipidemia, glucose intolerance, a prothrombotic state, central obesity, and hypertension.

In the Canadian Study of Health Assessment and Risk in Ethnic groups (SHARE) (Anand *et al.*, 2000) South Asians were more likely to have diabetes than Chinese and European (overall P = 0.03), were more frequently diagnosed as having impaired glucose tolerance (overall P = 0.03), and had higher mean fasting blood glucose (overall P = 0.0001). In a case-control study of patients with a first MI (Gerstein *et al.*, 1999), South Asians were more likely to have impaired fasting glucose (OR 3.2; 95% CI 1.5 to 6.9), impaired glucose tolerance (OR 4.1; 95% CI 2.3 to 7.2), or diabetes (OR 5.5; 95% CI 3.3 to 9.0) than controls. Even after excluding participants with diabetes, patients with impaired glucose tolerance, and impaired fasting glucose South Asians were still more likely to have an fasting blood glucose (FBG) in the third (5.2 to 6.3mmol/l) and fourth quartile (> 6.3 mmol/L), OR 6 (95% CI 3.3 to 10.9) and OR 3.4 (95% CI 1.9 to 5.8). These odds ratios were independent of lipid concentrations, smoking, abdominal obesity, and insulin concentrations. This study showed glucose elevation above a relatively low concentration appears to be a continuous risk factor for cardiovascular disease in South Asians. It is possible, however, that some undiagnosed diabetics were included in this analysis. The results suggest that glucose elevation short of diabetes is an independent marker for atherosclerosis in South Asians as well as in Caucasians.

2.5.3 Methods of Comparison of dysglycaemia in South Asians and Caucasians

Data from the Health Survey for England 1999 (HSE 1999) was used to study ethnic differences in blood glucose and HbA1c concentrations.

2.5.3.1 The Health Survey for England series

The Health Survey for England (HSE) comprises a series of annual surveys beginning in 1991. The series is part of an overall programme of surveys commissioned by the UK Department of Health and designed to provide regular information on various aspects of the nation's health. All surveys have covered the adult population aged 16 and over living in private households in England and Wales. The sampling frame for the HSE ensures the group is nationally representative of people of different ages, sex, geographic area and socio-demographic circumstances. Each eligible person was interviewed face to face. They were also visited by a nurse who made a number of simple clinical measurements and obtained a sample of blood.

In 1999 in order to increase the number of informants from the six most populous minority ethnic groups: Black Caribbean, Indian, Pakistani, Bangladeshi, Chinese and Irish the design included a 'boost' component, designed solely to yield additional interviews with these groups. Cardiovascular diseases were included as a special topic for adults. At least 71% of eligible boost sample households adults were interviewed, 47-63% of South Asians had their blood pressure measured, and 33-54% agreed to give a blood sample.

From the HSE 1999 dataset, Caucasians and South Asians aged 35-69 years with no history of myocardial infarction (MI), angina, stroke, diabetes or taking lipid lowering drugs, and with fasting blood glucose $\leq$7.77mmol/l (140 mg/100) were

identified (Table 2.3). Values of FBG and glycosylated haemoglobin were compared between Caucasians and South Asians.

Table 2.3 Selection of subjects from HSE 1999 for investigating dysglycaemia by ethnicity

	Caucasian	South Asian
Aged 35-69 years	753	1678
History of CVD (MI, angina, or stroke)	38	119
Diabetes or FBG ≥7.77 mmol/l	22	193
HbA1c not measured (missing)	268	831
Remained number for analysis	425	535

2.5.3.2 Statistical analysis

Statistical analysis was performed using SPSS version 11.2. Fasting blood glucose and glycosylated haemoglobin averages were used for analysis. The independent students t-test was used to compare South Asian and Caucasian groups where necessary. Adjusted means were derived and compared using analysis of covariance model. Spearman correlation coefficient was used to assess associations between FBG and glycosylated haemoglobin in each ethnic group. The Fisher's z-score transformation was employed to compute the significance of the difference between two correlations in South Asians and Caucasians (Blalock, 1972). Each correlation coefficient was transformed into a z-score by dividing the correlation plus 1, by the same correlation minus 1. Then the natural log of the absolute value of the result divided by 2. The difference between the two z-scores was divided by the standard error of difference between the two correlations (SE=SQRT[(1/(n1-3) + (1/(n2-3)].

For all tests, the alpha level for statistical significance was 0.05.

2.5.4 Comparison of dysglycaemia in South Asians and Caucasians in HSE 1999

Table 2.4 shows baseline characteristics of Caucasians and South Asians included in the analysis. Caucasians were older than South Asians (6.1 year; 95% CI 4.3 to 7.2), had higher mean systolic blood pressure (mean difference [Δ] 4.0 mm/Hg; 95% CI 1.6 to 6.5), total and HDL cholesterol (Δ 0.3 mmol/l; 95% CI 0.2 to 0.4) and (Δ 0.2 mmol/l; 95% CI 0.1 to 0.3) respectively. Caucasians were more than twice as likely to smoke than South Asians, $P < 0.0001$. Other than diastolic blood pressure, the differences in coronary risk factors between South Asians and Caucasians were all statistically significant.

HbA1c levels ranged from 4.3 to 7.7% in South Asians and 4.5 to 6.7% in Caucasians. HbA1c level correlated with FBG in both Caucasians and South Asians, Spearman $r = 0.28$ ($P < 0.001$) and Spearman $r = 0.36$ ($P < 0.001$) respectively. The difference in the correlations between two groups was not statistically significant; Δ 0.08 (SE = 0.06), $P > 0.05$.

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Table 2.4 Characteristics of selected Caucasians and South Asians in HSE 1999

	Caucasians (n=425) Mean (95%CI) or %	**South Asians (n=535)** Mean (95%CI) or %
Age* (year)	51.7 (50.5 to 53.0)	45.6 (44.8 to 46.5)
Sex *(men)	169 (39.8%)	253 (47.3%)
Systolic blood pressure* (mmHg)	133.8 (131.9 to 135.7)	129.8 (128.1 to 131.4)
Diastolic blood pressure (mmHg)	76.0 (74.8 to 77.2)	76.5 (75.5 to 77.6)
Total cholesterol* (mmol/l)	5.6 (5.5 to 5.7)	5.3 (5.2 to 5.4)
HDL cholesterol* (mmol/l)	1.47 (1.42 to 1.51)	1.28 (1.25 to 1.31)
Fasting blood glucose (mmol/l)*	5.25 (5.17 to 5.32)	5.40 (5.32 to 5.47)
HbA1c (%)*	5.45 (5.40 to 5.51)	5.77 (5.72 to 5.81)
Smoking*	131 (30.8%)	76 (14.2%)

* P < 0.001

Table 2.5 displays ethnicity by overall quartiles of HbA1c. The distribution of HbA1c in South Asians was shifted to the right as compared with that of Caucasians (Figure 2.1). Caucasians had proportionately more HbA1c values in quartiles I and II, whilst 48% of South Asians were in the 3rd and 4th quartiles compared to 27% of Caucasian participants.

Table 2.5 Haemoglobin A_{1c} measurements in non-diabetic Caucasians and South Asians in HSE 1999

	Mean (95% CI)	Median (IQR*)	Quartile I	Quartile II	Quartile III	Quartile IV
Caucasians	5.6 (5.5 to 5.6)	5.6 (5.3 to 5.8)	4.5 – 5.3	5.4 – 5.6	5.7 – 5.8	5.9 – 10.3
South Asians	5.9 (5.8 to 5.9)	5.8 (5.6 to 6.1)	3.2 – 5.5	5.6 – 5.8	5.9 – 6.0	6.1 – 13.3
Total	5.7 (5.7 to 5.8)	5.7 (5.4 to 5.9)	3.20-5.40	5.41-5.70	5.71-5.90	5.91-13.30

*IQR: Interquartile

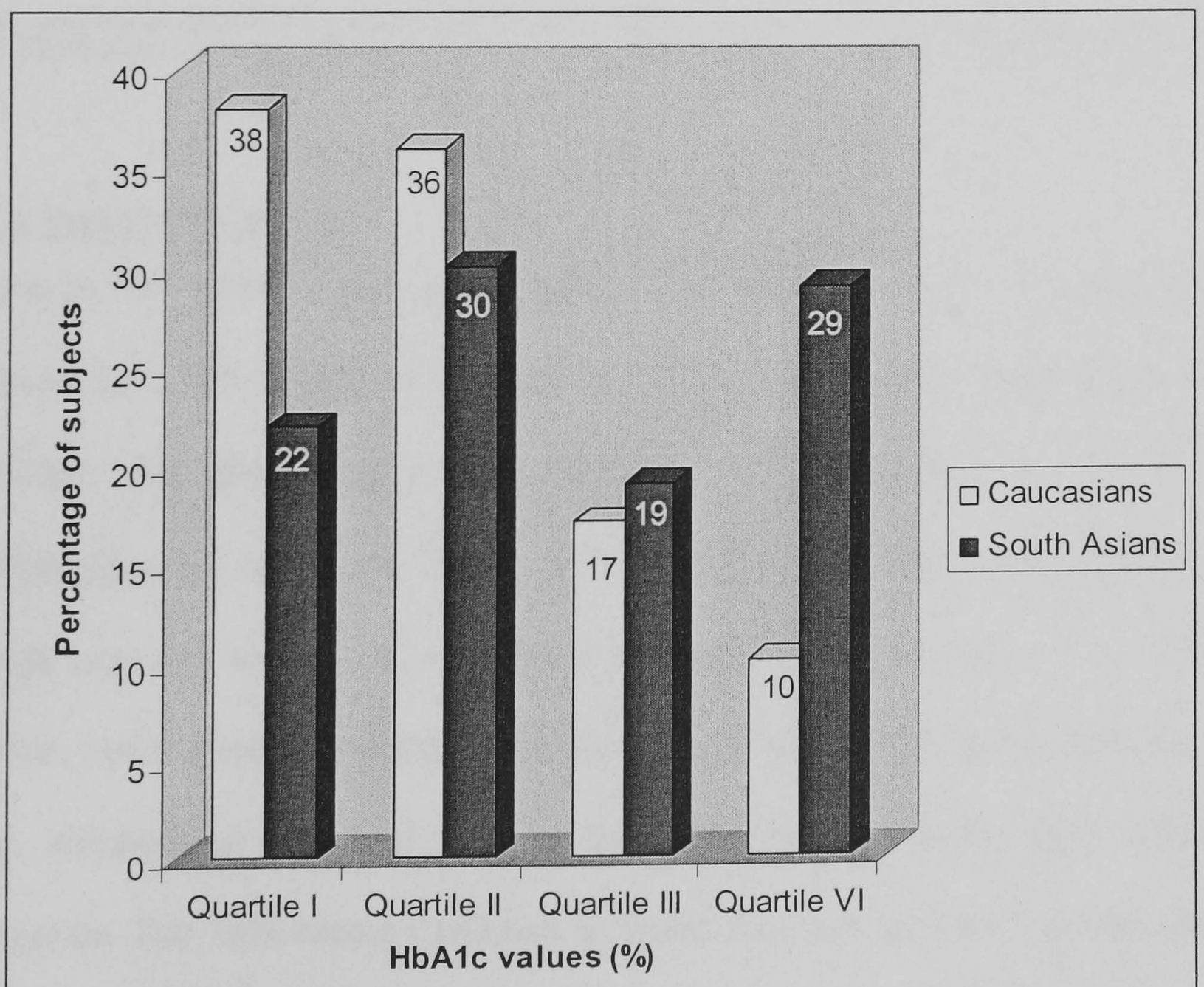

Figure 2.1 HbA1c values in South Asians and Caucasians in different quartiles

Mean difference of FBG and HbA1c between South Asians and Caucasians are shown in the Table 2.6. South Asians had significantly higher fasting blood glucose and HbA1c compared to Caucasians after adjustment for age, sex, systolic BP, total and HDL cholesterol, and smoking status.

Table 2.6 Univariate analysis of fasting blood glucose and Glycated haemoglobin in selected Caucasians and South Asians in HSE 1999

	Mean differences (95% CI)	**P value***
Fasting blood glucose (mmol/l)	0.15 (0.06 to 0.25)	P = 0.001
Glycosylated haemoglobin (%)	0.3 (0.2 to 0.3)	P < 0.001

*After adjustment for age, sex, systolic BP, total & HDL cholesterol, and smoking status

2.6 DISCUSSION

Despite the almost universal acceptance of the increased risk of cardiovascular disease in South Asians, the evidence to support this from longitudinal studies is limited. The Khattar study (Khattar *et al.*, 2000) suggests a risk of CHD independent of other risk factors 1.79 higher is consistent with evidence from cross-sectional surveys. In contrast the larger UKPDS (Stevens *et al.*, 2001), a robust randomised controlled trial confined to patients with diabetes, failed to show any independent effect of South Asian ethnicity with fairly tight confidence intervals. The 79% excess CHD risk in South Asians is the best estimate and will be used in further modelling of CHD and CVD risk for this ethnic group in this

thesis. However this estimate is derived from a single study of hypertensive patients with higher proportion of men (about 80%).

This discrepancy would seem to be explained at least in part by a difference in glycaemia in the non-diabetic South Asian and Caucasian populations, and the strong evidence of a link between this level of glycaemia and risk of cardiovascular disease. However, South Asian diabetic patients also have higher HBA1c than Caucasians. The excess dysglycaemia may represent part of the insulin resistance syndrome common in South Asians (McKeigue *et al.*, 1991). The reasons for the enhanced susceptibility to insulin resistance are disputed. A genetic predisposition has been postulated (Chaturvedi, 2003), although no specific polymorphism has been isolated. In general social and economic differences are associated with inequalities in CHD although this link in UK South Asians is controversial. Europeans fared better in some indicators of socio-economic status and South Asian in others (Bhopal *et al.*, 2002). None of the longitudinal studies I identified accounted for socio-economic status. In South India people with middle income socioeconomic status had a higher intake of calories, fat and sugar compared to low income groups who had a statistically significant lower prevalence of metabolic syndrome (Mohan *et al.*, 2001).

Although the Khattar and UKPDS studies were in specific groups at high risk of CHD their results were used because of a dearth of population based prospective epidemiological cohort studies. The number of South Asians subjects in the Khattar study was small and these results must be interpreted with this in mind. Neither study differentiated between different groups within the South Asian population. Bhopal et al (Bhopal *et al.*, 1999) however reported considerable

heterogeneity within South Asians, Indians being least and Bangladeshi most disadvantaged in terms of coronary risk.

Only English language databases were searched and as a result, it is possible that some data published in native languages in the Indian subcontinent was missed.

These results suggest that there is an increased risk of CHD in South Asians unexplained by differences in traditional risk factors. Although conventional risk factors are qualitatively similar in South Asians their quantitative impact may be different (Yusuf *et al.*, 2004). At least part of the higher CHD risk in South Asians may be due to differences in blood sugar in non-diabetic subjects. This is consistent with Gerstein and colleagues (Gerstein *et al.*, 1999) finding of a graded risk of MI with glucose elevations within the normal range in South Asians. If these observations are confirmed, the population attributable risk of dysglycaemia may be several times greater than the population attributable risk of diabetes alone. This may lead to consideration of the diagnosis of a pre-diabetic state in South Asian people. Randomised controlled trials confirm that effective lifestyle intervention can prevent or delay the progression to type 2 diabetes in groups at high risk, such as overweight people with impaired glucose tolerance (Narayan *et al.*, 2002). Unfortunately it has been shown that people from the South Asian groups participate less in sport and recreational activities when compared to the general population (Hayes *et al.*, 2002; Erens & Primatesta, 1999; Johnson, 2000). Targeted promotion of lifestyle modifications to people with pre-diabetes could be applied in South Asians. However health promotion in ethnic minority groups requires an additional major effort to understand attitudes, beliefs, and barriers to

lifestyle modifications so that advised changes are appropriate. Unwin *et al.* (1998) carried out a secondary analysis of the Newcastle heart project on the prevalence of diabetes and pre-diabetes, age and sex adjusted using standard population of England and Wales. The prevalence of diabetes and pre-diabetes in South Asians were reported as 20.1% and 30.5% respectively. One fifth of the South Asian population have diabetes and need a clinical approach to targeting and treating. An additional third of the population could therefore be categorized as having pre-diabetes and need effective lifestyle intervention. This would be an immediate and difficult challenge for general practitioners. Further work is required to confirm the hypothesis and to develop a validated risk prediction tool to guide intervention decisions for South Asians.

For the expatriate population, the effect of migration on coronary risk is also important. Between countries comparisons (UK and India) have shown that migration confers a higher risk of CHD with an increase in body weight, serum cholesterol, and blood pressure (Bhatnagar *et al.*, 1995). There is additionally a trend towards the acquisition of westernized behaviours consistent with a sedentary lifestyle, high salt and fat and low fiber diet and new stresses. The likelihood of an increase in insulin resistance, its expression as frank diabetes mellitus and glucose intolerance probably increases on migration (Misra & Vikram, 2004). A combination of these factors may therefore unmask the underlying genetic risk of CHD.

CHAPTER 3

PREDICTING CORONARY RISK IN UK SOUTH ASIANS: AN ADJUSTMENT METHOD FOR FRAMINGHAM BASED TOOLS

3.1 INTRODUCTION

A basic principle of prevention of cardiovascular disease (CVD) is that the intensity of risk-reduction therapy should be adjusted to a person's absolute risk. Hence, the first step in selection of any therapy is to assess a person's risk status. Risk in diabetic South Asians is predicted by classical risk factors whilst risk in the non-diabetic population is 79% greater than predicted (chapter 2 of this thesis). This figure is grater than that suggested in current guideline (JBS-1, 1998) which used an increment of 50% for South Asian people. However they give no justification or evidence base for this figure. Given the apparent variation in risk between groups within the South Asian community it is probable that for some the excess risk above Caucasians is only 50%. However this figure of 79% remains the best evidence based of estimate of risk ratio.

Because of the increased risk of coronary heart disease (CHD), many people of South Asian descent should be eligible for lifestyle recommendations and a greater use of antihypertensive and lipid lowering drugs for the primary prevention of CHD. However, use of such treatments is usually guided by an explicit assessment of risk, and currently available tools which do not take account of ethnic specific factors are accepted as inaccurate for this group. This means that South Asians may receive less preventive treatment than appropriate either because their risk is underestimated or because they are excluded from the risk assessment process completely.

The risk of developing CHD depends on a number of determinants. The first attempt at assessing the absolute risk of CHD date back to 1973 when the Committee on Reduction of Risk of Heart Attack and Stroke of the American

Heart Association published the "Coronary Risk Handbook" with the estimates derived from the Framingham Heart Study (Lindsay & Gaw, 2004). This study identified several risk factors that interact in a deleterious manner to have a cumulative impact on the incidence of CVD. The effect of these risk factors in the population was encapsulated in a mathematical time to failure model which has been used as the basis of several tools for the prediction of individual risk (Anderson *et al.*, 1991). The rationale for estimating total CVD risk based on the major risk factors is that: "

(a) CVD is multifactorial in origin;

(b) risk factors tend to cluster;

(c) co-existent risk factor tend to have a multiplicative effect on CVD risk.

The level of any single risk factor in isolation is an inadequate guide to overall cardiovascular risk and further intervention. For the same blood pressure level some people are eligible for antihypertensive therapy and others not, depending on their absolute risk of developing CVD. Absolute CVD risk is expressed as a probability (% chance) of developing CVD over a defined period of time, e.g. 20% risk over 10 years means the person has 20% chance of developing CVD in the next 10 years. This cumulative score does not aim to provide a precise risk indicator for a disease of such complexity but it does provide the healthcare practitioner and patient with a better estimation of overall risk where several risk factors are present. This risk based threshold does not preclude treatment of extreme values of single risk factors. As the number of patients with severe hypertension or familial hypercholestrolaemia in a population like Framingham is small the accuracy of the risk factor equation may not capture the impact of blood pressure or cholesterol at these extreme values. In addition extreme values of risk

factors may necessitate treatment because they are associated with adverse outcomes not encapsulated in the Framingham equation e.g. renal failure consequent to malignant hypertension.

Most risk functions are based on logistic regression, Cox regression, or time to failure statistical models. Whilst the first two can only provide information about the likelihood or not of suffering an outcome or not within a fixed time interval the results are often simplistically converted to a rate and applied to different time intervals. An advantage of the time to failure models is that risk of events for a range of time intervals can be considered (Anderson *et al.,* 1991).

In order for multivariable risk assessment and treatment guidelines to have optimal use and acceptability, we need to be confident that absolute risk prediction functions can be transported to other settings beyond those in which they were originally developed. The Diverse Population Collaborative Group (DPCG, 2002) reported that traditional risk factors are qualitatively associated with CHD mortality in a diverse set of population using person-level data from 161,955 participants in 16 cohort studies. However significant heterogeneity was observed in three aspects: risk ordering, magnitude of relative risk, and estimation of absolute risk.

The Framingham equation works reasonably well among both black and white American men and women for prediction of CHD events within 5 years of follow-up. However, it systematically overestimated the risk among Japanese-origin American and Hispanic men and American Indian (members of Indian tribal nations who live in the United States) women. It could however be recalibrated for

these groups (D'Agostino *et al.*, 2001). It also predicts the risk of cardiovascular events accurately in an ethnically mixed cohort, 85% European, in New Zealand (Milne *et al.*, 2003). The Framingham prediction function has been validated for European populations to predict future risk of CHD (Haq *et al.*, 1999) but may overestimate risk of CHD in other ethnic groups with different rates of CHD. A study in the British population contrasting Framingham risk with annual hospital in-patient admission data reported that the risk function estimates CVD events well according to annual number of CVD events derived from the 2001 UK hospital in-patient episode statistics (Shearer *et al.*, 2005). In contrast the British regional heart study investigators reported an overestimation of the risk of CHD mortality by the Framingham equation in their prospective cohort study of men, aged 40-59 years at entry (Brindle *et al.*, 2003). There are other reports indicating that the Framingham equation overestimates risk in Italy and Denmark in Europe (Menotti *et al.*, 2000; Thomsen *et al.*, 2002). This overestimation is probably reflecting the lower incidence in those countries with a lower CHD mortality rate. However the relative risks did not differ significantly with the Framingham population in Denmark study (Thomsen *et al.,* 2002). Similarly the Framingham function estimates were more than double the observed risk of CHD observed in north east Spain (Marrugat *et al.*, 2003). Even where the Framingham equation has been shown to overestimate CHD risk significantly, it still provides a reasonable ranking of risk or estimate of relative risk and implies that those at highest risk would be identified independently of the model that has been chosen. Because of this simple adjustment has produced tolerable estimates of absolute risk in some populations (Laurier *et al.*, 1994).

Cardiovascular risk assessment has an impact on treatment allocation in primary prevention since clinical guidelines tend to employ predicted absolute values as a tool for clinical decision making. Whilst population level lifestyle changes should be made by everyone aggressive preventive treatment and intervention are only justified if a patient's absolute risk exceeds a certain cut off point. In this context, it is important that the prediction of individual absolute risk be valid. Inaccuracies will lead either to people being exposed to the adverse effects of treatment with very little chance of benefit or deprive them of substantial benefit. Grover and colleagues (Grover *et al.*, 1995) studied community based doctors and showed that their assessment of absolute risk of coronary disease was inaccurate without a risk prediction tool. They were, however, much better at assessing relative CHD risk. As a result algorithms, functions, and scores have an important role in clinical practice in the prediction of the probability of a subsequent cardiovascular event in individuals initially free of symptomatic heart and other vascular disease. Several factors may be responsible for the inaccuracy of a risk prediction model in diverse populations including: differences in CVD prevalence and/or diversity in the prevalence and distribution of risk factors. When testing the performance of a clinical prediction model in different populations, the accuracy of the predicted probability has two components (calibration and discrimination) which both need to be assessed (Justice *et al.*, 1999). A well-calibrated model has predictions that are neither too high nor too low i.e. the baseline risk is correctly assessed (the estimates are close to a "real" probability). A model that discriminates well ranks individual risk in the correct order, i.e. between cases with "event" and "no event". Unfortunately, there are no data linking individual risk factors with future incidence of CVD that can be used to test the validity of the Framingham equation

in the South Asian ethnic minority against either of these criteria.

In the case of a systematic overestimation or underestimation of risk, transporting a prediction function from one setting to another requires recalibration. D'Agostino and colleagues tested the validity and transportability of the Framingham CHD prediction function in male and female black Americans (D'Agostino *et al.*, 2001). The sex-specific Framingham CHD prediction functions perform well among whites and blacks in different setting and can be applied to other ethnic groups after recalibration for different prevalences of risk factors and underlying rates of CHD events. Likewise the recalibrated Framingham function has become an effective method of estimating the CVD risk in north east Spain (Marrugat *et al.*, 2003). Little is known about the accuracy of the Framingham equation for predicting risk in South Asians although it is believed to order estimated risk (Cappuccio *et al.*, 2002). Having a recalibration for South Asians would need a cohort study with sufficient fatal and non-fatal cardiovascular endpoints or a well established CVD register and the prevalence of their risk factors. No single cohort study sufficiently large for this purpose is available for the UK South Asian population. Brindle and colleagues have recently developed a model using available risk factor and disease prevalence information in the absence of prospective data for black and ethnic minority groups (personal communication). This model may potentially improve identification of high risk people in ethnic minorities but still requires refinement and validation.

In practice three different forms of scoring systems are being used:

- Computer based scoring systems provide the probability displayed as a

percentage of suffering a cardiovascular event within a specified period of time (usually 10 years). Users enter the required risk factor values, and the software provides the risk estimate. Examples include "The Boehringer-Mannheim Infarct Risk Calculator" (Lindsay & Gaw, 2004) which is similar to an ordinary calculator, "The Joint British Societies' Cardiac Risk Assessor Software" (JBS-1, 1998), or "The UK Prospective Diabetes Study (UKPDS) Risk Engine" (Stevens *et al.,* 2001).

- In paper based tools values in tables, graphs, or cells matrices of different colours represent different CHD or CVD risk levels or categories. Examples of this are "The Joint British Societies' CVD risk prediction charts" (JBS-2, 2005), "The Sheffield Table" (Wallis *et al.,* 2000), "The SCORE project risk estimator" (Conroy *et al.,* 2003) and "The New Zealand Table" (Jackson, 2000). They are generally based on age, gender, total to HDL cholesterol ratio, systolic blood pressure, smoking habit, and diabetes. Such charts do provide a pictorial representative of risk which may facilitate patient (and doctors) comprehension.
- Summation of different points to score risk factors is the basis of the third scoring system. Points scoring systems are easily derived from parameters in logistic or Cox proportional statistical models. Depending upon the strength of the covariate in the analysis points are attributed to individual risk factors. Summing the points can then provide a numerical estimate of risk via a look-up table. This method is employed by the National Cholesterol Education Programme (ATP-III, 2001).

Multidimensional risk factor interaction is however difficult to represent in a single two dimensional table or chart and most invoke some form of approximation or use

only a sub-set of risk factors.

The various systems use different endpoints such as; fatal and non-fatal CVD or CHD and CVD mortality alone or combined. Including all fatal and non-fatal CVD events provides a better estimate of true burden of total CVD risk. However different patients may attribute quite unequal weights to the various endpoints e.g. many, but not all, people believe severe disabling stroke is a fate worse than death (Solomon *et al.*, 1994; Gage *et al.*, 1996). Risk threshold for professional intervention (lifestyle and appropriate drug therapies) is an important property of any risk prediction tools. Currently updated guidelines have suggested ≥20% CVD risk over 10 years, which is equivalent to a CHD risk of ≥15 over the same period (Yeo & Yeo, 2002), as the intervention threshold.

When the clinical risk prediction tool is implemented as software or in a calculator which provides a numerical estimate of risk a simple ethnic factor multiplier can be applied to the estimated risk. Where the tool categorizes patients into nominal risk groups e.g. low, intermediate or high or indicates only eligibility or not for treatment no similar simple adjustment can be used.

3.2 AIM AND OBJECTIVES

- To identify a method for adjusting the input to Framingham equations for use in non-diabetic South Asian individuals to accommodate their 79% greater risk of CHD and apply this to the simple practical paper based tools.
- To confirm the discriminatory ability of this adjustment method in a South Asian sample in separating those above and below a 20% cardiovascular event risk threshold.

3.3 METHODS

3.3.1 Population

In testing different methods of adjustment typical distributions of risk factors were ensured by using values from a large UK population survey.

3.3.1.1 Health Survey for England Series

Two datasets of the health survey for England series have been used:

- The HSE 1998 dataset (HSE, 1998) was used to examine the mathematical effect of different adjustment methods in risk factor distributions derived from a large number of subjects similar to the Framingham Study population.
- For sensitivity analysis, the HSE 1999 dataset (HSE, 1999) which provides a representative sample of South Asians living in England and Wales was used.

Using HSE 1998:

The HSE 1998 dataset was used to examine the distribution of CHD risk in people without pre-existing symptomatic disease and to test the mathematical properties of different adjustment methods. In the HSE 1998 study 9,208 people were interviewed, 58% had their blood pressure measured, and 49% agreed to give a blood sample. For analysis, those with angina, myocardial infarction, stroke, or treatment with lipid lowering drugs were excluded. In addition, 2440 subjects with one or more of the variables necessary for risk calculation missing were excluded from any analysis (Figure 3.1 - a).

Using HSE 1999:

The HSE 1999 dataset was used to examine the sensitivity and specificity of the adjustments to the Framingham equation in South Asian subjects without vascular disease. In this HSE dataset adults were interviewed at 71% of known eligible

boost sample households, 33 - 54% of South Asians had their blood pressure measured, and 33-61% agreed to give a blood sample. The exclusion and inclusion criteria were the same as those applied to the HSE 1998 and are shown in the Figure 3.1 – b.

The number of subjects for analysis is different here from the number of selected subjects for dysglycaemia analysis in chapter 2 of this thesis (2.5.3.1-page 37). This discrepancy is explained by exclusion of people without fasting blood glucose ≥7.77 mmol/l (140 mg/100) as well as missing data for the variables under investigation in each chapter.

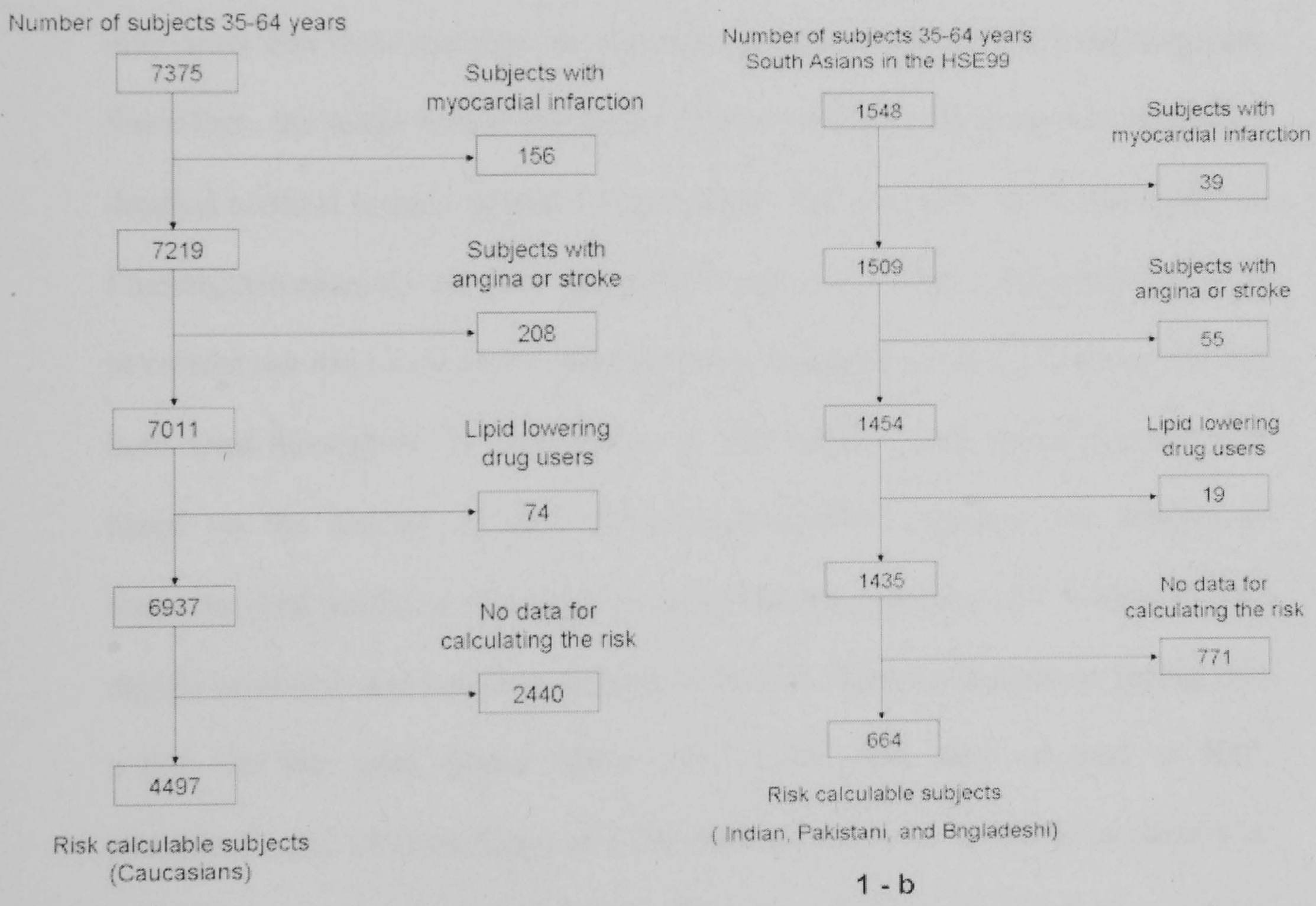

Figure 3.1 Selection of subjects from the HSE 1998 (1-a) and HSE 1999 (1-b) investigation of adjustment methods

3.3.2 Prediction equation

The magnitude of the absolute risk of CHD is commonly expressed as the per cent chance of suffering a fatal or non-fatal coronary event over the next 5 or 10 years.

3.3.2.1 The Framingham equation

The Framingham equation derived from the Framingham Heart Study was used as a standard for predicting the risk of CHD in people who had no history of vascular disease. As background to the use of this equation it is important to know a little about how it was developed. In 1948, 5209 men and women between the ages of 30 and 62 from the town of Framingham, Massachusetts were recruited for this study and began the first round of extensive physical examinations and lifestyle interviews that were analyzed for common patterns related to CVD development. Since then, the subjects have continued to return to the study every two years for a detailed medical history, physical examination, and laboratory tests. Although the Framingham equation has been updated (Wilson *et al.*, 1998), risk prediction tools in current use are based on the older equation (Anderson *et al.*, 1991) and this has been used throughout for consistency. In the original study blood pressure was based on the average of two office measurements, diabetes was defined as treatment with insulin or oral agents or a fasting blood glucose of 7.77 mmol/l (140 mg/dl) or above, and smoking as being a current cigarette smoker or having quit within the last year. These along with gender, age, ratio of total to HDL cholesterol, and ECG evidence of LVH were shown to be powerful predictors of future CHD in a time to failure model. There is no information available regarding the left ventricular hypertrophy in the HSE series and it was assumed that subjects have no LVH. In addition South Asians have similar ECG voltage to Caucasians which suggests a similar prevalence of LVH (Spencer *et al.*, 2004).

The definition of CHD used in the risk function- includes fatal and non-fatal MI, acute coronary insufficiency and new onset angina pectoris. Box 3.1 shows the Framingham risk equations for CHD events based on the coefficients for the Framingham regression model. Risk derived from the Framingham equation was multiplied by a factor of 1.79 to provide the reference risk in non-diabetic South Asians identified in the HSE 1998 dataset (chapter 2, this thesis).

Box 3.1 Framingham risk equation for coronary heart disease events

$$\mu = 15.5305 + 28.4441 (sex_{female}) - 1.4792 (LN_{age})^2 - 14.4588 ((LN_{age})(sex_{female})) + 1.8515 ((LN_{age})^2(sex_{female})) - 0.9119 (LN_{systolic\ blood\ pressure}) - 0.2767(cigarettes\ smoking) - 0.7181 (LN_{total\ :\ HDL\text{-}C}) - 0.1759 (diabetes) - 0.1999 (diabetes \times sex)$$

****

Log sigma = $0.9145 - 0.2784 \times \mu$

Sigma = EXP (Log sigma)

****

U = $(Log_{10} - \mu) / sigma$

Framingham CHD events = 100*(1-(EXP(-1*(EXP(U)))))

****

Systolic blood pressure measured in mmHg and age in years. Variables cigarettes smoking, diabetes and female gender are set to 1 when present and 0 when absent.

3.3.3 Method of adjustment

Feasible adjustments, which might be applied to the paper-based risk prediction tools such as "the Joint Societies Chart" and "the Sheffield Table" to identify South

Asians warranting treatment, were studied. Continuous independent risk factor variables included in the Framingham equation, which might be manipulated simply to allow for the increased risk observed in non-diabetic South Asians were selected. The different adjustments investigated were:

- fixed increments to the age,
- total cholesterol (TC),
- TC: HDL cholesterol ratio,
- and systolic blood pressure and multipliers for the TC: HDL cholesterol ratio.

Table 3.1 describes the different adjustment methods.

Table 3.1 Different adjustments to the Framingham equation used to approximate a 1.79 fold increase in risk

Variable	Adjustment method
Age	Addition of 1 to 10 years to the age
Total cholesterol (TC)	Addition of 0.5 to 3.2 mmol/l to the TC
(TC:HDL cholesterol) ratio	Addition of 0.5 to 2.0 to the (TC:HDL cholesterol) ratio
(TC:HDL cholesterol) ratio	Multiplying the (TC:HDL cholesterol) ratio by 1.1 to 2.0
Systolic blood pressure	Addition of 10 to 60 mm Hg to the systolic blood pressure

To ensure a representative distribution of risk factors on which to test the adjustments, risk factor data from 4497 individuals identified from the HSE 1998 dataset, was used. For each individual the Framingham equation was used to calculate a baseline CHD risk and then inserted modified values for the risk factor under study, on each occasion estimating the ratio of new risk to baseline risk. Interpolation allowed selection of the value of adjustment of the risk factor that

gave a mean ratio of adjusted to baseline risk closest to 1.79.

Distribution and dispersion of individual ratios of adjusted to baseline risk were then investigated. Where distributions were non-normal, a Bootstrap method (Bradley & Gill, 1983) was used to estimate 95% confidence intervals. A sample of a size of 10,000 was generated from the data by random sampling with replacement. The sample was sorted into ascending order and the value of the 250th provided the lower 95% confidence limit while the value of the 9750th that of the upper 95% confidence limit.

3.3.4 Test of sensitivity and specificity

Diagnostic accuracy is a fundamental characteristic of a test that measures the test's ability to discriminate among alternative states. The receiver-operating characteristic curve (ROC curve) (Zweig & Campbell, 1993) provides a pure index of accuracy by demonstrating the limits of a test's ability to distinguish between two different states. Information in the Table 3.1 gives a measure of scientific accuracy of the various adjustments but the ROC curve demonstrates how well an adjustment function discriminates between two states in practice. The ROC curve was used to compare the different adjustments in their primary role of identifying South Asian individuals above or below a given threshold using risk factor information from HSE 1999. To maintain consistency with current UK guidelines the 10-year CHD event risk threshold of 15% was investigated. The proportion of subjects with a CHD risk greater than 30% was too small to allow any meaningful analysis. Sensitivity against one minus the specificity was plotted for different values of each of the adjustment methods (adding to the age, TC, systolic blood pressure, TC: HDL ratio, and multiplying TC: HDL ratio). The area under the curve was calculated for each method to determine the most accurate in this role.

3.4 RESULTS

3.4.1 Adjustment methods

In the HSE 1998, 4497 subjects provided sufficient information to have their risk of a first CHD event calculated by the Framingham equation (Table 3.2).

Table 3.2 Basic characteristics of CHD risk factors in eligible subjects in HSE 1998

Characteristics	Mean (SD) or number (%)
Number of subjects	4497
Age (years)	44 (8)
Gender (female)	2444 (54.3%)
Diastolic Blood Pressure (mmHg)	76.2 (11.6)
Systolic Blood Pressure (mmHg)	132.9 (17.0)
Total cholesterol (mmol/l)	5.7 (1.1)
HDL cholesterol (mmol/l)	1.45 (0.4)
Diabetes	64 (1.4%)
Cigarette smokers	1098 (24.4%)

The effects of the four methods of adjustment on prediction risk used are shown in Figure 3.2. All adjustments produced a graded monotonic, almost linear increase in risk. By interpolation it was possible to select a value for each adjustment factor that would provide mean increment in risk of 1.79. For practicality an integer or real number with limited number of decimal places was chosen as the optimal value of the adjustment factor. The effect of using this modification on individual risk estimates was then studied.

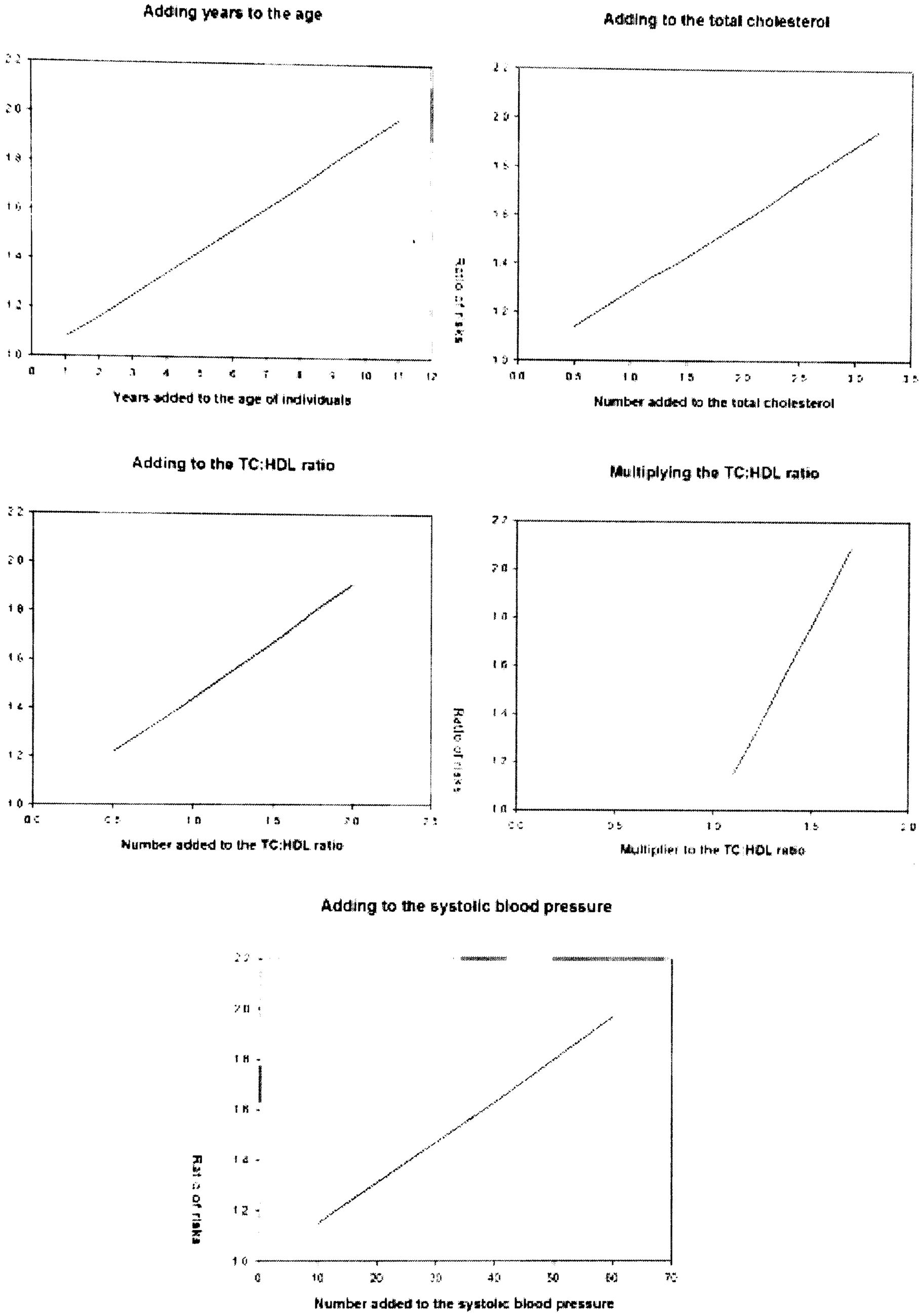

Figure 3.2 Different methods used for adjustment the Framingham equation

The simplest adjustment that of adding years to age produced a wide range of individual relative increments in predicted risk over ten years. The precision of

other methods was better although these would be slightly more complex to implement with a paper-based tool, Table 3.3 shows distribution of risk ratios of the different adjustment methods around values which gave an increased mean ratio closest to a factor of 1.79.

Table 3.3 Distribution of individual ratios of adjusted to baseline risk with the different methods of adjustment

	Mean (95% CI*)	**Median (IQR**)**	**Range of values**
Age +10	1.88 (1.09 to 4.50)	1.60 (1.36 – 2.03)	1.04 – 7.86
TC +2.8	1.83 (1.29 to 2.92)	1.73 (1.55 – 2.04)	1.16 – 4.45
(TC/HDL) + 1.8	1.82 (1.18 to 3.30)	1.67 (1.42 – 2.05)	1.05 – 6.32
(TC/HDL) * 1.5	1.77 (1.34 to 2.44)	1.73 (1.56 to 1.93)	1.21 – 3.08
Systolic BP +50	1.80 (1.30 to 2.64)	1.74 (1.55 to 1.99)	1.19 – 3.68

*Confidence interval (calculated by Bootstrap method)

** Inter-quartile Range

3.4.2 Sensitivity and specificity

For each method sensitivity and specificity and ROC plots were used to compare the different adjustments in their role of identifying high-risk individuals. The

Framingham equation with risk multiplied by 1.79 was used as the standard for calculation of CHD risk and subjects were characterised as having a risk of greater or less than 15%. Their allocation according to an "adjusted" paper based method was compared with that according to the reference risk assessment. Table 3.4 shows sensitivity and specificity for the different adjustment methods.

Table 3.4 Sensitivity and Specificity for adjustment methods

	Sensitivity (%)	**Specificity (%)**
Age + 10	83.4	97.9
TC + 2.8	87.7	96.2
(TC:HDL) + 1.7	77.0	97.1
(TC:HDL) × 1.5	89.3	97.1
Systolic BP + 50	88.2	96.4

The areas under the curve are very close in four different methods (Figure 3.4). Although multiplying TC: HDL cholesterol ratio by 1.5 gave the largest area under the curve, 0.984, all the methods had an area greater than 0.903 and gave us acceptable accuracy in recognising South Asians above and below a 15% CHD risk threshold in UK South Asians.

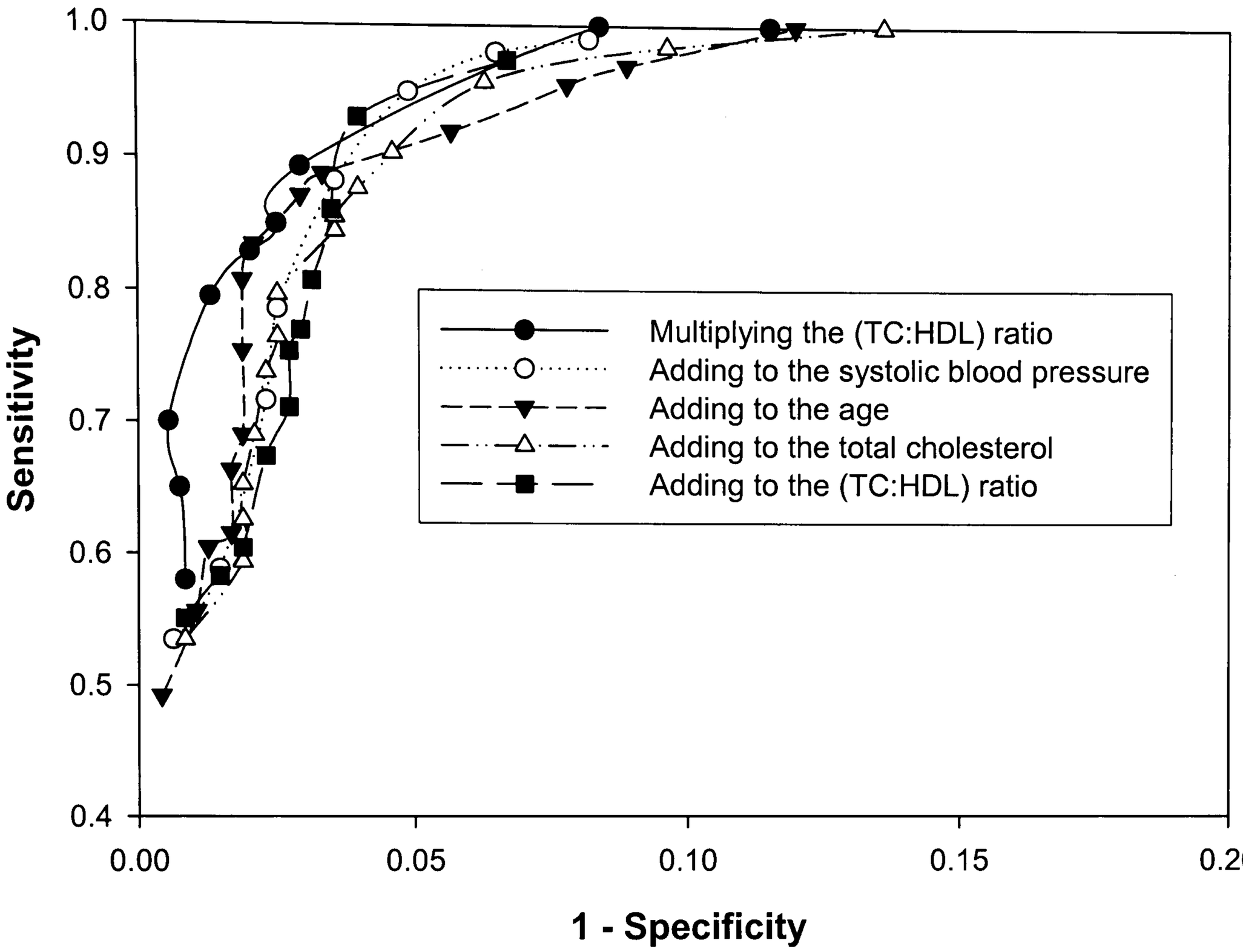

Figure 3.3 ROC plots of different adjustment factors in South Asians against a 10 year CHD event risk threshold of 15%

3.5 DISCUSSION

Increasingly risk prediction will be performed using computer-based algorithms and adjustments to these will be straightforward by multiplying calculated risk by 1.79 for UK South Asians. However paper based tools are still in wide use and need continued support. Any changes to algorithms that are simple to implement on a personal computer may be much less straightforward for use with charts or tables. It is tempting to use simple "rules of thumb" for adjustment but these may introduce unforeseen systematic inaccuracies. It has shown been that the 1.79

increased CHD risk in non-diabetic UK South Asians is most accurately accommodated by multiplying the TC: HDL cholesterol ratio by a factor of 1.5. Other methods, although more simple to achieve by mental arithmetic, are less precise and in some subjects may significantly underestimate or overestimate risk. However in their primary role of determining whether a patient is above or below a risk threshold adding 10 years to age has tolerable sensitivity and specificity. Adding to systolic blood pressure is equally sensitive and specific but use of this method would preclude use of some paper tools and would make risk incalculable for many subjects whose adjusted blood pressure would be out of the included range.

It has already been suggested that a lower CHD risk threshold should be used in UK South Asians but this is to allow for their greater risk of cardiovascular as opposed to coronary heart disease (Cappuccio *et al.*, 2002). However these authors did not test the accuracy of risk prediction tool in UK South Asians nor did they investigate the effects of specific thresholds.

Using 10-year CHD risk of 15% as a threshold for treatment rather than a 10-year CVD risk of 20% needs to be based on two assumptions:

1. that CHD risk is an accurate of CVD risk
2. and that the ratio of CHD risk to CVD risk is 3:4.

Yeo & Yeo (2002) showed that the second assumption does not hold mild hypertension in those aged 55-74 years or in women aged 35-54 years. Moreover the relationship between CVD and CHD differs in South Asians and Caucasians, the former group suffering more non-coronary vascular disease. Nevertheless the figure of a 79% excess is derived from an assessment of CVD risk an in this study

the ratio of CHD was even grater.

Bhopal *et al.* reported a 22% higher predicted risk of CHD, calculated by the Framingham model, for South Asian men compared to Caucasians in the Newcastle Heart Project population (Bhopal *et al.*, 2005). The small number of participants limited the analysis, however the hazard ratio adjusted for age and sex for observed CHD death in South Asian subjects compared to Caucasian was 2.2 (95% CI: 1.1 to 4.4). The standard mortality rate for CHD in South Asian men in England and Wales was 142 compare to the predicted risk by the Framingham model in their study, 122. Clearly these or similar data will be of great use in the future to refine the accuracy of any "ethnicity factor". Results of this chapter can currently be used to achieve the systematic evaluation of each individual for primary prevention of CHD in general practice.

CHAPTER 4

PREVENTION OF CORONARY HEART DISEASE WITH STATINS IN UK SOUTH ASIANS AND CAUCASIANS

4.1 INTRODUCTION

Coronary heart disease (CHD) is a preventable disease that kills more than 110,000 people in England every year, the biggest killer in the country. More than 1.4 million people suffer from angina and 275,000 people have a heart attack annually. Its prevention is a government priority in the UK and the Government is committed to reducing the death rate from coronary heart disease and stroke and related diseases in people under 75 by at least 40% (to 83.8 deaths per 100,000 population) by 2010. To this end Primary Health Care Teams and General Practitioners have the task of identifying all people at significant risk of cardiovascular disease but who have not yet developed symptoms and offer them appropriate advice and treatment to reduce their risks (NSF Standards 4, Preventing CHD in high risk patients) (NSF-CHD, 2000). In patients without symptomatic disease the absolute risk of developing CHD or other atherosclerotic disease during the subsequent 10 years is used to decide whether or not to advise drug treatment. The current risk threshold in the National Service Framework for coronary heart disease is a 10 year CHD risk of 30% but other guidelines (Williams *et al.*, 2004; JBS-2, 2005) suggest the lower threshold of a 20% cardiovascular disease (CVD) equivalent to a 15% risk of CHD. The secondary threshold for treatment of a total cholesterol of > 5.0 mmol/l (193 mg/100) is gradually being abandoned (Williams *et al.*, 2004) as evidence of benefit when treating patients with lower cholesterol concentration accumulates (HPS, 2002). Based on the NSF the interventions that patients at high risk of CHD, people without diagnosed CHD or other occlusive arterial disease with a CHD risk greater than 30% over ten years, should receive, unless contraindicated, are:

- Advice about how to stop smoking including advice on the use of nicotine replacement therapy
- Information about other modifiable risk factors and personalised advice about how they can be reduced (including advice about physical activity, diet, alcohol consumption, weight and diabetes)
- Advice and treatment to maintain blood pressure below 140/85 mm Hg
- Addition of statins to lower serum cholesterol concentrations either to less than 5 mmol/l (LDL cholesterol to below 3 mmol) or by 30% (whichever is greater)
- Meticulous control of blood pressure and glucose in people who also have diabetes

In clinical trials, antihypertensive therapy has been associated with reductions in:

(1) stroke incidence, averaging 2-35 percent;

(2) myocardial infarction (MI), averaging 2-33 percent;

(3) heart failure, averaging >50 percent (Neal *et al.*, 2000).

It is estimated that in patients with stage I hypertension (SBP 140–159 mmHg and/or DBP 90–99 mmHg) and additional cardiovascular risk factors, achieving a sustained 12 mmHg reduction in SBP over 10 years will prevent 1 CVD event for every 11 and 1 CVD death for every 27 patients treated, after correction for regression dilution bias. In the added presence of CVD or target organ damage, only 9 and 18 patients would require such BP reduction to prevent one CVD event and CVD death respectively (Ogden *et al.*, 2000). More than two-thirds of hypertensive individuals cannot be controlled on one drug and will require two or more antihypertensive agents selected from different drug classes. For example, in ALLHAT, 60 percent of those whose BP was controlled to <140/90 mmHg

received two or more agents, and only 30 percent overall were controlled on one drug (Cushman *et al.*, 2002).

Several large scale randomized controlled trials of statins have shown the impressive effect of statins in preventing cardiovascular events, including myocardial infarction and stroke (4S, 1994; Shepherd *et al.*, 1995; Sacks *et al.*, 1996; LIPID-Study, 1998; Downs *et al.*, 1998; LaRosa *et al.*, 1999; HPS, 2002; Serruys *et al.*, 2002; Shepherd *et al.*, 2002; ALLHAT-LLT, 2002; Sever *et al.*, 2003). The MRC/BHF Heart Protection Study (HPS) showed that the benefits of statins extended to a wider range of patients at risk of cardiovascular events, including those with peripheral vascular disease, cerebrovascular disease, diabetes (type I and type II) and hypertension (men over 65 years old) (HPS, 2002). On the other hand, a reduction in strokes was not observed in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) (Shepherd *et al.*, 2002), whilst there was no significant reduction in coronary events or all-cause mortality in the subjects randomized to pravastatin treatment in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Trial (ALLHAT-LLT, 2002). One possible explanation in this study was that the control group received usual care, and lipid lowering therapy was widely used by the time the study was completed, thus reducing the contrast between treatment and control. The Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) study also examined the effect of statin treatment in hypertensive patients (Sever *et al.*, 2003). Patients with a total cholesterol of less than 6.5 mmol/l were randomized to either statin or placebo. This part of the study was terminated early after a median follow-up of just 3.3 years showing a benefit that

was small in absolute terms but statistically significant. ASCOT-LLA is remarkable for the short duration of the study and the modest dosage of statin used.

Meta-analysis of the clinical trials of statins (Cheung *et al.*, 2004) showed that these drugs reduce coronary events and all-cause mortality, with no increase in non-coronary mortality. With the exception of pravastatin, statins also have a strong effect on reducing the incidence of stroke. Benefits accrue in men and women, hypertensives and normotensives, diabetics and non-diabetics, and particularly in smokers. Because of the evidence for widespread eligibility for statin treatment there was considerable concern about the cost of providing this to all suitable patients not only in terms of drugs but also personnel to prescribe and monitor treatment. It may be more cost-effective to treat those at the highest cardiovascular risk, for example patients with CHD, diabetes and multiple risk factors.

There is evidence of different responses to preventive treatment according to ethnicity. Not only may some groups to be at higher risk they may also respond differently to drug treatment e.g. Black and ACE inhibitors. There are no clinical trials or subgroups within trials investigating the treatment of either high blood pressure or hyperlipidaemia in South Asians and until recently it was impossible to estimate their CHD risk, the Framingham equation being acknowledged to underestimate risk in them. We have devised an evidence based adjustment to the Framingham equation to allow accurate estimation of CHD risk in this population in chapters 2 & 3.

4.2 AIM AND OBJECTIVES

To determine the prevalence of subjects eligible for primary and secondary prevention of coronary heart disease (CHD) among the British South Asian population and to compare that with the British Caucasians population.

4.3 METHODS

4.3.1 Study population

For this analysis, the Health Survey for England 1998 and 1999 (HSE 1999 and HSE 1998) datasets were used. From the two datasets 9950 and 1938 subjects (Caucasians and South Asians respectively) were in the age range 35-74 years covered by Framingham risk prediction tools (Fig 4.1). The Health Survey for England was described in chapter 2 in detail (2.5.3). All participants in these two surveys provided data about previous history of cardiovascular disease. Of those in the target age range, 3029 (30.4%) Caucasians and 915 (47.2%) South Asians did not have a total cholesterol (TC) measurement. The number remaining who had sufficient information to calculate vascular risk was used as the denominator for estimation of the prevalence of need for primary and secondary prevention and forms the basis of subsequent analysis. Based on the Heart Protection Study (HPS, 2002), subjects with total cholesterol higher than 3.5 mmol/l (135 mg/100) were deemed eligible for primary prevention if their CHD risk exceeded 30% or for secondary prevention if they had a history of vascular disease.

4.3.2 Secondary prevention

Full data about myocardial infarction, angina, and stroke were provided for 6868 Caucasians and 1003 South Asians. To estimate the prevalence of secondary prevention needs, those with a history of myocardial infarction; angina but no myocardial infarction; stroke, but no myocardial infarction or angina were

identified (Fig 4.1). Separate analyses were performed for a history of CVD based on self- reported and doctors diagnosis.

4.3.3 Primary prevention

None of the 7404 subjects without history of myocardial infarction, angina, or stroke was taking lipid-lowering drugs. However 129 subjects had to be excluded because they were missing one or more variables necessary for risk calculation (Fig 4.1), leaving 6360 Caucasians and 920 South Asians. For the purpose of this analysis, it was assumed that statin therapy would be considered after implementation of all other lifestyle strategies.

4.3.4 Prediction tools

The Framingham equation (Anderson, 1991) and age, sex, systolic blood pressure, smoking habit, history of diabetes, and total: high density lipoprotein cholesterol ratio from the HSE databases were used to estimate individual CHD risk in those to be considered for primary prevention. Left ventricular hypertrophy was assumed to be absent and there is no difference between South Asians and Caucasians. The definitions used for the required variables were:

- for systolic blood pressure, the mean of final two of three readings;
- for smoking habit, current cigarette smoking or smoking within the preceding year;
- for diabetes, treatment with insulin or an oral hypoglycaemic drug, or doctor diagnosed diabetes.

Risk in non-diabetic South Asians was adjusted by multiplying the predicted risk from the native Framingham equation by a factor of 1.79. The basis of this factor is described in detail in chapter 2 of this thesis. Calculated risks were categorised into

three groups: less than 15%, 15-30%, and more than 30% according to risk of CHD events per ten years.

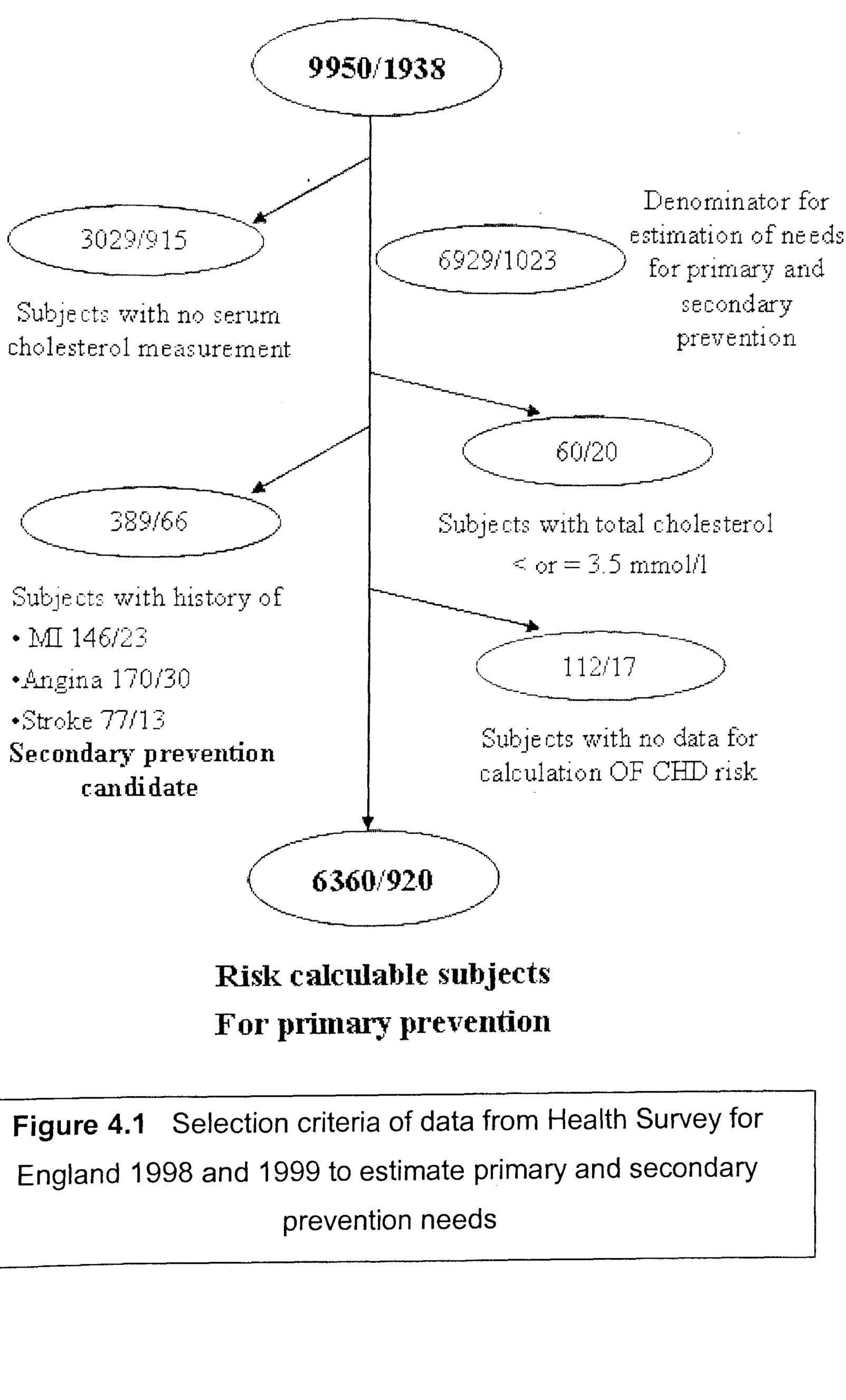

Figure 4.1 Selection criteria of data from Health Survey for England 1998 and 1999 to estimate primary and secondary prevention needs

4.3.5 Cost of treatment

The cost of lipid-lowering therapy was estimated assuming treatment with simvastatin at the dose used in the Heart Protection Study (40 mg daily). Drug costs were taken from the British National Formulary March 2005 (BNF, 2005) and were £3.90 per week (£202.00 per year). Costs relating to medical, nursing or laboratory services, other parallel strategies for a comprehensive package of risk reduction and also any saving resulting from prevention of CHD were not considered.

Number needed to treat (NNT) was calculated using the relative risk reduction for people without prior CHD derived from the HPS study , 0.226 (HPS, 2002) and the mean 10 year CHD risk in people with a 15% or more coronary event risk over the next 10 years (Figure 4.2). For secondary prevention the absolute risk reduction for major vascular event observed in the HPS was used.

4.3.6 Statistical analysis

Data analysis was performed using the Statistical package for Social Sciences (SPSS) for Windows, version 12.0.2. Basic characteristics of all subjects aged 35-74 years were compared between ethnic groups using *t*-tests and Chi-Square tests as appropriate. The proportion of South Asian subjects eligible for primary and secondary prevention was compared to that of Caucasians meeting the same eligibility criteria using the Chi- square test. Analysis of covariance and logistic regression were used to adjust for age and gender. Prevalence rates of cardiovascular diseases in each category were directly standardized to the combined age distribution of the groups being compared (South Asians and Caucasians).

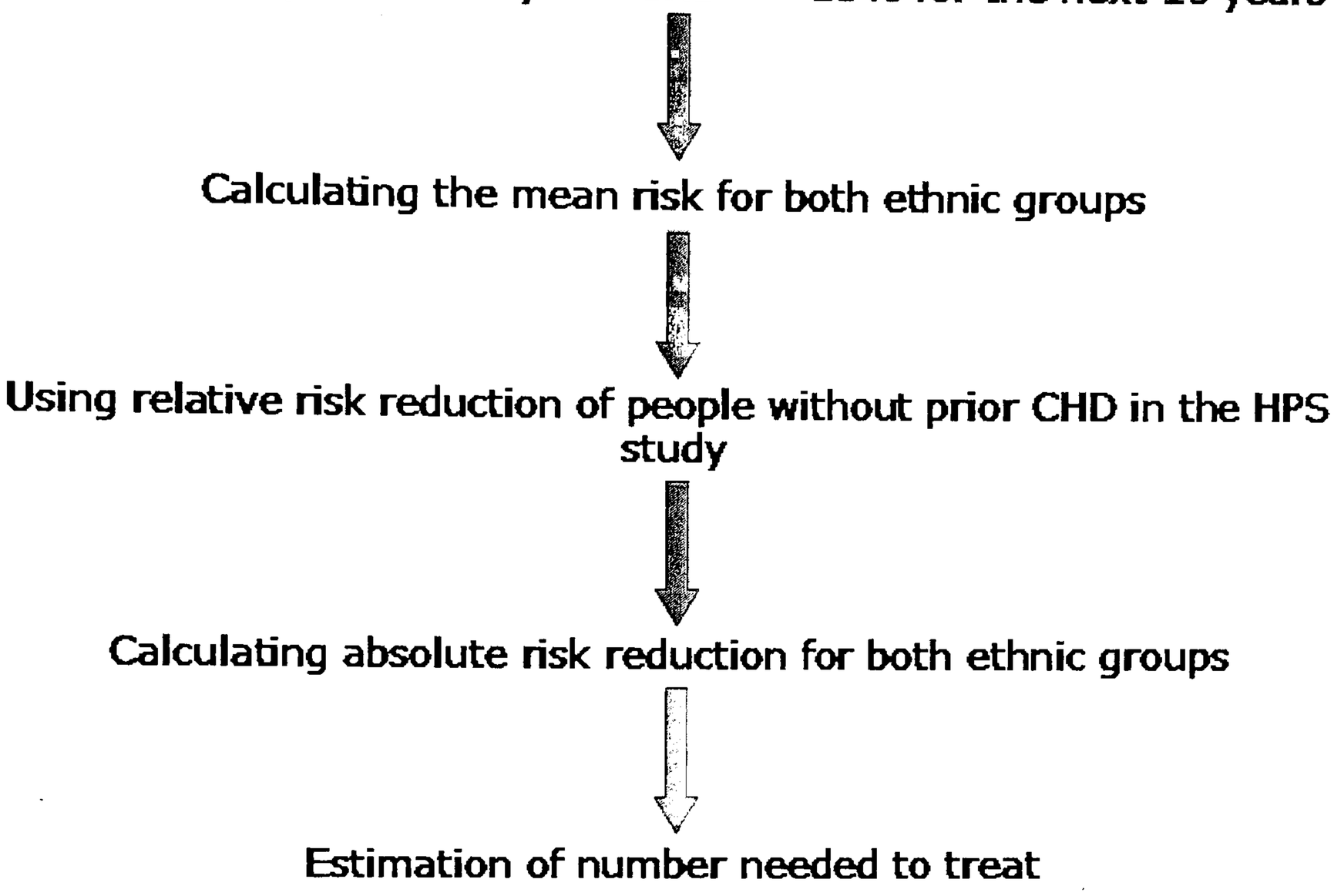

Figure 4.2 Calculating number needed to treat for primary prevention in South Asians and Caucasians

4.4 RESULTS

4.4.1 Characteristics of the population

Table 4.1 and 4.2 show mean data for all men (N = 5590) and women (N = 6298), aged 35 - 74 years, separated according to ethnicity and availability of serum cholesterol measurement. Participating South Asians were 3.9 years younger than Caucasians (95% CI: 3.3 to 4.4), $P < 0.0001$ after adjustment for sex.

As can be seen, a higher proportion of Caucasians of both sexes provided blood for a cholesterol measurement. Those with no cholesterol measurement tended to be

older, had higher systolic blood pressure and were more likely to have a history of cardiovascular disease (myocardial infarction, angina or stroke).

Table 4.1 Basic characteristics of men aged 35 -74 years according to presence of serum cholesterol measurement

	Caucasians		South Asians	
	TC measured	**TC not measured**	**TC measured**	**TC not measured**
Number	3255 (71%)	1320 (29%)	555 (55%)	460 (45%)
Total cholesterol (mmol/l) *	5.71 (5.67 to 5.74)	-	5.53 (5.44 to 5.61)	-
High density lipoprotein cholesterol (mmol/l) *	1.29 (1.27 to 1.30)	-	1.15 (1.12 to 1.17)	-
Age (years)	51.3 (50.1 to 51.7)	53.1 (52.5 to 53.7)	47.4 (46.5 to 48.3)	50.4 (49.4 to 51.4)
Systolic blood pressure (mmHg)	137.9 (137.3 to 138.5)	138.7 (137.3 to 140.0)	135.0 (133.5 to 136.5)	137.4 (134.2 to 140.7)
Diastolic blood pressure (mmHg)	79.8 (79.4 to 80.2)	79.2 (78.3 to 80.2)	79.8 (78.8 to 80.7)	80.1 (78.0 to 82.1)
Smokers (%)	885 (27.2%)	418 (31.7%)	166 (29.9%)	170 (37.0%)
Diabetes (%) *	105 (3.2%)	67 (5.1%)	73 (13.2%)	80 (17.4%)

* $P<0.01$ after adjustment for age
(Comparison between Caucasians and South Asians for whom cholesterol measurement was available)

Table 4.2 Basic characteristics of women aged 35 -74 years according to presence of serum cholesterol measurement

	Caucasians		South Asians	
	TC measured	**TC not measured**	**TC measured**	**TC not measured**
Number	3666 (69%)	1709 (31%)	468 (51%)	455 (49%)
Total cholesterol (mmol/l) *	5.77 (5.74 to 5.81)	-	5.20 (5.11 to 5.29)	-
High density lipoprotein cholesterol (mmol/l) *	1.57 (1.56 to 1.59)	-	1.35 (1.31 to 1.38)	-
Age (years)	51.4 (51.1 to 51.8)	53.2 (52.7 to 53.8)	46.3 (45.4 to 47.1)	48.8 (47.5 to 49.7)
Systolic blood pessure (mmHg)	133.4 (132.8 to 134.0)	137.1 (135.7 to 138.5)	131.0 (129.1 to 132.9)	133.1 (129.6 to 136.7)
Diastolic blood pressure (mmHg)	73.8 (73.4 to 74.2)	74.4 (73.5 to 75.2)	74.4 (73.4 to 75.5)	75.6 (73.7 to 77.4)
Smokers (%) *	1035 (28.2%)	503 (29.4%)	18 (3.8%)	12 (2.6%)
Diabetes (%) *	68 (1.9%)	62 (3.6%)	44 (9.4%)	54 (11.9%)

* P<0.01 after adjustment for age
(Comparison between Caucasians and South Asians for whom cholesterol measurement was available)

4.4.2 Cardiovascular disease risk factors

The mean total and high density lipoprotein cholesterol concentrations were higher in Caucasians than South Asians and the difference persisted after adjustment for age and sex, mean differences were 0.18 mmol/l (95% CI: 0.09 to 0.27, P = 0.002) and 0.20 mmol/l (95% CI: 0.18 to 0.23) respectively. More Caucasian women were smokers, odds ratio =9.8 (95% CI: 6.1 to 15.8). In general the prevalence of

diabetes in both genders was more than three times higher in South Asians, 11.5% versus 2.9% in Caucasians (Chi-Square Test, $P < 0.0001$).

4.4.3 Current lipid lowering treatment

Overall rates of current lipid lowering were similar in South Asians (3.8%) and Caucasians (3.1%) P= 0.227. However Caucasian women were nearly twice as likely to receive lipid-lowering drugs than South Asian women; 2.4% and 1.4% respectively; Chi-Square Test; P= 0.062.

4.4.4 Cardiovascular disease prevalence and secondary prevention needs

Figure 4.3 shows the age-standardized prevalence of cardiovascular disease in South Asian and Caucasian men and women.

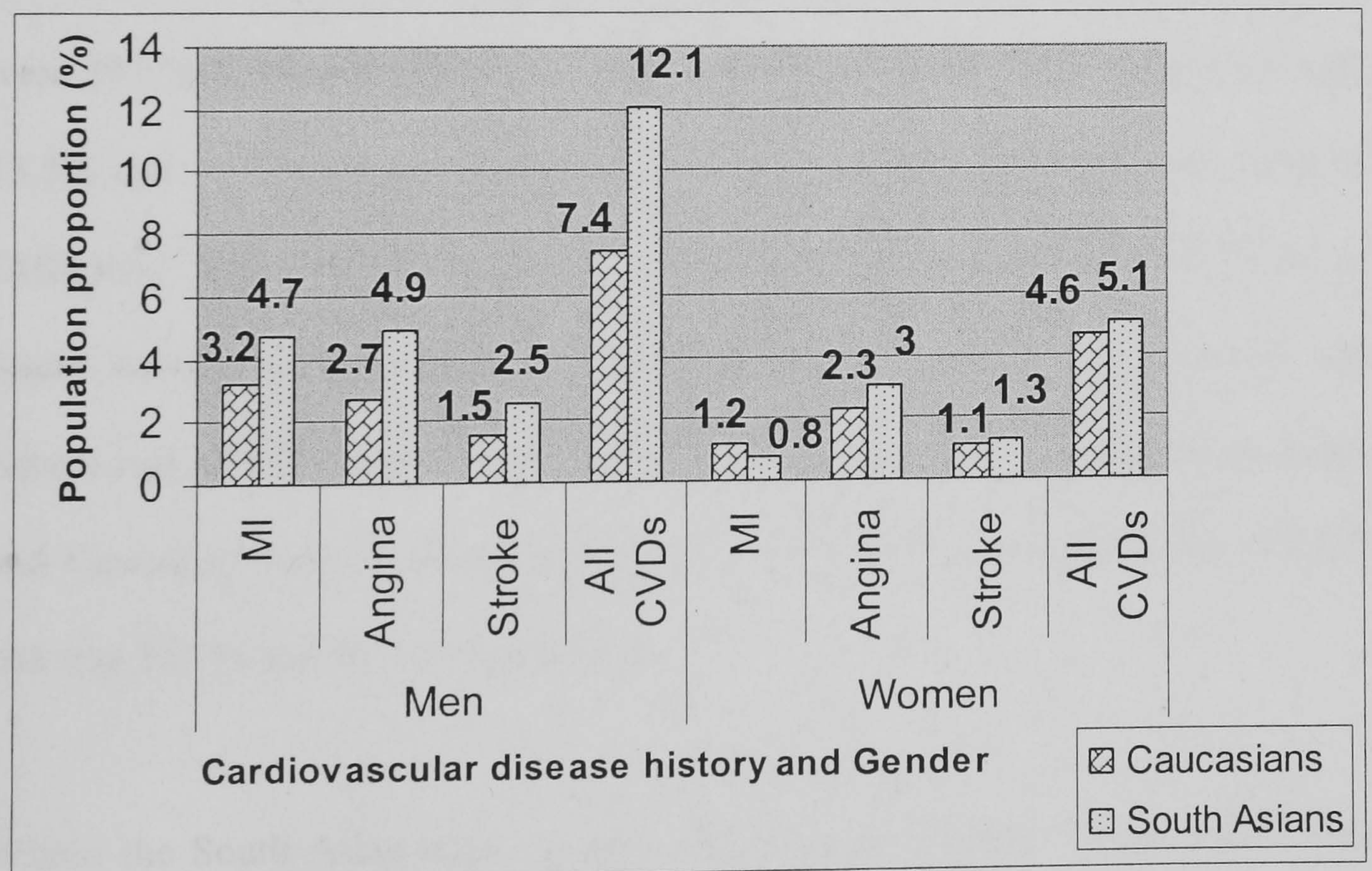

Figure 4.3 Age –standardized prevalence of cardiovascular disease in subjects aged 35-74 years including all participants with total cholesterol measurement

The prevalence of angina and history of previous stroke was higher in South Asian men and women than in Caucasians. Taking all cardiovascular diseases together, in men, 12.1% of South Asian and 7.4% of Caucasian would need to receive statins as secondary prevention, Chi-Square test, $P < 0.0001$. The secondary prevention needs in women were 4.6% for Caucasians and 5.1% for South Asians.

4.4.5 Candidates for Primary prevention

South Asians were more likely to be in the higher risk group for CHD events (Fig 4.4, 4.5). Because of this both South Asian men and women in all age groups were more than twice as likely to meet the eligibility criteria for drug treatment for the primary prevention of CHD than Caucasians ($P<0.001$). Overall 43 % of South Asian men were predicted to have a CHD risk > 15% (20% CVD risk), ranking from 20.0% at age 35-44 years to 98.0% at age 65-74 years. These proportions were 29.8%, 5.0%, and 90.0% in Caucasian men respectively. In women, overall, 13.5% and 7.2% of South Asian and Caucasian women were above this level of CHD risk. The most striking feature of those figures is that more than 93.0% of South Asian men and nearly 68.0% of Caucasian men aged 55-74 years would have a risk of CHD events of 15% or higher over 10 years. Among South Asian and Caucasian women, older than 55 years, the prevalence of this level of CHD risk was 55.7% and 18.5% respectively.

Within the South Asian ethnic groups both male and female Bangladeshis were more likely to be at higher CHD event risk when compared to Pakistanis and Indians (Table 4.3). However, the numbers in sub-groups of the South Asian population are too small to allow meaningful investigation of heterogeneity and comparison between groups.

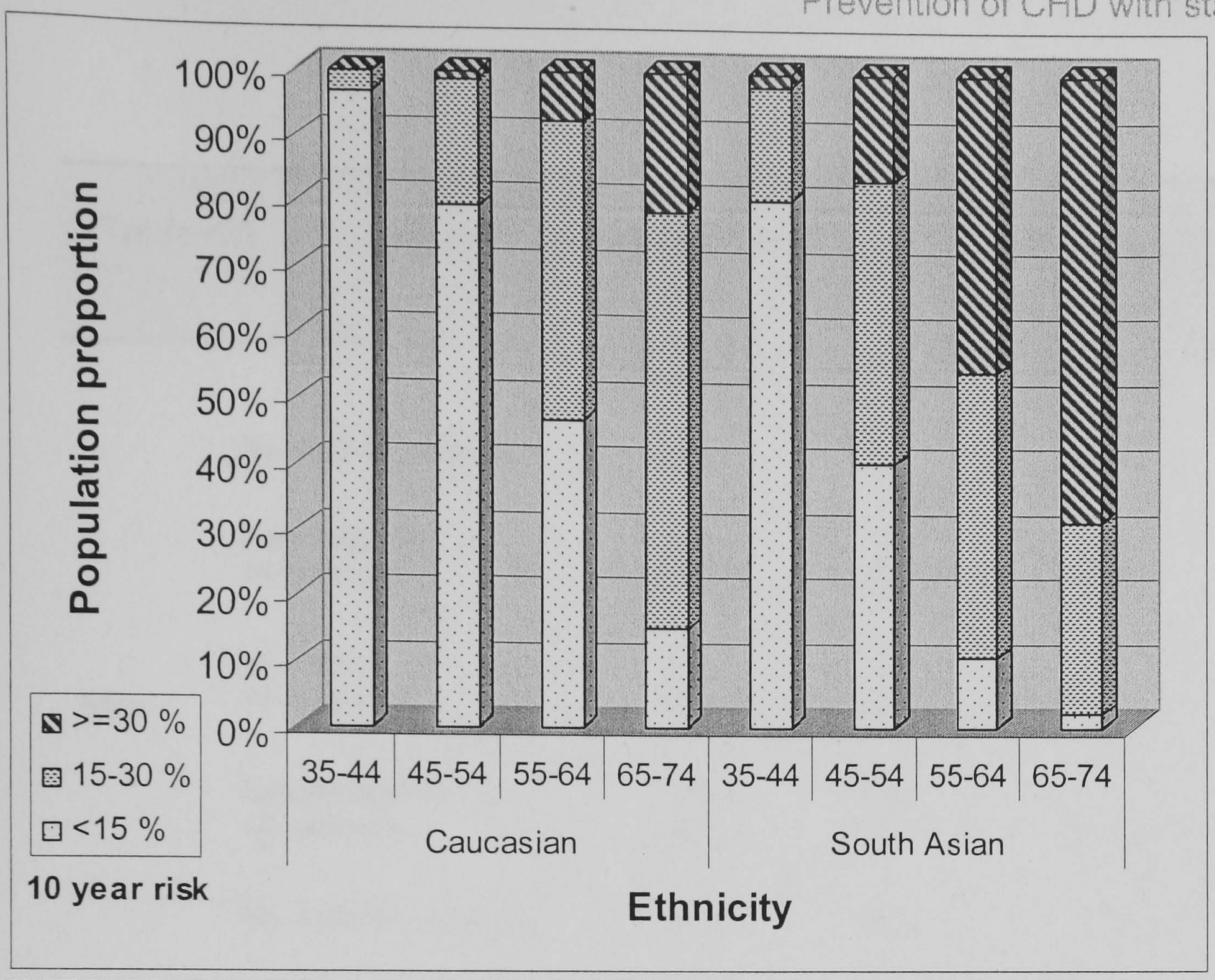

Figure 4.4 Candidates for primary prevention treatment in different age groups of South Asian and Caucasian men aged 35-74 years

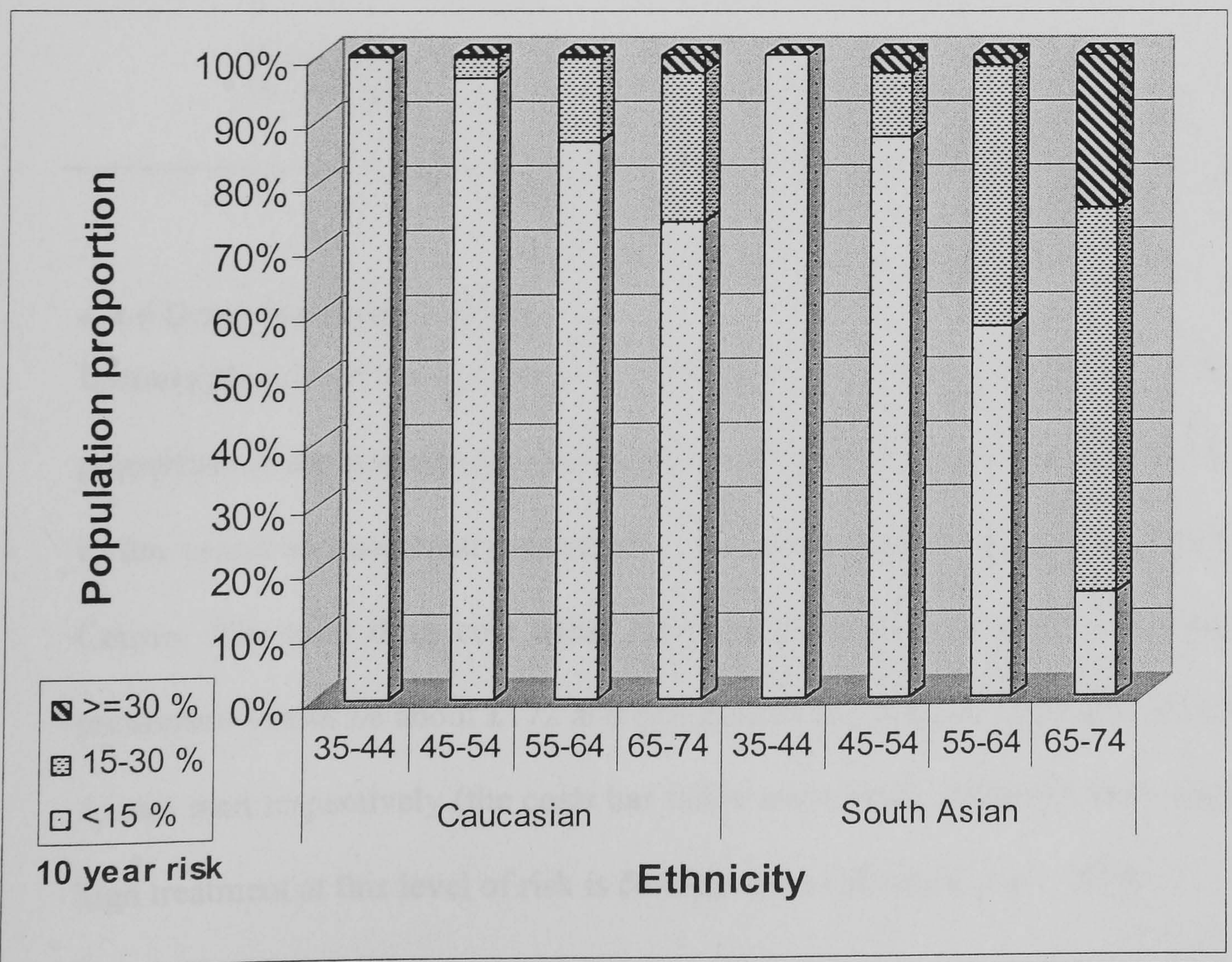

Figure 4.5 Candidates for primary prevention treatment in different age groups of South Asian and Caucasian women aged 35-74 years

Table 4.3 CHD event risk according to ethnic group in subjects aged 35-74 years

		Caucasian	Indian	Pakistani	Bangladeshi
Men	**No. with TC measured**	2946	254	145	91
	Less than 15% 10- year risk	2000 (67.9%)	136 (53.5%)	83 (57.2%)	38 (41.8%)
	15 – 30% 10- year risk	787 (26.7%)	75 (29.5%)	39 (26.9%)	29 (31.9%)
	Greater than 30% 10- year risk	159 (5.4%)	43 (16.9%)	23 (15.9%)	24 (26.4%)
Women	**No. with TC measured**	3412	256	116	58
	Less than 15% 10- year risk	3140 (92%)	220 (85.9%)	98 (84.5%)	47 (82.5%)
	15 – 30% 10- year risk	255 (7.5%)	31 (12.1%)	16 (13.8%)	8 (12.4%)
	Greater than 30% 10- year risk	17 (0.5%)	5 (2%)	2 (1.7%)	3 (5.2%)

4.4.6 Drug treatment costs

Extrapolating from the prevalence calculated in this study, Table 4.4 shows the proportion of the population who may be candidates for primary (>15% CHD risk in ten years) and secondary prevention; the total numbers are based on the 2001 Census. The total drug cost using simvastatin for both primary and secondary prevention would be about £172 and £18 million per year for Caucasian and South Asians men respectively (the costs has fallen since then). Although these costs are high treatment at this level of risk is cost-effective (Ebrahim *et al.,* 1999).

Approximately 9 people would need treatment for 10 years to prevent one coronary event as a secondary prevention, at a cost of £1,818.00 per event prevented. In primary prevention 36 and 29 Caucasian and South Asian men aged 35-69 years would need statins therapy for 10 years to prevent one coronary event, at a cost of £7,277.00 and £5,858.00 per event prevented respectively. More women need treatment for 10 years to prevent an event; 44 Caucasians and 41 South Asians with costs of £8,888.00 and £8,282.00 per CHD event prevented respectively.

Table 4.4 Implications of primary* and secondary prevention in UK population aged 35-74 years

	Men		Women	
	Caucasians (n=6698930)	**South Asians (n=325194)**	**Caucasians (n=7053059)**	**South Asians (n=302837)**
Total requiring treatment for primary and secondary prevention	850,764 (12.7%)	89,428 (27.5%)	894,28 (4.2%)	20,896 (6.9%)
Total cost (million pounds)	£171.9	£18.1	£59.8	£4.2

* CHD risk > 15% in ten years (equivalent to CVD risk > 20% over ten years)

4.5 DISCUSSION

The current work predicts the number of British South Asians eligible for lipid lowering treatment based on guideline specified risk thresholds and an ethnically adjusted risk estimate. More South Asian men aged 35-74 years, 18.4% (95% CI: 14.9 to 21.8), are at the NSF-CHD risk level (>30%) which warrants lipid-lowering treatment, whilst the proportion of Caucasians, at 5.4% (95% CI: 4.6 to 6.2) is much lower. The picture in women is similar with 2.3% (95% CI: 0.9 to 3.8) and 0.5% (95% CI: 0.3 to 0.7) of South Asian and Caucasian women respectively being eligible.

For secondary prevention, 12.1% (95% CI: 9.3 to 14.8) of South Asian and 7.4% (95% CI: 6.4 to 8.2) of Caucasian men are candidates for drug treatment. Fewer women are eligible with a fractionally higher need in South Asians at 5.1% (95% CI: 3.2 to 7.3) compared with 4.6% (3.9 to 5.3) in Caucasians.

4.5.1 CVD risk investigation in ethnic minorities and sample bias

Any study of ethnic differences in cardiovascular risk distribution requires a representative sample. The HSE 1999 is well designed to provide this with an ideal sample frame and response rates for interview of 71-92% in adults in all ethnic groups. However no data were available about non-respondents to interview and 44 - 48% of the South Asians and 27% of the Caucasians had no total cholesterol measurements. Although this leaves the data open to response bias it is unlikely that superior information could be achieved by any method depending on voluntary consent to providing information and samples. It is therefore important to consider the possible implications of any bias present. Subjects not providing a sample for total cholesterol were much more likely to have a history of previous vascular disease, had higher blood pressure and more commonly smoked (Table 4.1 & 4.2).

Even amongst respondents without a prior history of vascular disease blood pressure and smoking prevalence were higher in those not providing a blood sample. Davis *et al.* reported a higher cardiovascular risk in non-responders to the British family heart study (Daveis *et al.*, 1994). Any bias is therefore likely to underestimate the need for treatment. However I estimate that the impact of any such bias would be small. Assuming the cholesterol values were identical in groups who did not provide blood samples would change the percentage eligible for treatment by only 0.2% in men. In addition, with an assumption based on the Davis report of 3.21% higher total cholesterol concentration in non-respondents to total cholesterol measurement the proportions of people with CHD risk > 30% only would increase by 0.5% and 0.3% in men and women respectively.

Furthermore the low response rate to cholesterol sampling does not detract from the comparison of ethnic groups in their need for primary prevention treatment.

4.5.2 Accuracy of the Framingham equation

A study in the British population contrasting Framingham risk with annual hospital in-patient admission data reported that the risk function estimates CVD events well according to annual number of CVD events derived from the 2001 UK hospital in-patient episode statistics (Shearer *et al.*, 2005). There are however populations within the UK for whom Framingham may overestimate risk (Brindle *et al.*, 2003). The assumption that no-one had LVH of the severity used as a risk predictor in the Framingham equation is unlikely to be a major source of bias as its prevalence even in hypertensive populations is exceedingly low (Levy, 1988). Although use of on treatment blood pressure rather than pre-treatment may bias estimates of CHD risk the proportion of Caucasians and South Asians who received antihypertensive treatment was similar. It has been shown in chapter 2 of this thesis that a

reasonable estimate of CHD risk in non-diabetic South Asians is derived by multiplying risk from the Framingham equation by a factor of 1.79. The validity of this estimate might be in further question for women as it is derived from data mostly in men (about 80%). Ethnicity clearly impacts on risk in South Asian women who have a similar prevalence of CVD to that of Caucasian women despite dramatically lower rates of smoking. The impact of most known risk factors for CVD does not vary with gender and it is likely that a finding in men can, with caution, be extrapolated to women. Coronary risk in diabetic South Asians is similar to that in Caucasians (personal communication, UKPDS group). Whatever the accuracy of the Framingham equation, this currently forms the basis for calculating risk in clinical practice and is central to judging eligibility for treatment. Therefore under or over estimation of risk by this equation should not effect the accuracy of predictions of the number of patients likely to be offered treatment for primary prevention.

4.5.3 Different total cholesterol thresholds

Ul Haq *et al.* (1996) used data from subjects aged 35-69 years in the Health Survey for England 1993 with serum cholesterol higher than 5.5 mmol/l to calculate the number of possible candidates, aged 35-69, for secondary and primary prevention. They reported 5.9% and 3.6% of men and women, respectively, might be candidates for lipid-lowering treatment for secondary prevention and 6.2% of men and 0.4% of women for primary prevention, CHD risk over 10 years ≥ 15%. Their estimates are similar to my findings suggesting that abandoning the cholesterol threshold in the NSF impacts little on the need for statin treatment. 98% of those with a history of CVD had cholesterol > 3.5 mmol/l and if we assume that all with such history were above the cholesterol threshold data from those without a

measurement of cholesterol concentration can be included in my estimates of the need for secondary prevention. Eligibility for statins will then be slightly higher in Caucasian men and women, 10.8% and 5.7% respectively compared to 9.8% in South Asian men, and 4.5% in women.

4.5.4 Updated guidelines

Initial recommendations were that a threshold of 30% over 10 year CHD event risk be used to judge eligibility for statin treatment. This has now been modified to a CVD risk threshold of 20%, approximately equivalent to CHD risk threshold of 15% (Williams *et al.*, 2004; JBS-2, 2005). As can be see from Figure 4 and 5 this will increase the numbers eligible for treatment dramatically but does not diminish the reported differences between South Asians and Caucasians. However the CHD : CVD risk ratio might be different in South Asian as this relationship is different for Caucasian men and women, and within each gender for younger and older groups (Yeo & Yeo, 2002). On this basis Cappuccio proposed an even lower threshold of CHD risk for ethnic minorities (Cappuccio *et al.*, 2002).

4.6 CONCLUSION

Although statins may be cost-effective and produce reasonable benefits both in Caucasians and South Asians providing appropriate treatment for the high numbers needing primary or secondary preventions (Table 4.4) will require substantial new resources and may well have a societal impact, the majority of the elderly becoming patients. 4.6% of the UK population aged 35-74 are South Asians whereas about 10% of possible candidates for primary and secondary preventions are from this group. Therefore South Asians will have to be specifically targeted in primary prevention strategies. In addition the management (manpower) costs of implementing the targets might be higher for South Asian population because of

the additional input from the specialist nurses and linked workers required for this particular group. These costs were estimated about 40% higher in the United Kingdom Asian Diabetes Study (UKADS) compared to costs in the UK Prospective Diabetes Study (UKPDS) (O'Hare *et al.*, 2004).

Underpinning these estimates of treatment need are the assumptions that desire for treatment, compliance, and effectiveness are identical between populations. Although patient factors are critical for the population effectiveness of drug interventions they have received little research attention.

CHAPTER 5

PATIENTS' ACCEPTANCE OF ANTIHYPERTENSIVE THERAPY TO PREVENT CARDIOVASCULAR DISEASE: A COMPARISON BETWEEN SOUTH ASIANS AND CAUCASIANS IN THE UK

5.1 INTRODUCTION

Increasingly patients' preferences and values are explicitly incorporated into decisions about treatment (Hayens *et al.*, 2002 & RPSGB, 1997). The importance of patients' involvement in decision-making is because of their right to know the risks and benefits they accept in undertaking treatment and the as yet unproven hope that this will improve compliance. Patients will bring a range of views to their decision amongst the treatment options, incorporating personal values, personal and family experience (e.g. illness), degree of aversion to risk, and willingness to take medicines (in general) (Devereaux *et al.*, 2001). Patients' priorities, in relation to treatment, may also differ from those of clinicians, and may lead to choices apparently contrary to guidelines which are usually derived from clinical trial evidence of safety and efficacy alone. Whilst many people wish to be involved in decisions about their medical treatment, most prescribing decisions are still not made jointly (Charles *et al.*, 1997). There are two key elements in any decision: the likelihood of any event consequent on the specific choice and the value of this outcome to the decision maker (Taylor, 2000). A patient's preference for one outcome over another is a reflection of the likelihood information provided as well as understanding of the outcome and the value they attitude to it. As the response to treatment is not absolutely guaranteed, patient's decisions are made in the uncertainty of whether the eventual outcome might or might not be the desired one. Patients make specific health decisions infrequently, and most decisions are made with little preparation or repetition. In contrast physicians have a relatively good understanding of the range of outcomes and the risks and benefits of treatment and are accustomed to making complex decisions. However, involving the patient in the decision making process brings a completely new set of circumstances into

play. The way of describing choices and the language used to describe possible outcomes have marked effects and may influence which options are eventually chosen. It is crucial that patients receive relevant and accurate information in a form that is amenable to them to assist in selecting the treatment option most appropriate for them.

The multifactorial nature of atherogenesis makes the process of cardiovascular prevention complex. Analysis of the results of randomised clinical trials has demonstrated that the risk of cardiovascular disease (CVD) determines the chance of benefiting from primary prevention drug therapy such as antihypertensive or lipid lowering therapy, such that those at highest risk gain greatest benefit (Anderson *et al.*, 1991; HPS, 2002). Current UK guidelines recommend treatment with antihypertensive drugs for those with mild hypertension whose 10 years CVD event risk is at least 20% (JBS-2, 2005). People of South Asian descent are at higher risk of CVD mainly because of an excess of dysglycaemia and frank diabetes. They should therefore have more to gain from primary prevention with lipid-lowering and antihypertensive drug treatment and as a consequence be more likely to be prescribed such treatment. Observational data do not however satisfactory support this. Age-standardized rates of lipid testing in South Asians and non-South Asian men, in 14 general practices in Manchester, were reported similar and the rate was higher in South Asian women compared to non-South Asian women (France *et al.*, 2003). Importantly in this study the change in cholesterol level on retesting did not differ between South Asians and other groups. There is however evidence that South Asians are less likely to receive preventive treatments. Patients in practices with a greater South Asian population are less

likely to be prescribed lipid lowering drugs (Patel *et al.*, 2002). During an average of nearly 5 years follow-up in a group of diabetic patients in Glasgow, South Asians were prescribed significantly fewer prescriptions for antihypertensive agents and had smaller improvement in blood pressure than Caucasians (Mukhopadhyay *et al.*, 2005).

5.1.1 Eliciting patient preference

Fundamental to eliciting patient preferences is the assumption that these already exist in the patient's mind, and that by presenting the patient with data in an appropriate way the choices be elicited (Llewellyn-Thomas *et al.*, 1982). In the process of eliciting patient preferences, information has to be provided on the outcomes, benefits, complications, and costs of each treatment. To elicit a patient's view about treatment two methodological approaches can be employed: "medical decision-making" and "probability trade-off" techniques. The first approach is derived from formal decision analysis, and is widely advocated for formulating health policy and constructing clinical guidelines. A decision analysis begins with construction of a formal decision tree which models the various outcome health states. Then, the probability that a particular treatment option will lead to each of the health states is estimated using the clinical literature relating the particular health-care problem. In the next stage the relative desirability of each outcome health state is estimated using a technique that generates utilities like the standard gamble. A patient's choice then depends indirectly upon their personal valuation of each possible health outcome. The "probability trade-off" approach is a direct assessment of patient preferences for treatment. It can be structured to illustrate in a highly graphic way the actual complex dilemmas patients often face and its procedures can be arranged as to engage the patient in explicitly considering the

trade-offs involved (Llewellyn-Thomas 1997). Patients are given information about the treatment options, outcomes, and probabilities. This information is presented sequentially and arranged in pairwise columns to permit gradual assimilation of the information as well as clear comparisons. Then the described efficacy of the treatment is systematically varied until patients switch their treatment preferences (Bowling & Ebrahim, 2001). In other words, the preferences of patients can be elicited by determining the smallest differences that they perceive as beneficial and which would warrant, after considering cost, inconvenience, and side effects of receiving treatment. This is termed the minimal clinically important difference (MCID) (Jaeschke *et al.*, 1989). Individuals participating in probability trade-off technique exercises are standing at the actual decision-point of treatment selection and looking down the decision tree towards the possible outcomes treatment (Man-Son-Hing *et al.*, 1996). This approach helps people to understand the uncertainties in the treatment choices and to articulate their preferences. Such a process may promote patient confidence in the decisions that are eventually taken, possibly leading to better compliance. In contrast in decision analysis the investigator stands at the outcome end of the decision tree, looks back through the tree using probabilistic and evaluative information gathered in the past to compute the expected utility of each treatment option, and draws conclusions about what the decision should be for future patients in the same clinical situation (Llewellyn-Thomas, 1997). The other important difference between these techniques is the method of decision making. In the decision-analysis approach the model is imposed a priori and is rigid whilst in the latter patients can utilise their own heuristics to make a choice for each scenario given.

The preference elicitation task can be described to the subjects using two approaches: titration (steadily changing one option) and ping-pong (going back and forward between options). Preferences are strongly influenced by the elicitation process and these two methods produced significantly different measurement on repeated testing (Lenert *et al.*, 1998). In addition presenting choices to patients within a neutral, positive, or a negative frame produces differing responses. The effect of framing has an important role in the elicitation process (Tversky & Kahneman, 1981; McNeil *et al.*, 1982). As preferences directly reflect the underlying values of the patient, there is a possibility that individuals will differ widely on which components they consider relevant to a particular decision and it is important to explicitly describe attributes of the outcomes of treatment using a systematic view of the literature and/or expert consensus (Taylor, 2000). As a result different principal dimensions of value in the choice between treatment options need to be clarified (e.g. safety, harms and inconvenience, benefits and survival effects, etc) to help individuals for informed decision making which project their attitudes.

Patients' views about preventive drug treatment have been gathered in a range of studies. Most using probability trade-off estimates of willingness show that patients are less enthusiastic for treatment than doctors or other clinicians and the median benefit demanded is often far greater than that demonstrated in any clinical trial (Steel, 2000; McAlister *et al.*, 2000; Lewis & Barton, 2003). However there are no previous studies which have measured antihypertensive preferences specifically in South Asians and compared them with Caucasians.

5.2 AIM OF THE STUDY

- To establish people's willingness to receive antihypertensive treatment for primary prevention of CVD
- To explore the relationship between ethnicity and individual attitude to prescribed antihypertensive as primary prevention drugs

5.3 METHODS

5.3.1 Participants

A sample of Sheffield residents aged 35-74 years with or without history of cardiovascular disease were interviewed. Names of potential participants were identified from the Sheffield Population Health Register which holds the names and addresses of all patients who are registered with a Sheffield General Practitioner. This list is maintained by Sheffield South East Primary Care Trust (PCT) on behalf of all four Sheffield PCTs and is updated on a regular basis (Coy *et al.*, 2002).

The computer program, Nam Pehchan (Nam Pehcham, version 1.1) was used to select possible South Asian names from which to sample. This computer programme was developed by Bradford City Council and Health Authority in the 1980's. The software contains a dictionary of South Asian names which it attempts to match against the complete name or the name stem (usually the first five characters of an individual's name) in order to identify a list of South Asians together with a language and religion marker for each person. Cummins *et al.* (1999) reported that this computer programme misclassified some names and produced inconsistent results across the United Kingdom's South Asian population. However, with the names from Yorkshire area, where the software was developed it performed satisfactory.

A sample of 1080 South Asian was selected. A group of Caucasians matched for age (± 5 years range), gender, and residence in the same Electoral Ward was then selected to give two similar groups. In an earlier study in Sheffield (Price & Skinner, 2003), South Asians had lower response rate (about half) compared with Caucasians. In an attempt to produce roughly equal numbers of South Asians and Caucasians eventually interviewed the size of the Caucasian group was reduced to 540 by a simple random selection process. No exclusions other than age were applied.

5.3.2 Preference measurement

A modified version of the tool developed by McAlister et al to elicit MCIDs for antihypertensive therapy was used (McAlister *et al.*, 2000).

5.3.2.1 Questionnaire

The questionnaire had two parts. The first part presented three hypothetical scenarios with different baseline cardiovascular risks. At each baseline risk of 10, 20, and 40% over 10 years participants MCIDs were identified. In the second part, subjects were asked to provide basic demographic data including age, sex, ethnicity, educational level, occupation, history of CVD, and whether they were in receipt of antihypertensive drugs.

5.3.2.2 Scenarios

Brief descriptions were given in lay terms about the personal impact of hypertension, myocardial infarction, stroke, and the effect and tolerability of drug treatment. After describing the treatment options and the potential outcomes participants were asked to choose between not accepting the therapy (given the baseline risk of an adverse outcome) and accepting the therapy (given a reduced risk of the adverse outcome but also incurring the inconvenience, cost and side effects associated with that therapy). Choices were presented to subjects both

graphically and numerically with risks expressed in positive and negative terms. The graphical presentation used 100 stick figure icons to show percent frequencies at risk and benefiting from treatment (Schwartz *et al.*, 1997; Gigerenzer, 1996; Elting *et al.*, 1999). To determine the MCID the event rates were varied back and forth by halving steps until participants switched from accepting to declining treatment or vice versa. Figure 5.1 is an illustration of steps for the scenario with a risk without treatment of (10%) over 10 years.

A Subjects' MCID for a given scenario is the smallest benefit for which he or she would accept treatment. If a subject chooses to accept therapy when the cardiovascular risk is reduced with treatment from 10% to 1%, 2%, 3% or 4% but not when the risk is reduced with treatment from 10% to 5%, his or her MCID will be 6% for this scenario (10 - 4 = 6%).

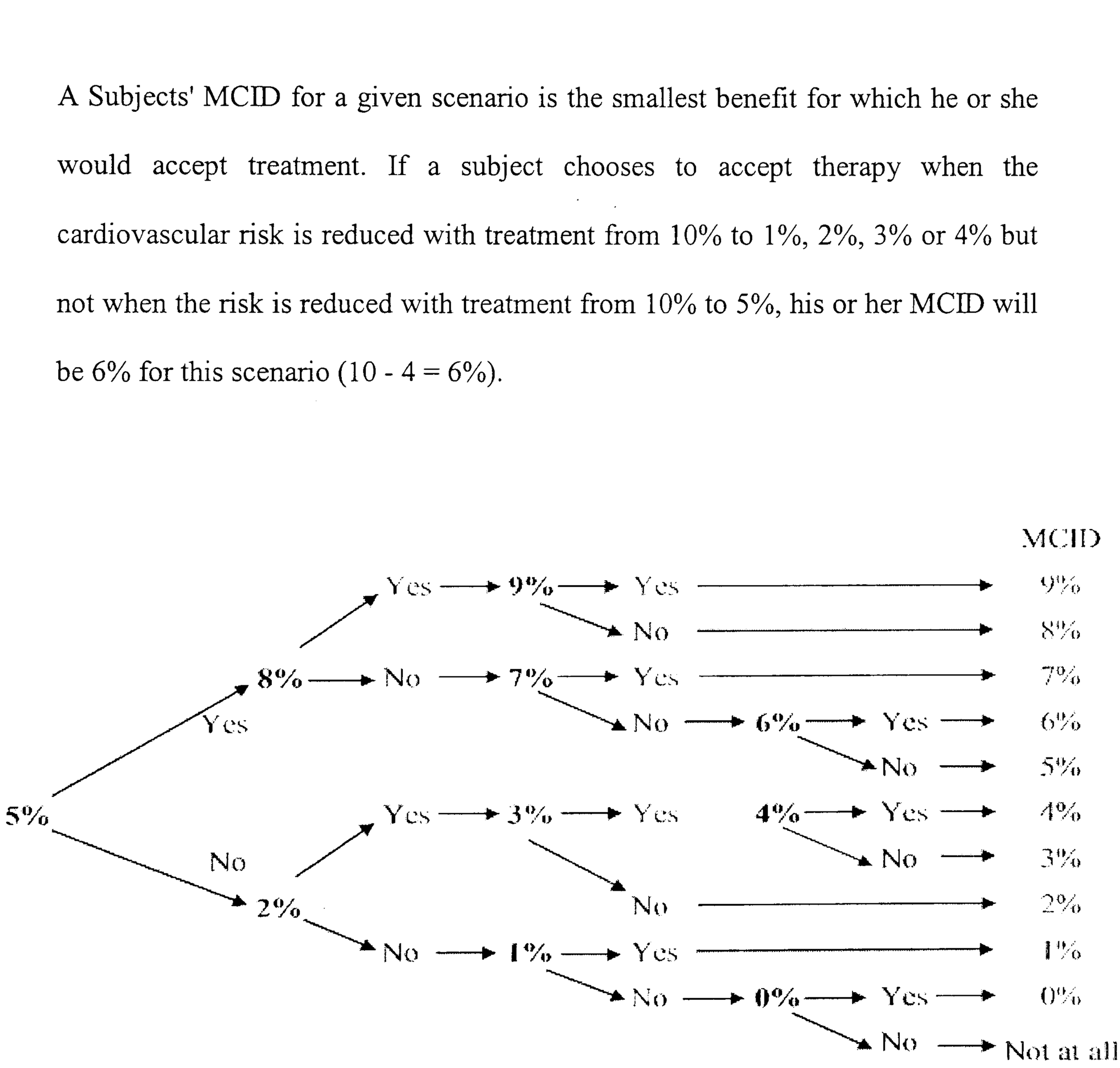

Figure 5.1 Steps for elicitation the MCID if a baseline heart attack and stroke risk without taking antihypertensive medication is 10% over the next 10 years (the scenario 1)

5.3.3 Study procedure

5.3.3.1 Making contact

The PCT identified the South Asian and Caucasian subjects, as described in participants- methods section in this chapter (page 94), and sent them a covering letter and an information sheet (appendix 1 & 3) via post in March 2004. Stamped addressed envelopes were provided for replies (appendix 4 & 5) to the research group. Names of the respondents from the information sheet was determined and fed these back to the PCT. The difference between the full list of names held by the PCT and the respondents was used by them to produce a list of non-respondents. Up to two reminders (appendix 2) were mailed to people who had not replied within two weeks after each mail shot by this method which maintained confidentiality. Then positive respondents were contacted to arrange a convenient time for interview. These were held in participants' homes or at the hospital according to participants' preference. Travel expenses were offered if interviews took place at the hospital. The background information (appendix 8) was sent to each interviewee after setting the date of interview to make sure she/he had enough time to read it before the interview appointment.

5.3.3.2 Collecting data

An interviewer fluent in the appropriate language to each non-English speaking informant was allocated so that the interview could be conducted in the informant's own language. Interviewers were recruited from native speakers of these languages amongst clinical students and health professionals and underwent specific training. The complexity of the study requires that a number of procedures in the interview be described in detail and it was essential that this process was as reproducible as possible. Interviewers attended two training sessions and also received a manual

of operation for the interview (appendix 7). To ensure that participants had all information required before embarking on the study answers to the following question were provided in the training sessions:

- What is the study trying to find out?
- What is involved in the study?
- How participants have been chosen?
- What is involved in the interview?
- What is involved in the questionnaire and scenarios?
- Where the interview will take place?
- What is in the interview process? (explaining the information sheet, signing the consent form (appendix 6) , using the standard method for presenting background information and scenarios).

Most importantly potential interviewers also undertook role-play of the actual interview to help standardize the process.

5.3.3.3 Translation of the survey material

All letters of invitation, survey materials and questionnaires were translated into five languages: Hindi, Gujarati, Punjabi, Urdu, and Bengali to elicit individual responses and avoid the use of other household members as interpreters. Translators were qualified members of the UK Institute of Translation & Interpretation (http://www.iti.org.uk/).

5.3.4 Sample size

McAlister et al (McAlister *et al.*, 2000) reported mean patients' MCID for 10% CHD risk in 5 year as 4.0, SD (σ) =3.73 (calculated from 95% CI). A difference of one percent in MCID ($\mu_1 - \mu_2$) or greater between South Asians and Caucasians is likely to be of practical importance. The risk of Type I and II errors

accepted were 5% (α) and 20% (β) respectively; therefore, the calculated sample size was 216 in both South Asian and Caucasian groups.

$$n = \frac{f(\alpha,\beta)\times\sigma^2\times 2}{(\mu_1-\mu_2)} = \frac{7.9\times 13.7\times 2}{1} = 216$$

Price and Skinner (Price & Skinner, 2003) reported 30% and 50% response rates to an earlier postal questionnaire for South Asians and Caucasians in Sheffield respectively. It was assumed that the response rates for interview would be lower, perhaps 20% for South Asians and 40% for Caucasians. The numbers of letters distributed to achieve the estimated sample size were therefore 540 in Caucasians and 1080 for South Asian ethnic groups.

5.3.5 Data analysis

Responses from completed surveys were entered into the Statistical Package for the Social Sciences (SPSS) for Windows version 11.5. Maximum MCIDs in a given scenario were assigned to participants who indicated that they would never take medication at all (10, 20, and 40 in scenarios 1, 2, and 3 respectively). The distribution of the MCIDs in all three scenarios was assessed. The minimal clinically important differences of South Asians and Caucasians were compared using the Mann-Whitney test. The proportions of South Asians and Caucasians choosing treatment in each case were compared using the Chi-square and Fisher's Exact tests. For all tests, the alpha level for statistical significance was 0.05.

Socioeconomic status was measured using Carstairs deprivation scores (Carstairs & Morris, 1991) an indicator based on male unemployment, overcrowding, social class, and car ownership using data from the 2001 UK census. This index was constructed by Carstairs and Morris for the analysis of Scottish health data.

However it has been used as a discriminator of health status in England. In addition, the social class of participants between South Asians and Caucasians was analysed based on the categories for job titles developed by the National Statistics Socio Economic Status Classification -2001.

5.3.6 Ethics

The study protocol was approved by the South Sheffield Research Ethics Committee. Written consent was obtained prior to the interview for all participants and all responses were kept confidential.

5.4 RESULTS

During the 3 months of interview (from April 2005, to July 2005), 110 South Asians and 153 Caucasians were interviewed by 14 interviewers (6 for South Asians). Table 5.1 gives details of the responses to the invitation letters.

More Caucasians replied to the initial invitation letter, 126 (81.8%) compared to 61 (55.5%) South Asians (Chi-square test, $P<0.0001$). In contrast nearly half of the South Asians replied after the first or second reminders.

Interviews averaged 30-45 minutes and characteristics of participants are shown in the Table 5.2. More than 60% of women and about 58% of men had a positive history of CVD in their first-degree relatives (Table 5.2). No statistically significant differences were found in the prevalence of a personal or family history of CVD or current treatment with antihypertensive medications between South Asians and Caucasians of either gender. There were trends however for all these to be greater in South Asian respondents seen most strongly in South Asian women who were more likely to have a family history of CVD ($P = 0.06$).

Table 5.1 Details of responses to the invitation letters in South Asians and Caucasians

	South Asians	Caucasians
Letters sent	1080	540
Letters returned by post (addressee unknown or has gone away)	47 (4.4%)	25 (4.6%)
Responses received	416 (40.3%)	322 (62.5%)
Interview accepted	138 (13.4%)	163 (31.7%)
Interview declined	263 (25.5%)	159 (30.9%)
Refused or moved when contacted by research team	9	10
Error in ethnicity allocation by software	18	0
Died before being interviewed	1	0
Participants who were interviewed	110 (10.6%)	153 (29.7%)

Up to 17% of participants in both ethnic groups indicated that they would not take medication however great the benefit, but this proportion declined with increasing CVD risk, Figure 5.2. The proportion of South Asian men unwilling to take medication regardless of benefit was higher than Caucasians for all scenarios. The reverse trend was seen in women apart from in the highest risk scenario in which Caucasian women were less likely to refuse the treatment compared to South Asians. A subgroup of 9 participants (5 south Asians and 4 Caucasians) turned down medication in all three scenarios.

Table 5.2 Characteristics of participants by gender and ethnicity

	Men		Women	
	South Asians (n = 58)	**Caucasians (n = 75)**	**South Asians (n = 52)**	**Caucasians (n = 77)**
Age, mean (SD)	50.2 (11.6)	52.2 (12.0)	52.0 (11.2)	51.7 (10.7)
Years of education				
< 6 yr	0	0	5 (9.8%)	0
6-12 yr	26 (44.8%)	30 (40.0%)	23 (45.1%)	31 (39.7%)
> 12yr	32 (55.2%)	45 (60.0%)	23 (45.1%)	47 (60.3%)
Family history of CVD	34 (58.6%)	43 (57.3%)	40 (76.9%)	47 (61.0%)
History of CVD	13 (22.4%)	14 (18.7%)	7 (13.5%)	7 (9.1%)
Currently taking BP lowering medications	19 (32.8%)	15 (20.0%)	11 (21.2%)	9 (11.7%)

The distribution of MCIDs chosen was heavily skewed and medians were therefore estimated and non-parametric hypothesis tests employed. There was a strong positive correlation between the individual MCIDs expressed in scenario 1 and 3 for both ethnicities, Spearman rho = 0.77, $P < 0.0001$ and Spearman rho = 0.69, $P < 0.0001$ in South Asians and Caucasians respectively. The overall median MCIDs for Caucasians was 4% in all scenarios (Table 5.3). Whilst for South Asians median MCIDs were 1%, 2%, and 1% in scenarios 1, 2 and 3 respectively. Differences between both ethnic groups, independent of gender, were statistically

significant in scenario 1, P=0.002, but not in scenarios 2 and 3, P=0.24 and P=0.06 respectively.

Generally South Asians required less benefit before accepting treatment in all three scenarios (10, 20, and 40% CVD in 10 years) compared to Caucasians, Table 5.3. The trend is consistent across the groups but was not statistically significant in men. In both ethnic groups participants who were taking blood pressure lowering medications had a lower MCID compared to those who were not, in all three scenarios ($P < 0.0001$, Man-Whitney U test). In addition people with a personal or family history of CVD had lower MCIDs in both ethnic groups although the trend was not consistently statistically significant.

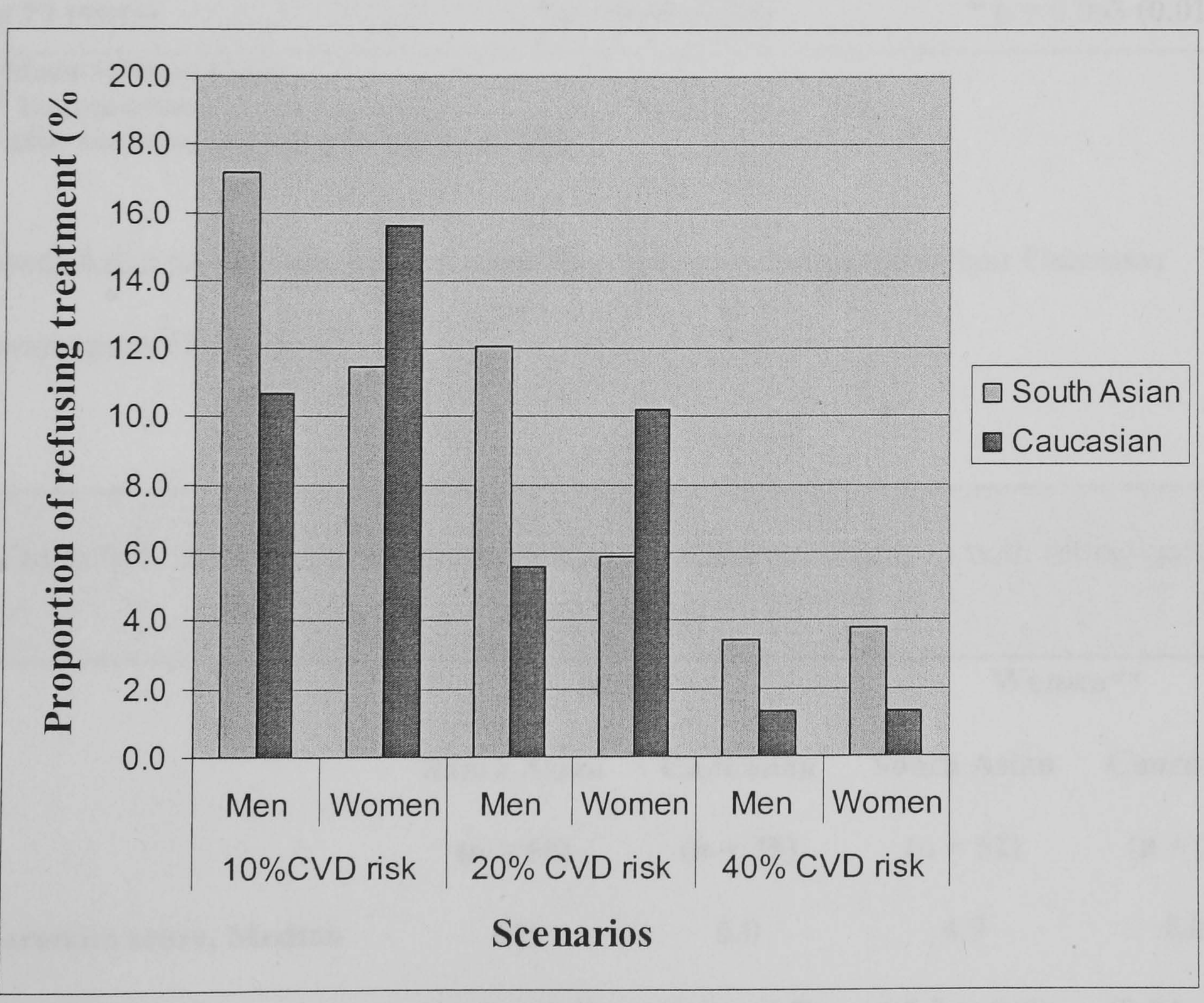

Figure 5.2 Medication refused according to scenario, gender and ethnicity

Table 5.3 Minimal clinically important differences for the blood pressure lowering medication in South Asian and Caucasian men and women

		Men		Women	
		South Asians (n = 58)	**Caucasians (n = 75)**	**South Asians (n = 52)**	**Caucasians (n = 77)**
Scenario 1 (10% CHD risk in 10 years)	**Median (IQR**)**	1.5 (1 - 9)	3 (1 - 7)	1 (1 – 5)	5 (2 - 9)
		* p = 0.32 (0.40)		*** p = 0.001 (0.001)**	
Scenario 2 (20% CHD risk in 10 years)	**Median (IQR)**	3 (1 - 14)	4 (1 - 6)	1 (1 – 10)	5 (1 – 11.3)
		* p = 0.64 (0.59)		*** p = 0.032 (0.018)**	
Scenario 3 (40% CHD risk in 10 years)	**Median (IQR)**	1 (1 – 12.3)	4 (1 – 8)	1 (1 – 6)	4.5 (1–10.3)
		* p = 0.44 (0.28)		* p = 0.063 **(0.017)**	

*** Mann-Whitney U test**
**** Interquartiles**
§ After excluding subjects with history of CVD

South Asian participants lived in more deprived areas compared to their Caucasian counterparts (Table 5.4).

Table 5.4 Median and interquartiles of the Carstairs score in both ethnic groups by gender

	Men*		**Women****	
	South Asian (n = 58)	**Caucasian (n = 75)**	**South Asian (n = 52)**	**Caucasian (n = 77)**
Carstairs score, Median	6.0	6.0	4.9	6.0
(interquartiles)	(-1.0 to 8.0)	(1.9 to 9.5)	(-0.3 to 6.9)	(2.6 to 8.0)

* P=0.035, ** P=0.020 (Mann –Whitney U test)

Socio-economic status classification according to occupation could only be derived for males but showed markedly different distributions for the two ethnic groups, $P < 0.0001$ (Figure 5.3). More than 55% of South Asians had manual occupations whereas more than 63% of Caucasians had managerial occupations. Socio-economic scores derived from area of residence had no statistically significant effect on the MCIDs comparing South Asians and Caucasians.

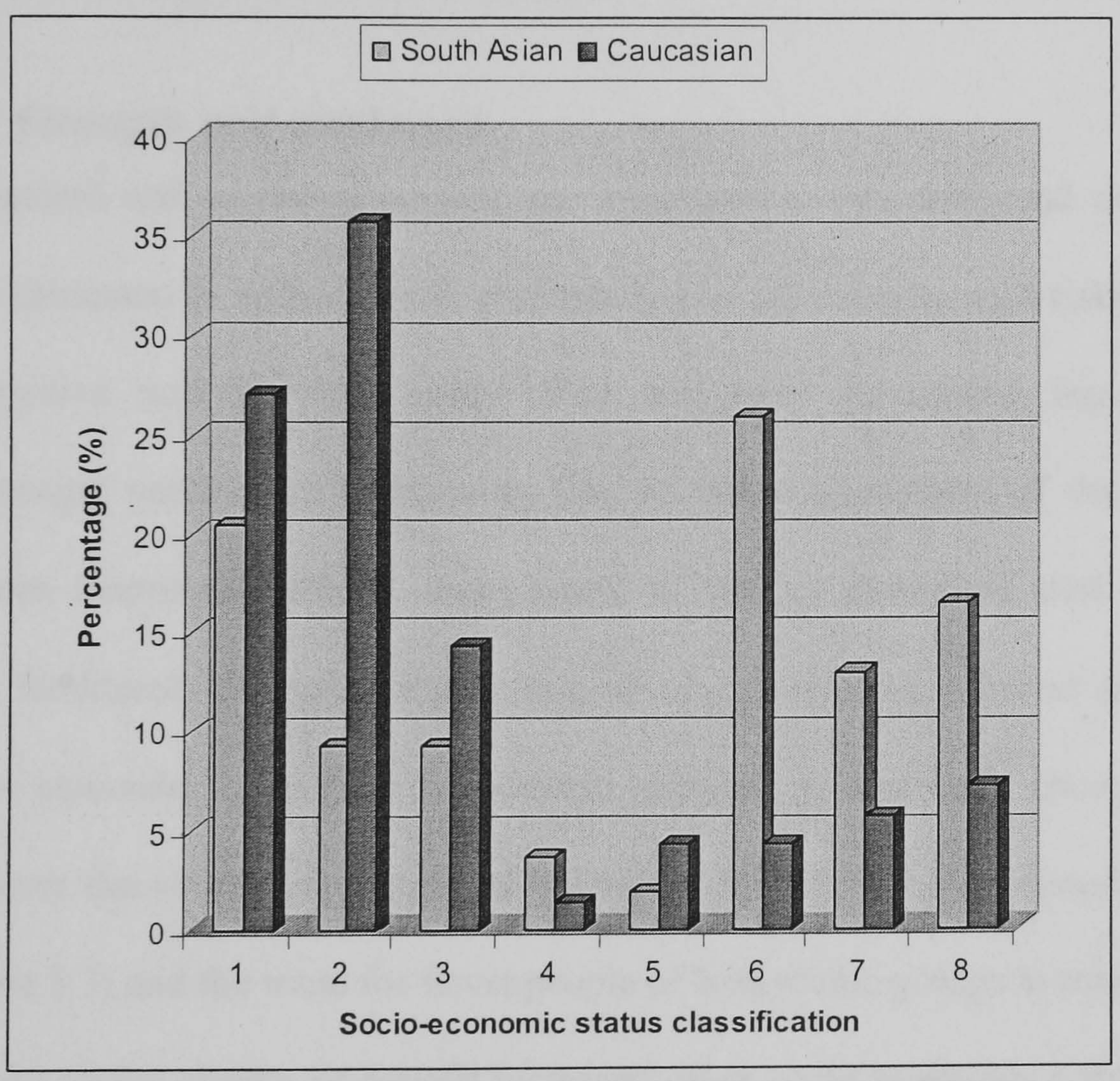

Figure 5.3 Socio-economic status classification in males by ethnicity

1 - Higher managerial
2 - Lower managerial
3 – Intermediate
4 - Small employers
5 - Lower supervisory and craft
6 - Semi-routine occupations
7 - Routine occupations
8 - Never worked (students)

5.5 DISCUSSION

South Asian women given relevant information accepted antihypertensive therapy offering lower benefits than Caucasian women for all three scenarios (Table 5.3). The picture in men is more complex with a greater proportion of South Asian men totally declining treatment in all scenarios. However amongst those South Asian men who would accept treatment the picture was similar to that in women. Similar analysis excluding people who refused to take medication gave corresponding results for both genders in most scenarios.

5.5.1 Strength and weakness

A standard and validated method was employed in this study and outcome data were presented to subjects both graphically and numerically with risks expression in positive and negative terms. This will have minimized framing effects influencing participants' selections. Use of visual illustration of the differences between treatments' effects, using icons, as well as numerical rates should also have facilitated understanding (Elting *et al.*, 1999). Nevertheless the complex issues associated with lack of personal certainty makes such choices difficult. However the strong correlation of individual MCIDs between scenarios 1 and 3 (Figure 5.3) and the trend for fewer people of both ethnic groups to reject treatment outright as the chance of benefit increased gives some reassurance that responses were not random and that complexity did not prevent rational decision-making.

In an attempt to guard against interviewer bias the interviewers were trained using standard training materials combined with a role-playing session, and used interviewers of identical ethnicity to that of the participant. Apart from the formal training and role-playing there was no check to assess consistency between interviewers.

Whilst the sampling frame was representative of the Sheffield population our results may have been subject to selection bias, because of the low response rate in both ethnic groups. Based on the reported response rate to an earlier postal questionnaire study in Sheffield it was expected the response rates for an interview to be about 20% for South Asians and 40% for Caucasians. In practice overall responses (both yes and no) in our study were similar to the earlier study but positive responses for interview were less than expected in both ethnic groups. More women than men responded to this study, about 56% of non-respondents were men in both ethnicities. Non-respondents were 3.1 years younger in Caucasians and half a year in South Asian. They were more likely to live in deprived areas. In addition a post-hoc power calculation showed that the achieved sample size of 220-260 provides a power of 80.1 - 86.3% for comparison between South Asians as a whole with Caucasians.

Trewby et al. (2002) showed that people with a history of CVD would accept treatment for smaller benefit. The comparison therefore was repeated between South Asians and Caucasians after excluding subjects with history of CVD. As is shown in the Table 3 the differences in MCID between South Asians and Caucasians persisted in all scenarios in both genders except scenario one in women (Table 5.3). Similarly results were largely unaltered by excluding subjects who were taking antihypertensive drugs. MCID differences changed only in scenario two for in women.

Familiarities with CVD and concern about its prevention may have motivated people to participate in this research which could bias the MCIDs recorded. Fear of

stroke was reported as the most important factor influencing the MCID of warfarin therapy for the treatment of nonvalvular atrial fibrillation (Man-Son-Hing *et al.*, 1996).

One possible explanation for these ethnic differences might be the higher prevalence of personal or family history of CVD or current receipt of antihypertensive treatment in South Asians but these factors would not explain the high rate of treatment refusal by South Asian men.

Although the importance of standardized procedures for translation of instruments to other languages to ensure equivalency of translations was recognized, funding did not allow this check. All documents were translated using formal translation methods by translators recommended in the UK Institute of Translation & Interpretation website.

Socio-economic status classification based on occupation is only presented for male subjects (Figure 5.3). Occupational status is an important component of socioeconomic status, summarizing the power, income and educational requirements associated with various positions in the occupational structure. It reflects the outcome of educational attainment, provides information about the skills and credentials required to obtain a job, and the associated monetary and other rewards (Burgard *et al.,* 2003). However its validity might be in question because of difficulties in categorizing occupations. Failure to find a statistically significant difference of acceptance for antihypertensive therapy between South Asian and Caucasian men in this study might be due to the small number of

subjects in the different categories of this occupation classification. This classification is a national standard by the Office of National Statistics (http://www.statistics.gov.uk/) and they do not recommend any adjustment for different ethnic groups.

5.5.2 Ethnic differences in use of preventive medicine

In contrast to the higher cardiovascular morbidity and mortality among South Asian people in the United Kingdom, South Asian patients are less likely to be prescribed lipid-lowering drugs (Patel *et al.*, 2005). This is not due to differences in rate of testing lipids (France *et al.*, 2003) but might be related to use of tools such as Framingham which underestimate risk in South Asians and the use of specific total cholesterol thresholds. For a given risk South Asians will tend to have a lower total cholesterol concentration. Despite significantly lower baseline blood pressure levels among diabetic South Asian patients, the level of improvement over a mean period of 5.3 years in routine clinical practice was smaller in South Asians, compared to Europeans, commensurate with the significantly smaller proportion of South Asians who were on anti-hypertensive medication (Mukhopadhyay *et al.*, 2005). In this retrospective analysis it was also notable that use of insulin therapy was no higher in South Asians despite greater year-on-year deterioration in HbA_{1c}, suggesting a deficit of South Asian insulin-treated Type 2 diabetes patients. Slightly greater reductions over time in systolic and diastolic blood pressure in European when compared with the South Asian diabetic patients have been reported in Blackburn, north-west England (McElduff *et al.*, 2005). Possible explanations for poorer control in South Asians may include less intensive treatment, biological differences in response, and poorer compliance. Our results show South Asians acceptance of primary prevention treatment is similar, if not

greater than, that for Caucasians. A difference in treatment acceptance is therefore unlikely to explain differences in prescribing patterns.

5.5.3 Guidelines *v* patients wishes

It appears irrational that some participants were unwilling to take therapy even when told it would abolish their personal risk of CVD. This pattern has been reported before (Man-Son-Hing *et al.*, 1996; Reed *et al.*, 1993; McAlister *et al.*, 2000) and it may be important to understand whether this reflects contrasting priorities between patients and clinicians or a flaw in the methods used to elicit patients' wishes. Similar disagreements were reported when the results of decision analysis were compared with guidelines for preventive warfarin therapy in atrial fibrillation patients (Protheroe *et al.*, 2000; Lip *et al.*, 2002). These illustrate the contradiction in our current approach to patients when we are supposed to be providing them with choice and putting them and their biographical experience at the centre of decisions but at the same time following practice based on research evidence (Sweeney & Heath 2006).

One advantage of the MCID approach is that is a reflection of the decision making process patients may use in practice taking information provided by their nurse or doctor along with their own personal values to make a decision.

5.5.4 What proportion of informed patients might be expected to refuse treatment

In the current guidelines (Williams *et al.*, 2004; JBS-2, 2005) the threshold for initiating treatment in patients with mild hypertension is a 20% CVD risk in the next ten years. Given a 20% relative risk reduction with antihypertensive therapy this corresponds to a 10-year MCID of 4%. Judged from our 20% CVD in 10 years

scenario 36-52% of Caucasians and South Asians would decline antihypertensive therapy at this level of risk. The existence of such subgroups points to the need for decision aids that can incorporate patients' individualized risk factors and make explicit their achievable risk reduction, given various modifications in their risk profiles (Llewllyn-Thomas *et al.*, 1997). It is a matter of debate whether it is a doctors role to try to change patients views.

5.6 CONCLUSION

In conclusion South Asian participants were at least likely as Caucasians to accept antihypertensive treatment for primary prevention should be targeted for this type of treatment. Differences may in part be explored by different health and demographic factors between South Asians and Caucasians e.g. the former being more likely have a personal or family history of CVD. However given that this reflect the population burden of disease for these 2 groups this should still translate into a greater desire for treatment amongst South Asians at large.

CHAPTER 6

BLOOD PRESSURE CONTROL IN SOUTH ASIANS AND CAUCASIANS IN THE UK

6.1 INTRODUCTION

Blood pressure has an approximately normal distribution in the population and those in the upper tail of the distribution are described as having high blood pressure or hypertension. Although high blood pressure is not in itself a symptomatic illness it is known to be a risk factor for cardiovascular disease (CVD) as it increases the likelihood of future stroke, coronary heart disease (CHD), and heart failure (Vasan *et al.,* 2001; Kannel, 1996). No cause can be found in the vast majority of people with high blood pressure, and for these it is described as essential hypertension. Lifestyle factors such as: obesity, lack of exercise, excessive alcohol consumption, and too much salt in the diet can however exacerbate high blood pressure.

Both systolic and diastolic blood pressures have continuous relationships with the risk of developing CVD (MacMahon *et al.,* 1990). This relationship is consistent in different populations, in younger and older subjects, in men and women, and is independent of other cardiovascular risk factors. Several clinical trials have demonstrated a reduction in cardiovascular events as a result of lowering blood pressure (Turnbull *et al.,* 2003). A reduction in blood pressure by an average of 12/6 mm Hg can be expected to reduce stroke by 40% and CHD by 20%. This definition of hypertension as a risk factor worthy of treatment is largely pragmatic and based on inclusion criteria in those clinical trials which showed benefits of blood pressure lowering in terms of reducing CVD. Hypertension is commonly defined in adults as a clinic systolic blood pressure $\geq$ 140 mm Hg and/or a diastolic blood pressure $\geq$ 90 mm Hg. In patients with diabetes the benefit from drug treatment of hypertension may be greater and there is evidence that greater

blood pressure reduction down to a target of 130/85 provides greater benefit. Recent guidelines advise these separates targets for diabetic patients. The size of benefit from blood pressure lowering is dependent on pre-treatment risk. Although no risk directed stratification has been performed in trials, post-hoc analyses show that some groups e.g. white women who are at low risk gain little or may even be harmed by drug treatment of mild hypertension. For this reason a dual threshold of both risk and blood pressure is used to determine whether or not to institute drug treatment of mild hypertension. Hypertensive patients with systolic pressures 140-159 mm Hg or diastolic pressures 90-90 mm Hg only warrant intervention with drug therapy if their total CVD risk over the subsequent ten years is ≥ 20%. In contrast patients with end organ damage have identified themselves as at high risk and automatically warrant treatment of hypertension. Indeed the HOPE (Yusuf *et al.,* 2000) and PROGRESS (Staessen, 2001) studies suggest that for these groups antihypertensive drug treatment may be of benefit independent of blood pressure. Hypertension is one of several cardiovascular risk factors and should be treated as part of a multiple risk factor strategy. Measurement should be done using accurate, validated, and well maintained monitors with an appropriate cuff size (Williams *et al.,* 2004).

Differences in the prevalence of raised blood pressure among minority ethnic groups have been found across the world and in different areas in England. Some, (Cappuccio *et al.,*1997; Chaturvedi *et al.,* 1993) but not all studies, (Cruickshank *et al.,* 1983) showed higher rates of raised blood pressure among people of South Asian origin. A study based on self-reporting, which investigated differences among subgroups within the South Asian communities as well as Whites, found

that people from the White, Pakistani and Bangladeshi groups reported similar rates of diagnosed hypertension, while Indians reported lower rates (Nazroo, 1997). Using combined data from Health Surveys for England (HSE) 1992-1996, it can be seen that South Asian men older than 40 years are more likely to be hypertensive (systolic BP ≥ 160 mm Hg or diastolic BP ≥ 95 mm Hg, or be on antihypertensive medication) compared to Whites (OR 1.9; 95% CI 1.4 to 2.4), after adjustment for age, BMI, smoking status, alcohol consumption, and social class (Primatesta *et al.,* 2000). However the numbers of South Asians included in this analysis were small and reported mean blood pressure levels may be insufficiently robust.

Agyemang & Bhopal (2003) reported discrepancies between the results of different studies in the prevalence of hypertension in South Asians living in the UK. Some reported lower mean systolic blood pressures, while others showed higher diastolic pressures in South Asian men. In women, more studies showed lower systolic blood pressures and higher diastolic pressures.

In order to make an accurate assessment of the effectiveness of health programmes aimed at controlling high blood pressure, it is important first, to establish the mean blood pressure levels and the prevalence of hypertension in the population, particularly amongst the different ethnic groups, and secondly, to determine the proportion of people achieving adequate blood pressure control on antihypertensive treatment. The 'rule of halves' is a device used to illustrate the inadequacy of blood pressure management. This suggested that only 50% of hypertensives are diagnosed, and of these only 50% are treated, with only 50% of those on treatment being well controlled (Meade *et al,* 1978). As a consequence

only 1 in 8 of those with hypertension both receives antihypertensive therapy and achieves adequate blood pressure control. There is some evidence that this proportion may have changed at least in Western countries (Marques-Vidal & Tuomilehto, 1997). Colhoun and colleagues reported the rates for awareness, treatment, and control of hypertension (SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg) as 40%, 26%, and 6% respectively in England using data from the Health Survey for England 1994 (Colhoun *et al.,* 1998). Rates of detection, treatment, and control of high blood pressure among the UK South Asians appear similar to those of the Caucasians (Lane & Lip, 2001).

6.2 AIM AND OBJECTIVES

- To investigate the prevalence, treatment, and control of hypertension in the UK South Asian and Caucasian populations using HSE 1998 and 1999 datasets
- To explore the need for treatment in undiagnosed hypertensives in both UK South Asian and Caucasian communities (≥ 20% CVD risk over ten years)

6.3 METHODS

6.3.1 Participants

Data from Health Surveys for England 1998, 1999, and 2003 were used to study ethnic differences in blood control. More details regarding the methodology of this survey can be found in chapters 2 & 3 (2.5.3 & 3.2.1). People older than 35 years were included in the analysis determining the prevalence hypertension.

6.3.2 Blood pressure definition

In the Health Survey for England blood pressures were measured three times. To allow for the alerting response the mean of the second and third blood pressure measurements has been used in the current analysis. The value of the first reading

has been discarded. The definition of hypertension used was: SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg or being on antihypertensive medications. As some antihypertensive drugs are used for conditions other than blood pressure control drug treatment of hypertension was defined as taking one of the four common classes of antihypertensive medications (diuretics, beta blockers, calcium antagonists, and angiotensin converting enzyme inhibitors) prescribed by a doctor for the treatment of high blood pressure. Hypertension control was defined as receiving antihypertensive medication with measured systolic blood pressure and diastolic blood pressure less than nominal treatment targets, ≤140/85 mmHg in people without renal impairment, diabetes, or established CVD (Williams *et al.,* 2004).

6.3.3 Prediction tool

In those subjects aged 35-75 years with undiagnosed high blood pressure the Framingham equation was used to predict CVD risk. Risk derived from the Framingham equation was multiplied by a factor of 1.79 to provide a more accurate risk estimate for non-diabetic South Asians. This adjustment to predicted risk is described in details in chapter 2 of this thesis. Further discussion about the relationship between CVD and CHD risk is provided in the discussion sections of chapters 3 and 4. It remains a possible limitation to work introduced here.

6.3.4 Statistical Analysis

Analysis was carried out using Statistical Package for Social Sciences (SPSS) for windows software version 12.0. The proportion of South Asian participants eligible for treatment of hypertension (as defined above) and subjects who were taking antihypertensive drugs was compared with that of Caucasians, meeting the same eligibility criteria, using the Chi-square test. Analysis of variance and logistic

regression were used to adjust for age, gender and the presence of other cardiovascular risk factors.

6.4 RESULTS

The data from a total of 24,115 men and women (21,717 Caucasian and 2,398 South Asians) 35 years and older from HSE 98, 99, and 2003 were used in the analysis. Characteristics of participants included in the analysis broken down by gender and ethnicity are shown in Tables 6.1 to 6.4. Systolic and diastolic blood pressures were lower in 2003 compared to 1998-99 in both ethnic groups in both men and women. These differences were statistically significant after adjustment for age in Caucasians but not for systolic blood pressure in South Asian men or for diastolic blood pressure in South Asian women. The trends in blood pressure were however consistent between groups and the non-significant p-values in South Asians are likely due to smaller numbers of subjects available for analysis in these groups.

Table 6.1 Characteristics of South Asian men older than 35 years by the year of study

	1998-99 (% or 95% CI)	2003 (% or 95% CI)	p-value	p-value after adjustment for age
Number	1042	160	---	
Age	50.2 (49.5 – 50.9)	50.4 (48.9 – 52.0)	0.77	----
Systolic blood pressure	136.0 (134.5 – 137.4)	134.4 (131.5 – 137.2)	0.33	0.194
Diastolic blood pressure	79.8 (78.9 – 80.6)	76.7 (74.9 – 78.5)	0.003	0.006
Total Cholesterol	5.52 (5.43 – 5.60)	5.58 (5.35 – 5.82)	0.56	0.554
HDL-cholesterol	1.14 (1.11 – 1.17)	1.26 (1.20 – 1.32)	*	*
History of **Stroke**	28 (2.7%)	4 (2.0%)	0.89	
History of **Myocardial infarction**	62 (6.0%)	4 (2.0%)	0.07	
History of **Angina**	76 (7.4%)	10 (6.3%)	0.63	
Diabetes	154 (14.8%)	24 (15.0%)	0.94	
Current cigarette smoker	292 (28.0%)	21 (19.4%)	< 0.001	

** HDL-cholesterol analysis was carried out by different methods in 1999 and 2003 consequently the 2003 data are not directly comparable with those in 1998.*

Table 6.2 Characteristics of Caucasian men older than 35 years by the year of study

	1998-99 (% or 95% CI)	2003 (% or 95% CI)	p-value	p-value after adjustment for age
Number	5158	4520	---	
Age	55.6 (55.2 – 56.0)	56.3 (55.9 – 56.7)	< 0.0001	----
Systolic blood pressure	139.4 (138.8 – 139.9)	137.2 (136.6 – 137.7)	< 0.0001	< 0.0001
Diastolic blood pressure	79.6 (79.2 – 79.9)	74.7 (74.3 – 75.0)	< 0.0001	< 0.0001
Total Cholesterol	5.68 (5.65 – 5.72)	5.90 (5.85 – 5.94)	< 0.0001	< 0.0001
HDL-cholesterol	1.29 (1.28 – 1.30)	1.40 (1.39 – 1.41)	*	*
History of **Stroke**	171 (3.3%)	169 (3.7%)	0.26	
History of **Myocardial infarction**	302 (5.9%)	285 (6.3%)	0.35	
History of **Angina**	388 (7.5%)	352 (7.8%)	0.62	
Diabetes	225 (4.4%)	269 (6.0%)	< 0.0001	
Current cigarette smoker	1282 (24.9%)	960 (21.2%)	< 0.0001	

** HDL-cholesterol analysis was carried out by different methods in 1999 and 2003 consequently the 2003 data are not directly comparable with those in 1998.*

Table 6.3 Characteristics of South Asian women older than 35 years by the year of study

	1998-99 (% or 95% CI)	2003 (% or 95% CI)	p-value	p-value after adjustment for age
Number	944	172	---	
Age	48.4 (47.7 – 49.1)	48.0 (46.6 – 49.3)	0.60	----
Systolic blood pressure	132.2 (130.5 – 133.4)	127.5 (124.3 – 130.7)	0.011	0.002
Diastolic blood pressure	74.9 (74.0 – 75.8)	73.9 (72.0 – 75.7)	0.32	0.269
Total Cholesterol	5.22 (5.13 – 5.31)	5.47 (5.24 – 5.71)	0.032	0.033
HDL-cholesterol	1.34 (1.31 – 1.38)	1.53 (1.44 – 1.62)	*	*
History of **Stroke**	8 (0.9%)	4 (2.3%)	0.08	
History of **Myocardial infarction**	10 (1.1)	1 (0.6%)	0.56	
History of **Angina**	28 (3.0%)	6 (3.5%)	0.68	
Diabetes	91 (9.6%)	16 (9.3%)	0.89	
Current cigarette smoker	24 (2.5%)	6 (3.5%)	0.48	

** HDL-cholesterol analysis was carried out by different methods in 1999 and 2003 consequently the 2003 data are not directly comparable with those in 1998.*

Table 6.4 Characteristics of Caucasian women older than 35 years by the year of study

	1998-99 (% or 95% CI)	2003 (% or 95% CI)	p-value	p-value after adjustment for age
Number	6323	5716	---	
Age	56.6 (56.3 – 57.0)	57.1 (56.7 – 57.5)	0.066	----
Systolic blood pressure	137.0 (136.4 – 135.8)	133.9 (133.3 – 134.5)	< 0.0001	< 0.0001
Diastolic blood pressure	74.3 (74.0 – 74.6)	73.1 (72.8 – 73.4)	< 0.0001	< 0.0001
Total Cholesterol	5.85 (5.81 – 5.88)	5.99 (5.95 – 6.03)	< 0.0001	< 0.0001
HDL-cholesterol	1.58 (1.57 – 1.59)	1.68 (1.66 – 1.69)	*	*
History of Stroke	183 (2.9%)	179 (3.1%)	0.45	
History of Myocardial infarction	161 (2.5%)	171 (2.4%)	0.61	
History of Angina	350 (5.5%)	278 (5.2%)	0.22	
Diabetes	193 (3.1%)	246 (4.3%)	< 0.0001	
Current cigarette smoker	1557 (24.6%)	1288 (22.5%)	0.007	

** HDL-cholesterol analysis was carried out by different methods in 1999 and 2003 consequently the 2003 data are not directly comparable with those in 1998.*

Tables 6.5 & 6.6 show the prevalence of hypertension, as diagnosed by a doctor or with SBP and/or DBP $\geq$ 140/90 mm Hg measured by the survey nurse among the two ethnic groups based on those who had blood pressure measurements. The overall prevalence of hypertension was higher in Caucasians compared with South Asians. Prevalence of diagnosed or undiagnosed hypertension was similar in 2003 compared to 1998-99 in Caucasian and South Asian men and women, Tables 6.5 & 6.6.

More South Asian and Caucasian men and women were diagnosed as hypertensive in year 2003 compared to year 1998-99, Tables 6.7 & 6.8. These improvements in diagnosis are statistically significant in both gender in Caucasian and South Asian. In addition undiagnosed hypertension declined in both groups.

Table 6.5 Prevalence of high blood pressure in men with blood pressure measurement by ethnicity and year of study

	South Asian		Caucasian	
	1998-99	**2003**	**1998-99**	**2003**
	(714)	**(99)**	**(4398)**	**(3009)**
Diagnosed hypertension or	326	48	2356	1576
BP ≥ 140/90	**45.7%**	**48.5%**	**53.6%**	**52.4%**
Normal blood pressure	388	51	2042	1433
	54.3%	**51.5%**	**46.4%**	**47.6%**

** (Comparison between year 2003 and 1998-99 in each ethnicity)*

P= 0.59 (South Asians), P= 0.31 (Caucasians)

Table 6.6 Prevalence of high blood pressure in women with blood pressure measurement by ethnicity and year of study

	South Asian		Caucasian	
	1998-99	**2003**	**1998-99**	**2003**
	(626)	**(107)**	**(5220)**	**(3688)**
Diagnosed hypertension or	232	39	2455	1722
BP ≥ 140/90	**37.1%**	**36.4%**	**47.0%**	**46.7%**
Normal blood pressure	394	68	2765	1966
	62.9%	**63.6%**	**53.0%**	**53.3%**

** (Comparison between year 2003 and 1998-99 in each ethnicity)*

P= 0.90 (South Asians), P= 0.75 (Caucasians)

Table 6.7 Diagnosis of hypertension by a doctor in all hypertensive men by ethnicity and year of study

	South Asian		Caucasian	
	1998-99	**2003**	**1998-99**	**2003**
	(326)	**(48)**	**(2356)**	**(1576)**
Diagnosed hypertension	152 **46.6%**	33 **68.8%**	1077 **45.7%**	989 **62.8%**
Undiagnosed hypertension	174 **53.4%**	15 **31.3%**	1279 **54.3%**	587 **37.2%**

** (Comparison of diagnosed hypertension between year 2003 and 1998-99 in each ethnicity)*

South Asian: OR $_{\text{diagnosed/undiagnosed hypertension}}$ = 2.5 (95% CI 1.3 to 4.8), P = 0.004

Caucasian: OR $_{\text{diagnosed/undiagnosed hypertension}}$ = 2.0 (95% CI 1.8 to 2.3), P < 0.0001

Table 6.8 Diagnosis hypertension by a doctor in all hypertensive women by ethnicity and year of study

	South Asian		Caucasian	
	1998-99	**2003**	**1998-99**	**2003**
	(232)	**(39)**	**(2455)**	**(1722)**
Diagnosed hypertension	103 **44.4%**	31 **79.5%**	1328 **54.1%**	1113 **64.6%**
Undiagnosed hypertension	129 **55.6%**	8 **20.5%**	1127 **45.9**	609 **35.4%**

** (Comparison of diagnosed hypertension between year 2003 and 1998-99 in each ethnicity)*

South Asian: OR $_{\text{diagnosed/undiagnosed hypertension}}$ = 4.9 (95% CI 2.1 to 11.0), P < 0.0001

Caucasian: OR $_{\text{diagnosed/undiagnosed hypertension}}$ = 1.6 (95% CI 1.4 to 1.8), P < 0.0001

More than a half of the hypertensive men of both ethnicities received antihypertensive in 2003. Although the trend with time was similar in both ethnic groups the change in this proportion was only statistically significant in Caucasians, Table 6.9.

Receipt of antihypertensive drug treatment in diagnosed hypertensive South Asian women was similar in 2003 and 1998-99 in contrast to the significant increase seen in Caucasian women during the same period of time, Table 6.10.

Tables 6.11 & 6.12 show the adequacy of blood pressure control in South Asian and Caucasian men and women receiving treatment for hypertension. Effective treatment was higher in both genders in the Caucasian population and in South Asian women in 2003 when compared with 1998-99. The trend of improvement in adequate treatment was statistically significant for all groups except South Asian men.

Table 6.9 Receiving antihypertensive in diagnosed hypertensive men by ethnicity and year of study

	South Asian		Caucasian	
	1998-99	**2003**	**1998-99**	**2003**
	(152)	**(33)**	**(1077)**	**(989)**
On treatment	77 **50.7%**	22 **66.7%**	461 **42.8%**	565 **57.1%**
Not treated	75 **49.3%**	11 **33.3%**	616 **57.2%**	424 **42.9%**

** (Comparison of diagnosed hypertension between year 2003 and 1998-99 in each ethnicity)*

South Asian: OR $_{\text{on treatment/not treated}}$ = 1.9 (95% CI 0.9 to 4.3), P < 0.095

Caucasian: OR $_{\text{on treatment/not treated}}$ = 1.8 (95% CI 1.5 to 2.1), P < 0.0001

Table 6.10 Receiving antihypertensive in diagnosed hypertensive women by ethnicity and year of study

	South Asian		Caucasian	
	1998-99	**2003**	**1998-99**	**2003**
	(103)	**(31)**	**(1328)**	**(1113)**
On treatment	52 **50.5%%**	16 **51.6%**	698 **52.6%**	728 **65.4%**
Not treated	51 **49.5%**	15 **48.4%**	630 **47.4%**	385 **34.6%**

** (Comparison of diagnosed hypertension between year 2003 and 1998-99 in each ethnicity)*

South Asian: OR $_{\text{on treatment/not treated}}$ = 1.1 (95% CI 0.5 to 2.2), P = 0.91

Caucasian: OR $_{\text{on treatment/not treated}}$ = 1.7 (95% CI 1.4 to 2.0), P < 0.0001

Table 6.11 High blood pressure control (≤140/85 mmHg) in hypertensive men on treatment by ethnicity and year of study

	South Asian		Caucasian	
	1998-99	**2003**	**1998-99**	**2003**
	(77)	**(22)**	**(461)**	**(565)**
Treated and controlled BP *	23	5	125	215
	29.9%	**22.7%**	**27.1%**	**38.1%**
Treated but not controlled	54	17	336	350
BP *	**70.1%**	**77.3%**	**72.9%**	**61.9%**

** (Comparison of controlled BP between year 2003 and 1998-99 in each ethnicity)*

South Asian: OR $_{\text{controlled/not controlled BP}}$ = 0.7 (95% CI 0.2 to 2.1), P = 0.51

Caucasian: OR $_{\text{controlled/not controlled BP}}$ = 1.7 (95% CI 1.3 to 2.2), P < 0.0001

Table 6.12 High blood pressure control (≤140/85 mmHg) in hypertensive women on treatment by ethnicity and year of study

	South Asian		Caucasian	
	1998-99	**2003**	**1998-99**	**2003**
	(52)	**(16)**	**(698)**	**(728)**
Treated and controlled BP *	15	10	169	247
	28.8%	**62.5%**	**24.2%**	**33.9%**
Treated but not controlled	37	6	529	481
BP *	**71.2%**	**37.5%**	**75.8%**	**66.1%**

** (Comparison of controlled BP between year 2003 and 1998-99 in each ethnicity)*

South Asian: OR $_{\text{controlled/not controlled BP}}$ = 4.1 (95% CI 1.3 to 13.3), P = 0.015

Caucasian: OR $_{\text{controlled/not controlled BP}}$ = 1.6 (95% CI 1.3 to 2.0), P < 0.0001

Table 6.13 & 6.14 show the number of antihypertensive drugs taken by South Asian and Caucasian men and women. A high proportion of subjects in both ethnic groups was taking only one drug in 1998-99. This decreased by 2003 in Caucasian men and women and in South Asian men. Consequently more in these groups were taking two or more tablets in 2003. Changes in South Asians women were in the opposite direction but due to the small numbers this may be a chance finding.

Table 6.13 Number of antihypertensive drugs prescribed for blood pressure control in treated hypertensive men by gender and year

	South Asian		Caucasian	
	1998-99	**2003**	**1998-99**	**2003**
	(77)	**(22)**	**(461)**	**(565)**
1 tablet	48 **62.3%**	12 **54.5%**	293 **63.6%**	250 **44.2%**
2 tablets or more	29 **37.7%**	10 **45.5%**	168 **36.4%**	315 **55.8%**

Table 6.14 Number of antihypertensive drugs prescribed for blood pressure control in treated hypertension women by gender and year

	South Asian		Caucasian	
	1998-99	**2003**	**1998-99**	**2003**
	(52)	**(16)**	**(698)**	**(728)**
1 tablet	33 **63.5%**	13 **81.3%**	416 **59.6%**	325 **44.6%**
2 tablets or more	19 **36.5%**	3 **18.8%**	282 **40.4%**	403 **55.4%**

Under current guidelines only those with a CVD risk ≥20% and mild hypertension (SBP and/or DBP > 140/80 mm Hg) warrant drug treatment. 47.3% and 84.6% of Caucasian and South Asian men, in the HSE 2003 dataset, receiving no treatment had blood pressures above threshold (140/90 mm Hg) and 10 years CVD risk ≥ 20% and were therefore eligible for treatment, Table 6.15. More South Asian women need to be targeted for treatment compared to Caucasians in 2003, 18.3% *v* 10.4% respectively, Table 6.16.

Table 6.15 Treatment needs in men with untreated hypertension (diagnosed or not) aged 35-75 without previous CVD

	South Asian		Caucasian	
	1998-99 (148)	2003 (13)	1998-99 (1160)	2003 (556)
CVD risk ≥20% (treatment indicated)	108 **73.0%**	11 **84.6%**	640 **55.2%**	263 **47.3%**
CVD risk < 20%	40 **27.0%**	2 **15.4%**	520 **44.8%**	293 **52.7%**

Table 6.16 Treatment needs in women with untreated hypertension (diagnosed or not) aged 35-75 without previous CVD

	South Asian		Caucasian	
	1998-99	2003	1998-99	2003
	(109)	(10)	(1112)	(588)
CVD risk ≥20% (treatment indicated)	40 **36.7%**	2 **20.0%**	203 **18.3%**	61 **10.4%**
CVD risk < 20%	69 **63.3%**	8 **80.0%**	909 **81.7%**	527 **89.6%**

6.5 DISCUSSION

This analysis shows that South Asian men and women had lower systolic blood pressures but higher diastolic pressures in 1998-99 and 2003 compared with their Caucasian counterparts. Hypertension (diagnosed by a doctor or blood pressure ≥ 140/90) was more common in Caucasians than South Asians. South Asian men and Caucasian men and women were more likely to have their hypertension diagnosed. However the prevalence of uncontrolled hypertension was higher in South Asian men than in Caucasian men. In contrast South Asian women were less likely to have uncontrolled hypertension than their Caucasian counterparts. Because of their greater risk of CVD South Asian men and women should be targeted for treatment intervention.

Based on the recent guidelines (JBS-2, 2005) people with mild hypertension SBP 140-160 DBP 90-100 need a 10 year CVD risk estimation and people with moderate hypertension (SBP ≥160 and/or DBP ≥100) need drug therapy as well as lifestyle intervention. In this analysis eligibility for treatment within the hypertensive population was judged according to estimated risk alone. In practice some patients with low risk (< 20%) but moderate blood pressure (SBP and/or DBP ≥ 160/100) will receive treatment (Williams *et al.,* 2004). As South Asians have on average lower systolic pressure but higher risk the population falling into this low risk high blood pressure group will be smaller than Caucasians. The estimated difference between ethnicities in need for treatment will therefore be slightly exaggerated.

The large nationally distributed random sample of the HSE 1998-99 overcomes some of the potential problems of sample bias in other studies (for example, in studies based on GP lists, those registered with a doctor might be more likely to self-report than the non-registered; and workplace studies which deal with a population less likely to have ill health than those who are not working). There is however still the possibility of non-response bias and if response in South Asians less than that in Caucasians this could have a differential effect. The number of South Asian subjects in the HSE 2003 is too small for a robust analysis of changes with time and the numbers can only give an idea of the trends of blood pressure and its control. In addition it did not allow me investigate differences between subgroups within South Asian community. Past studies showed marked heterogeneity among South Asian subgroups, with Indians having similar blood pressure to Whites, Pakistanis having slightly lower pressures and Bangladeshis

having the lowest blood pressures (Agyemang & Bhopal, 2003). Part of this inconsistency can probably be explained by the differences between studies in terms of age and gender of samples, definition of South Asians, and geographical variation between London (comparatively high blood pressure in South Asians) and the rest of the UK (comparatively low or similar blood pressure).

CHAPTER 7

GENERAL DISCUSSION

7.1 GENERAL FINDINGS

It is clear that South Asians living in the West have substantially greater relative (coronary heart disease) CHD mortality and morbidity than the general population. Despite this statistic originally being identified 3 decades ago there remain huge gaps in our understanding of the causes and natural history of CHD in this group. Such knowledge is necessary to solve current challenges in disease control. This thesis has demonstrated that:

- The greater risk of CHD in South Asians is not explained well by differences between them and the Caucasian population in either the values or impact of conventional risk factors alone. Risk in non-diabetic South Asians appears to be underestimated by a risk function based on classical risk factors alone. Although based on a single study of hypertensive men CVD risk in South Asians was 79% greater. In contrast risk of CHD in a study of newly diagnosed diabetics was similar in South Asians and Caucasians. This apparent discrepancy in relative risk between diabetic and non-diabetic cohorts may be because non-diabetic South Asians had a higher fasting blood glucose and HbA1c than Caucasians after adjustment for other CHD risk factors. This dysglycaemia may explain part of the excess susceptibility of South Asians to CHD although it is not clear that is the only explanation.

- A simple adjustment method was devised to allow current paper-based risk estimation tools to be used for the UK South Asian population. Adding 10 years to age, although crude, provides adequate sensitivity and specificity to take into account an "ethnicity factor" accounting for average risk in individual South Asians in general practices still using paper-based risk

prediction methods. This will help South Asians who are currently poorly served by risk estimation tools but are a group at greater need of treatment for primary prevention of CVD.

- More UK South Asian men and women, 12.1% (95% CI: 9.3 to 14.8) and 5.1% (3.2 to 7.3) respectively, are candidates for secondary prevention of CVD than Caucasian men and women, 7.4% (6.4 to 8.2) and 4.6% (3.9 to 5.3) respectively. This is due to a greater prevalence of symptomatic CVD in this population. Based on the above suggested ethnically adjusted risk estimate, 18.4% (95% CI: 14.9 to 21.8) of South Asian men aged 35-74 have CHD risk ≥ 30% over 10 years. These people need lipid-lowering therapy according to the National Service Framework for CHD. Eligibility for intervention in Caucasian men is less than one-third that of South Asians. Similarly South Asian women have a greater need for primary prevention than Caucasian women, 2.3% (95% CI: 0.9 to 3.8) and 0.5% (0.3 to 0.7) being eligible respectively. Using the threshold recommended by the current guidelines overall 43 % of South Asian men were predicted to have a CHD risk > 15% (20% CVD risk). This proportion was 29.8% in Caucasian men. In women, overall, 13.5% and 7.2% of South Asian and Caucasian women respectively were above this level of CHD risk and eligible for intervention treatment

- South Asians are at least equally accepting of treatment as Caucasians when given information about the personal impact of hypertension, MI, and stroke, and the effect and tolerability of antihypertensive treatment.

Outright rejection of treatment, independent of the size of benefit, was however more common in South Asian men.

- Hypertensive South Asian men and women eligible for treatment are more likely to be identified by doctors than Caucasians despite them having on average lower systolic and diastolic blood pressures. Importantly and in contrast uncontrolled hypertension is more common in South Asian men than in Caucasians. This could be due to a variety of reasons; e.g. hypertension control is different and more difficult to be controlled in South Asians, more adverse effects happened in South Asians who take antihypertensives, or there might be more treatment rejection in this ethnic group.

7.2 STRENGTH AND WEAKNESSES OF THIS THESIS

The major hurdle in studying health in ethnic minorities is the dearth of high quality published epidemiological information. The estimate of the "ethnicity factor" is based on a single small observational study of 528 (62% men) and 106 (79% men) hypertensive Caucasian and South Asian patients respectively (Khattar *et al.,* 2000). Similarly, our knowledge of the ethnic risk difference in patients with diabetes is based on the results of a single study. This was however a much larger controlled trial of differing intensities of treatment for diabetes and included 432 South Asians, 32.6% of whom were women.

It is likely that there are differences between individual ethnic groups within the South Asian community. Unfortunately, the data available are insufficient to provide separate adjustments for each ethnic group (Indian, Pakistani, and Bangladeshi). In addition, there is some suggestion of an age effect on the differences between South Asians and Caucasians implying a possible difference

between 1st and subsequent generation immigrants. If this were confirmed any adjustment method might need to be recalibrated for second and subsequent generation South Asians.

6.2.1 Low response rate

The HSE datasets were used in several areas in this thesis. Low response rates to the request for a blood sample, especially in South Asians, might be a weakness in using this source of information. Nearly one thirds of Caucasian and half of South Asian adults aged 35-74 years did not have a measurement of plasma total cholesterol. This might introduce non-response bias leading to a biased estimate of risk and requirement of treatment. Non-respondents (those without blood cholesterol measurement) were excluded from the analysis of current thesis and this group had higher blood pressures, were more commonly cigarette smokers, and would therefore be at higher risk. However assuming as much as 3% higher total cholesterol in non-respondents would only increase the proportion of subjects eligible for treatment by 0.5% and 0.3% in men and women respectively. Interestingly the proportions of South Asians who were interviewed and visited by a nurse were similar to Caucasians. Lower rates of agreement to give blood samples might be due to language, cultural, or religious barriers in the survey process for South Asians. Despite these weaknesses the Health Survey for England series are the best available national representative datasets. It is likely that the alternative of using local social settings as the research framework to achieve higher response rates might violate the nationally representativeness of the data.

A low overall response rate was also seen in my patients' acceptance study and this again might introduce weakness because only about half and two-thirds of South Asians and Caucasians approached were interviewed. However this hides the fact that a considerable proportion of recipients of the approach letter did respond, 40% and 62.5% of South Asians and Caucasians respectively. However as has been seen before about 63% of South Asians respondents made a positive decision not to participate compared to the about half of Caucasians respondents who made a negative response. This low response rate was despite including a translated approach letter in five South Asian languages in the invitation pack to increase accessibility. These low rates might be due to concern about being involved in a face-to-face interview or misunderstanding of the inclusion criteria for this research. Feedback suggested that potential participants thought the interview was only for people with a history of CVD. Of note is that subjects who did not agree to be interviewed were more likely to live in deprived areas compared with subjects who did participate. However investigation of the relationship between deprivation and readiness to take medication suggested that this was unlikely to be an important source of bias.

This is probably as robust an answer as it is possible to achieve for this research question. The high rate of cardiovascular disease in the South Asian community and the previous suggestion that they receive less rather than more preventive treatment made it crucially important to make a quantitative estimate of any differences in attitude towards drug treatment. Although a higher response rate would have been ideal it is unlikely to be achieved by any method which comply with current standards of research ethics. The problems introduced by poor response generally relate to the selection bias. To overcome this bias methods of

enhancing response rates, described in Chapter 5, were employed. In addition using the Population Health Register as the sampling frame gave me the opportunity of targeting all individuals living in Sheffield with an equal chance. It was tried to avoid introducing information bias by providing similar and standard basic information of cardiovascular disease and hypertension to both ethnic groups. Although identified forms of bias can be investigated and where possible adjusted for it is still possible that there are as yet unidentified sources of bias in these data.

6.2.2 Performance of CVD risk assessment

Although there is no strong evidence supporting the assumption that cardiovascular risk assessment performed by a clinician improves health outcomes (Brindle *et al.*, 2006) this forms the basis of policy for prevention of CVD. The Framingham Study of cardiovascular diseases and its risk prediction equation is known to all cardiologists, most epidemiologists, many physicians, and even some laypersons. The Framingham risk score is valid for its original population but its external validity and accuracy in other populations has been questioned (D'Agostino *et al.*, 2001). Whilst effective in ranking risk in all populations investigated its estimate of absolute risk may be biased. Several groups have tried to recalibrate the equation against population measures of morbidity and mortality or have suggested different thresholds to allow acceptable prediction of risk for groups other than those individuals in the original study. Adding factors like first degree family history of CVD and an index of social deprivation might improve the discriminatory ability of this risk prediction function still further (Brindle *et al.*, 2005). However each additional factor included would need subsequent validation. Also the incidence of CVD seems to be changing with time independent of variation in risk factors such that any prediction function accurate today may be

inaccurate tomorrow. Whatever the current accuracy of the Framingham equation in the UK population, this forms the basis for calculating risk in clinical practice and is central to judging eligibility for antihypertensive, lipid-lowering and aspirin treatment. As South Asians and Caucasians have similar values of traditional cardiovascular risk factors under or over estimation of risk by this equation should not affect my predictions of the number of patients likely to be offered treatment for primary prevention in the UK population.

Cardiovascular risk estimated by the Framingham and related scores is misleading in guiding treatment decisions among people at different levels of social deprivation. Tunstall-Pedoe & Woodward (2006) reported that the estimated effect of being in the highest 20% of deprivation rather than the lowest 20% is equivalent in risk scoring terms to 10 years or more in age or to a diagnosis of diabetes. 48% (95%CI 44% to 52%) underestimation by the Framingham risk score was reported in manual workers in West Scotland (12,000 men and women) compared to 31% (19 to 40%) in non-manual participants (Brindle *et al.*, 2005). This underestimation was worse among people from deprived areas (P=0.0017). Recalibration of the Framingham score for manual and non-manual subjects would add a substantial number of individuals mainly from manual social classes to those eligible for primary prevention treatment. These data suggest that as used currently risk scoring tools foster relative undertreatment of the socially deprived, exacerbating the social gradients in disease, which national policies seek to minimise. Their use has the potentially undesirable attribute of directing treatment towards higher social classes whose risk is overestimated and away from lower social classes whose risk is underestimated. This may be exacerbated further by the availability

of low dose statin without prescription. Class differences in risk may have more effect on South Asians as they are disadvantaged socio-economically compared to Caucasians. Added to this is the discrepancy in deprivation between different South Asian groups which might explain intra-ethnic differences in CVD risk. The interaction between deprivation and ethnicity when predicting CVD ideally could be modelled to explore this relationship further. Of note is that a statistically significant effect on the MCIDs comparing South Asians and Caucasians of area of residence, a crude surrogate for social status, was not found.

7.3 FUTURE WORK

6.3.1 Needs for prospective studies

The considerably increase in mortality and morbidity of CHD in South Asians and the size of this ethnic group in the UK highlights the need for both a large British cross-sectional study to investigate the prevalence of CHD risk factors in the local Indian, Pakistani, and Bangladeshi population and a prospective cohort study to examine their impact. This is a necessary first step to facilitate intensive focussed risk factor modification strategies which need to be devised specific for this racial group. One step in this direction is the London Life Sciences Prospective Population Cohort, the LOLIPOP study, (Chambers *et al.,* 2006) a large cohort study of South Asian and European men and women, which is being assembled as part of a cardiovascular community programme in west London to identify genetic and environmental factors underlying the increased rates of CHD, obesity, diabetes, and renal failure in Indian Asians compared to Northern Europeans. 24,000 participants (half South Asians) are to be recruited by the end of 2006 and data collection will include long-term storage of blood samples for biochemical and genetic analysis. This research may answer some of the questions regarding

the susceptibility of South Asians to coronary disease and the importance of current risk factors in South Asians.

6.3.2 Targeting South Asians for medical treatment

It is important that any measures for UK South Asians be applied sensitively and effectively to improve the quantity and quality of preventive care provided for them. Although there are no clinical trials that directly support drug treatment for specific ethnic groups like South Asians this should be used for treatment of dyslipidemia and hypertension. Given the similar risk factors and pathophisiology in this group the default assumption must be that such treatment will be as effective as in the Caucasian population studied. In the absence of evidence of clear differences between ethnic groups these drugs should be seen as necessary treatment to reduce and prevent clinical cardiovascular events regardless of the baseline level of each individual risk factor as long as there is trial evidence of benefit for that cohort. For example the Heart Protection Study (HPS, 2002) showed clear benefit from cholesterol lowering in patients whose blood cholesterol concentrations were well within the normal range. However trial evidence must be interpreted with some caution because of lack of significant involvement of ethnic minorities. There remains the possibility of ethnic differences in drug metabolism leading to possible drug toxicity or alternatively lack of efficacy (Levy & Polatsek, 2002; Burroughs *et al.,* 2002). Further uncertainty relates to the treatment thresholds and targets for ethnic minorities. Targets for blood pressure control are reasonably well established but are based mainly on studies in Caucasians. Thresholds in current guidelines (Williams *et al.,* 2004; JBS-2, 2005) are moving towards ones based on overall CVD risk as the determinant for intervention but retaining levels of need for a systolic or diastolic blood pressure ≥ 140/90 mmHg

as an additional requirement. This emphasizes that there may be need for a definition of ethnic specific thresholds as well as recalibration of the risk equation. With normal blood pressures being quite different in the various ethnic groups it is possible that the blood pressure at which risk increases varies with ethnicity. Investigation of risk prediction functions to date has simply not had the power to detect such potential differences. Cholesterol targets, although enshrined in guidelines are based only on post-hoc extrapolation, again from trials in Caucasians. Just as with thresholds for treatment it is certainly plausible that different ethnic groups would have different optimal targets. Perhaps a more important question is whether the incidence of adverse effects is any different. This might impact on compliance with preventive treatments which has not been investigated in the South Asian or other ethnic minority populations.

6.3.3 Preventing metabolic syndrome and diabetes

An important initial step to reduce the burden of CVD would be to prevent progression of high risk individuals to developing diabetes (Lakka *et al.*, 2002). It is possible that identification of metabolic syndrome would be one simple way to recognise those at high risk especially when waist measurement is a simple diagnostic criterion (Alberti *et al.*, 2005). Encouraging South Asians to make such measurement themselves might be an easy method for identifying at risk individuals and giving them information to improve their lifestyle especially if they have a family history of CVD. There are some data to suggest that involving patients in diagnosis makes them more committed to alter their risk factors (Kaplan *et al.*, 1989). Treating risk factors associated with the metabolic syndrome is a rational strategy not only to prevent CVD but also to reduce the incidence of type 2 diabetes in non-diabetic South Asians with dysglycaemia. Just as with thresholds

and targets it is important to consider whether the components of the metabolic syndrome should be redefined or have adjusted cut-points for South Asian people (Alberti *et al.*, 2005). Although levels of modifiable risk factors in migrant South Asians are far higher compared with their non-migrant relatives living in India they are still below levels seen in Caucasians (Ramachandaran *et al.*, 2001). This might suggest the threshold of "normality" used for the general population in western countries may be too high for South Asians and need to be reduced or adjusted. Most of these risk factors follow a continuum and cut-offs are arbitrarily defined based on centiles of the population distribution. For those population in which the distribution is shifted e.g. South Asians different diagnostic cut-offs might be appropriate.

Interruption of the renin-angiotensin system by angiotensin inhibitor enzymes (ACE) may improve insulin sensitivity (McFarlane *et al.*, 2003). Several trials, beginning with the Captopril Prevention Project (CAPPP) (Niklason *et al.*, 2004), suggest that ACE inhibitors reduce the incidence of type 2 diabetes in hypertensive patients. This might be seen as a reason to prefer ACE inhibitors as first line treatment for high blood pressure in South Asians. However their risk of stroke is proportionately higher and this class of drug is probably less protective against cerebrovascular disease than thiazide diuretics or calcium channel blockers (Jackson & Ramsay, 2002).

Management of the metabolic syndrome is usually focused on lifestyle intervention to reduce obesity by dietary change and increasing physical activity (Stone *et al.*, 2005). Unfortunately we have few data to show whether these are acceptable or effective in South Asians. In addition a great deal needs to be done to determine the causes for the increased susceptibility of South Asians to diabetes. It could be

possible that Caucasians are protected from diabetes by underlying genetic differences. Alternatively differences in socioeconomic situation and lifestyle might contribute. A further complication is added by the possibility that some ethnic groups might have greater susceptibility to diabetic complications. For example the high rates of diabetes in Pima Indians are not associated with huge elevation of CHD risk (Nelson *et al.,* 1990).

6.3.4 Reducing in smoking

Due to the strong evidence linking smoking and CVD (Anderson, 1991) smoking cessation is crucial to reduce the prevalence of these diseases. Of relevance here is the distinct ethnic differences in the prevalence of cigarette smoking which is particularly high in the Bangladeshi population (Erens *et al.,* 2001). This illustrates the importance of cultural factors in disease incidence and prevention.

6.3.5 Recalibrating the Framingham equation

The weaknesses of the Framingham function as currently implemented were discussed above. Use of a simple cheap recalibration of the Framingham function would allow estimates of absolute CHD risk as a means of identifying those South Asian people who need targeting for aggressive primary prevention strategies. Absolute risk estimation has also been proposed as a tool for motivating patients to comply with preventive strategies although there is little evidence to confirm the efficacy of such a ploy. It is however pressing now to provide an appropriate recalibration to prevent the high risk South Asian population being excluded from the current national strategy for primary prevention of CVD. Cappuccio *et al.* (2002) suggested a lower threshold of CHD risk for treating mild uncomplicated hypertension in people of South Asian origin. This was only necessary because the higher risk of stroke relative to MI in this population which made overall CVD risk

estimation using the calculated CHD risk inaccurate. As my adjustment factor is based on differences in CVD risk this is now unnecessary. It was suggested adding 10 years to the age of non-diabetic South Asians (chapter 2, this thesis). An alternative approach suggested by Brindle *et al.* (2006) in the recently launched ETHRISK, a web based risk calculator for British Black and minority ethnic groups, is estimation base on a population recalibration of the Framingham CHD and CVD risk equations. The ETHRISK model uses the prevalence ratios for CHD and CVD for each ethnic group compared to the general population, and adjusts for differences in mean risk factor levels (age, total cholesterol/HDL ratio, and systolic blood pressure) and prevalence of smoking between each ethnic group. They used hazard ratios and coefficients for CHD risk factors consistent with results from four contemporary British cardiovascular cohort studies and assumed similar hazard ratios in the different ethnic groups (Brindle *et al.*, 2006-b). These risk adjustment and recalibration tools could improve identification of high risk South Asians who might benefit from primary prevention therapy.

Another possible but as yet untested, method to achieve a simple cheap recalibration of existing risk equations would be to use data collected at the level of general practices. As computerized datasets are now widespread it would be possible to perform anonymous retrieval of CVD risk factors and mortality data. Although there is no standard software for the collection of patient information in primary care in the UK, the range of main systems is small. In addition, there are now software tools e.g. MYQUEST which can mine data from such databases without breaching patient confidentiality. Substantial work has already being performed with such databases looking for evidence of drug toxicity. These could be employed to derive risk prediction models for South Asians and other ethnic

minorities based on individual data rather than population averages. This would however require recording of ethnicity in general practices (Gill & Johnson, 1995) but should be ethically acceptable because of the anonymous use of the data. Perhaps an even more important use of these data would be an efficient rapid updating of derived prediction tools necessary because of the constant change in risk factors and their impact.

6.3.6 Tackling childhood obesity

Obesity in children is now reaching epidemic proportions internationally and probably reflects poor dietary habits and physical inactivity, resulting from societal changes in lifestyle. This may be one further explanation for differences in incidence of diabetes and CVD between groups. Childhood obesity differs between ethnic groups with South Asian children having an increased chance of being overweight and obese compared to the general population (Saxena *et al.,* 2004). Furthermore, factors associated with insulin resistance are apparent in childhood of South Asian origin (Whincup *et al.,* 2002). Childhood obesity increases the risk of obesity in adulthood and the risk of developing metabolic syndrome in adulthood (Vanhala *et al.,* 1998). Important here is the possibility of a change in impact of current risk factors in different generations of South Asian people. Identifying suitable risk-adjustment tools for the current South Asian population is only a first step. Since a growing proportion of people from ethnic minorities are UK-born, epidemiological research among second-generation Asians is necessary to re-examine the prevalence of risk factors of cardiovascular disease and to identify how disease patterns may be changing so that future interventions are correctly targeted. If the risk factor patterns are deteriorating in second-generation South Asians as some data might suggest the current high rates of CVD may only be a

prelude to even worse. One possible explanation of this change is that a mixture of westernized and traditional diet combined with physical inactivity is making second and subsequent generations of South Asians more vulnerable to CHD and CVD. This hypothesis will need to be investigated in the near future as well as examining prevention and management of childhood obesity in younger age South Asians if necessary targeting them at the school ages. This illustrates the need for the calibration of risk prediction tools in all population groups to be reassessed periodically to ensure their continued validity for future generations. Although changes in disease incidence do largely follow changes in risk factors a substantial proportion as yet remains unexplained. Some changes observed in South Asians may only reflect changes in the wider population where increasing obesity is not in fact worsening the incidence of CVD. Although after suggesting several new areas worthy of research in South Asians it is worth remembering that conducting research in CVD in South Asians, as a high risk group, is more likely to be cost-effective. Their higher event rates make it possible to investigate treatment efficacy in smaller studies.

6.3.7 Stress and acculturation

Popular opinion holds that stress is an important risk factor for coronary heart disease. However, compared with other major risk factors, psychosocial variables such as stress are difficult to define objectively. Several constructs within the broad conceptual framework of stress are increasingly regarded as being causally related to coronary heart disease (Hemingway & Marmot, 1999; Ferketic *et al.,* 2000; Rosengren, *et al.,* 2004) and approaches aimed at modifying these factors should be developed. The process of immigration and adjustment to another country is a source of considerable stress. Acculturative stress has been defined as the physical,

biological, social, cultural, and psychological difficulties faced by an immigrant (Krishnan & Berry, 1992). Those stresses towards acculturation and lack of integration to the western societies may contribute to the risk of CVD in South Asian migrants in addition to possible genetic and lifestyle issues considered above. Lack of social support, long working hours, having members of family in the original country, and lack of control in bringing up their children according to traditional values are some of sources of stress in Indian immigrants to the USA (Kalra *et al.,* 2004). More research on psychological and cultural factors should add to the understanding of the relationship between cultural factors, stress, and prevalence of CVD in South Asians. It might be of importance for adults' socio-cultural adaptation to have access to the special intercultural training programs advocated for easier social integration. It is likely that adults and children from second and further generations experience different stress in the final outcome of acculturation. This will make it necessary to adopt different approaches among children and adolescents in immigrant families with due consideration of their cultural and religious values. In addition current stress due to the societal response to terrorism largely attributed to Islamic fundamentalists may particularly affect Muslim immigrants and their families. It is yet to be seen whether this resolve or leads to a long-term source of stress and further changes in their socioeconomic situation.

6.3.8 Acceptance of preventive treatment

Perception of disease and taking medication, especially primary prevention, has generally been under-researched among ethnic groups. It affects patients' acceptance and their adherence or non-adherence to drug treatments. Indo-Asian patients with atrial fibrillation were significantly less aware of their cardiac

condition and its relationship with thromboembolism and stroke compared to Caucasians, P < 0.001, (Lip *et al.,* 2001). Importantly only a minority of them felt that their doctor had given them enough information about their warfarin therapy and also felt that they were careless about taking their medications. In diabetic patients, various factors may influence Pakistani and Indian patients' adherence to oral hypoglycaemia therapy such as: confidence in the British prescribers, perceptions of Western medications as efficacious, expectations that drugs should provide instant relief of symptoms, and beliefs that Western medicines can have detrimental effects if taken in excess or without traditional foodstuffs (Lawton *et al.*, 2005). Part of these perceptions among South Asians may derive from popular ideas about drugs on the Indian subcontinent. Second and subsequent generations may see drugs in different light and we have no information as to how health beliefs are changing with time. Health beliefs may well impact on concordance of treatment in South Asians and explain differences with Caucasians. Further research in concordance of preventive therapy is warranted in this ethnic group. Lack of awareness of individuals or holding different beliefs may reflect the prior knowledge and attitude on the effect of poor counselling and information provision to patients by health care professionals.

6.3.9 Culturally acceptable services

Health care professionals involved in cardiovascular rehabilitation are responsible for providing effective and appropriate services to all patients, regardless of their age, gender, and ethnicity. Language and other communication difficulties are likely to be particularly pertinent for members of some minority ethnic groups. Over half of South Asian patients have little or no understanding of spoken English with women and older people the least likely to speak English (Gerrish, 2001). The

limited use of professional interpreters, or bilingual health professional, and the concomitant heavy reliance on family members to translate highlights how ethnic minority patients and carers who are not fluent in English could be disadvantaged. For instance, in order to obtain a diagnosis of hypertension the informant must have visited the doctor, been able to explain their reason for attending, more difficult in context of asymptomatic disorder, and obtained an answer that they were able to understand and communicate persisting concerns to the doctor. The observed language barriers raise the possibility that advice on matters such as compliance with treatment regimens might not be fully understood. Psychological support of patients and carers is also severely restricted (Gerrish, 2001). Moreover, in this study the fact that follow-up visits were on occasions made for patients when there was no one available to interpret constrained on-going assessment of patients' needs. As South Asians have similar attitudes to taking antihypertensive treatment, when they were provided with full information, it is important that special support is in place to meet their specific cultural requirements so that their goal of avoiding CVD can be achieved. Patient should be made aware of the available support team (doctor, practice nurse, and others) before embarking on treatment that involves regular contacts with members of the team and essential follow-up visits. Current evidence suggests that diabetic South Asians have poorer glycaemic, blood pressure and lipid control than Caucasians (Chowdhury *et al.*, 2006; Mukhopadhyay *et al.*, 2005; McElduff *et al.*, 2005) which may simply reflect differences in interaction with their health teams given them equal acceptance of therapy. Interestingly differences between ethnic groups of how patients view some aspects of their general practices (GP) appear to have widened in over the past years. Based on the NHS patients survey programme in 1998

(Boreham *et al.*, 2003), White respondents reported the most favorable views or more positive experiences, whilst South Asian respondents tended to have the most negative experiences. By 2002, these differences between White and South Asian respondents had increased particularly in the following areas: prompt and convenient access to GPs (waiting times, difficulties with staff and convenience of surgery times); how patients said they were treated by GPs during physical examinations; whether respondents felt GPs listened to them; and whether respondents felt like making a complaint. The source of these widening differences is not clear but obviously needs for further studiy. The differences could arise from reorganizations in primary care services impacting differentially on areas with a high ethnic minority population or may reflect increasing confidence in the South Asians community to express negative views. Clearly dissatisfaction with the service providing preventive treatment can only impede its effectiveness. Primary care teams should work towards meeting the general needs of South Asian population and provide appropriate services for patients with symptomatic CVD or those at high risk of developing CVD.

Screening procedures based on chance of visits to general practices, e.g. hypertension, can be of importance dependent on the frequency of attending. Indicators and definitions in the Quality and Outcomes Framework (QOF, 2003), which is a component of the new General Medical Services contract for general practices introduced from April 2004, are based on the identification and control of individual risk factors (hypertension, diabetes, cigarette smoking) and not on the basis of overall CVD risk. This could unfortunately introduce indirect discrimination. Defining instead specific targets according to appropriately calculated risk would automatically flag hig risk ethnic minorities like South

Asians for enhanced intervention and could improve the quantity and quality of services provided for them.

6.3.10 Role of genetic factors

Tests of traditional risk factors and their failure alone to explain the greater coronary risk in South Asians highlights a possible role of genetics in the aetiology of CHD. The epidemic of CHD in South Asians as a consequence of westernization following migration to urban areas or immigration is postulated to have a root in adverse gene-environmental interactions (Samani & Sharma, 2005). It is important to note when considering this the implicit assumption that ethnic groupings defined on social, cultural and ethnographic grounds are equated with genetic homogeneity with little evidence to support this. Most of the large genetic projects in Western countries have excluded non-white (King, 2002) subjects and few genetic studies in CHD have been done in South Asians. However recruitment of ethnic minority groups into genetic studies may not be easy (Swanson & Ward, 1995) as the information provided will be sensitive to issues of culture and religion, as well as language.

6.3.11 Acceptance of behavioural modifications

Although the need for an acceptance of drug therapy for primary prevention of CVD have been looked it is necessary to consider the role of health behaviour and the possibility of modifying behaviour in preventive approaches. Less effort has been made to investigate the relationship between the cultural aspects of ethnicity and lifestyle risk factors for CVD. Changing behaviour in a health-enhancing way can be achieved by campaigns to increase knowledge and awareness of services to assist in risk reduction, but must include changes in individual beliefs and perceptions, or influence social norms. Simply changing knowledge and attitudes

alone may do little to modify behaviour. Delivering equitable services to modify risk factors in South Asians is faced by additional challenges above and beyond those for the Caucasian population such as; barriers to communication, lack of awareness by healthcare professionals of dietary habits, and cultural and religious matters specific to this ethnic group. Culturally sensitivity in delivering services is also an important issue. If significant change is to be made initiatives need to be developed to address these challenges. For instance arranging separate exercise sessions for South Asians may be more likely to encourage increased physically active when compared to the normal UK provision of mixed-gender facilities which are often poorly accepted because of cultural and religious beliefs. Lawton *et al.* (2006) reported that practical considerations (e.g. lack of time, lack of opportunities to partake in physical activities) were often interwoven with social rules and cultural expectations, such as the prioritization of obligations to kin, restrictions on (women) leaving the home (especially to enter mix-sex settings), and lack of socialization into sporting and other outdoor activities in influencing inactivity in Pakistani and Indian type 2 diabetes patients. Consequently motivation, beliefs, and cultural and religious issues need to be considered when providing cardiovascular rehabilitation programmes for South Asians. Kuppuswamy and his colleagues (2004) showed that culturally appropriate cardiac rehabilitation programmes could significantly improve uptake and adherence to such programmes. This randomised control parallel group trial studied a culturally focused cardiac rehabilitation programme in increasing uptake in participation amongst ethnic groups in East London (CADISAP).

Similarly it is possible that attitudes to other aspects of lifestyle changes might differ according to ethnic group. It is not known despite the importance of diet

whether South Asians have enthusiasm to take part and accept this type of interventions. For instance cultural values which encourage consumption of traditional food with high fat level, barriers to adaptation of cooking methods, or modifications to existing diet need to be recognized. Qualitative methods have been helpful in gathering some information in this area although quantitative confirmation is lacking. Asian Indians in focus groups in the USA identified specific advice required from nutritionists on how to modify Indian recipes to make them healthier. In addition they expressed their concerns regarding the individual lack of control and limited choice of food items at community functions, parties, and sites of worship (Kalra *et al.*, 2004). As is always of concern it is possible that these views were biased by methods of recruitments to the Focus Groups.

7.4 CONCLUSION

In this chapter findings of this thesis have been briefly summarized and other studies relevant to this area were considered. The published evidence suggests that primary care teams currently fail to target the South Asian people adequately. However, this population is keen to accept preventive treatment, and efforts should be focused on finding the best means to prevent mortality and morbidity in this susceptible group. Further research is required in many areas such as risk factor prevalence, risk estimation and recalibration, lifestyle intervention, and preventive drug therapy. Because this population is at high risk the benefits of appropriate research will also be high.

Although the evidence base for a CVD risk estimation procedure in South Asians is slight it is better that they have their risk estimated, albeit with less precision,

than be excluded from the risk estimation and management process completely. The present work provides a properly researched evidence base and adds support to recently proposed web-based method of risk estimation for ethnic minorities, the ETHRISK. Moreover, it provides its own very simple but in practice acceptable adjustment for currently used paper risk estimation tools.

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Appendix

Appendix 1 Covering letter

The University of Sheffield
Division of Clinical Sciences (South)
Clinical Pharmacology and Therapeutics: Floor L
The Royal Hallamshire Hospital, Glossop Road,
Sheffield S10 2JF, UK. Tel: (0114) 271 3664

Acceptance of antihypertensive therapy: effect of ethnicity
Researchers: Dr PR Jackson & Dr M Aarabi

Date

Dear Sir/Madam,

How keen are people to take tablets to prevent heart disease? A research Project

I am writing to ask if you would like to take part in a project to find out people's views about taking tablets to prevent heart disease. You are one of 1620 people in Sheffield who have been chosen to participate in this study which is being carried out by researchers from the Royal Hallamshire Hospital. Your involvement will help us to improve the treatment for patients at risk from heart disease.

Your name has been taken from Sheffield Primary Care Trusts' Information Service list, which holds the names and addresses of all people registered with local family doctors. This list is confidential to Sheffield Primary Care Trusts and is used only for the purposes of managing and planning health services.

Please read the enclosed Information Sheet which tells you more about the project. If you need help in reading the Information Sheet please contact the researcher, on 0114 271 3664.

If you would like to take part please complete the Reply Form to indicate a suitable way for us to contact you. Otherwise still return the form, but tick the box marked "Please do not contact me again". Nobody will be personally identified and no information will be passed on to anyone else. Please be assured that the information you give will be treated in the strictest confidence and the replies will only be seen by myself and the staff working with me on this study.

Yours sincerely

Dr P R Jackson
Honorary Consultant Physician
Reader in Medicine/Clinical Pharmacology and Therapeutics

Appendix 2 Follow-up letter

The University of Sheffield
Division of Clinical Sciences (South)
Clinical Pharmacology and Therapeutics: Floor L
The Royal Hallamshire Hospital, Glossop Road,
Sheffield S10 2JF, UK. Tel: (0114) 271 3664

Acceptance of antihypertensive therapy: effect of ethnicity
Researchers: Dr PR Jackson & Dr M Aarabi

Date

Dear Sir or Madam,

We wrote to you a couple of weeks ago about a research project gathering people's views about treatments to prevent heart disease. So far we have not had any reply. We know that sometimes such things are left for further consideration. If you would like to help us, please read the enclosed Information Sheet about a research project we are undertaking to gather people's views about treatments to prevent heart disease. If you are interested in helping then complete the Reply Form to indicate a suitable way for us to contact you. Otherwise please still return the form, but tick the box marked "Please do not contact me again".

Yours sincerely

Dr P R Jackson
Honorary Consultant Physician
Reader in Medicine/Clinical Pharmacology and Therapeutics

Appendix 3 Information sheet

The University of Sheffield
Division of Clinical Sciences (South)
Clinical Pharmacology and Therapeutics: Floor L
The Royal Hallamshire Hospital, Glossop Road,
Sheffield S10 2JF, UK. Tel: (0114) 271 3664

Acceptance of antihypertensive therapy: effect of ethnicity

Researchers: Dr PR Jackson & Dr M Aarabi

Introduction

We are Sheffield University researchers based at The Royal Hallamshire Hospital and are asking for your help to find out what influences whether people are happy to take tablets to prevent heart disease and how that varies in people from different cultures. Dr Aarabi is doing this research as part of his PhD degree. Please read this Information Sheet carefully and if you have any queries, don't hesitate to telephone us on (0114) 271 3664. Even if we can't speak to you immediately, one of our team will get back to you.

What is the study trying to find out?

People now want to know more about the drugs they are taking before starting any treatment. We want to find out how keen people are to take tablets to prevent heart disease when they are given the full facts about the tablets including side-effects, the disease, and the likely benefit gained. In particular we are interested to find whether there are differences between ethnic groups in the population in their wish to have

treatment. This information should help doctors planning health services and in giving advice to individual patients.

What is involved if I decide to help?

The study involves an interview with one of our researchers, who will visit your home at a time that is convenient to you. If you prefer the interview can be arranged at the Hallamshire Hospital. We will ensure that our interviewers are able to give information in a way that you can understand. They will describe the symptoms of some blood vessel diseases, what it is like to live with them and all about tablets to help prevent them. The interviewer will then ask you to imagine that you are a person who is at

risk of these diseases and to think about the treatment choices you might make. They will show you a number of diagrams which show how likely you are to benefit from treatment and all we ask is that you tell us whether you might decide to take treatment or not. We are not suggesting that you have any of these diseases, and are only asking for your opinion. If at any stage you become upset or tired with the questions, the interviewer will leave if you ask.

How have I been chosen?

It is very important when getting views about diseases and their treatments that we do not concentrate on people who are already ill and attending their doctors or the hospital. Because of that we are aiming to speak to a number of people in the community, some of whom may be ill, others who will be perfectly well. This letter has been posted to you

by Sheffield West Primary Care Trust on behalf of all four Sheffield PCTS. Your name has not been released to the researchers by the Trust and no medical or other information about you has been passed on.

What about my own state of health?

As we said before we know nothing about you or your health and it is important that we speak to people in all kinds of health. We will only ask a few simple questions about your health and whether you are taking any tablets, but won't ask any other questions.

Do I have to take part?

No. It is completely up to you to decide whether you want to want to take part in the study or not. If you do initially decide to go ahead, but then change your mind, we will not trouble you again once you have let us know.

If you would prefer not to help with the research and do not wish to be contacted again, please fill in the box on the response card and send it back to the research team. They will make sure that you are not contacted again. Otherwise you will receive a reminder letter in about 2 weeks time. If you do wish to

help, just fill in the positive box on the response form and we will contact you to arrange a convenient time and place for the interview.

If you decide not to help it will not influence your treatment by your own doctor or any of the hospitals now or in the future.

What will happen to the information I give?

Apart from when we first write to you and if we contact you to confirm the time to visit, we will not be using your name, address or telephone number. All information provide by you will be kept under a code number and not linked to your name. We will not release any information about you or anything that you tell us. We will eventually publish the results, but no one will be able to identify you or anything about you from our report.

What if I wish to complain about the way in which this study has been conducted?

If you have any cause to complain about any aspect of the way you have been approached or treated during the course of the study, the normal University and NHS complaints mechanisms are available to you and are not compromised in any way because you have taken part in a research study. If you would like to complain or have any concerns please contact Dr Jackson on Tel. (0114)271 2615. If you would prefer to use the normal University complaints procedure (contact Mr Richard Hudson, Research Consultative Unit, 85 Wilkinson Street, University of Sheffield, Tel: 0114 222 1448).

Thank you for taking the time to read this Information Sheet

Appendix 4 Reply form (South Asians)

<u>Reply Form</u> <u>for helping the research project</u>

"Acceptance of antihypertensive therapy: effect of ethnicity"

☐ **Yes, I would like to help. Please contact me on:**

Title:…… Last name……:…… First name:……

Telephone number:……..

Postal address: ……

……Post Code: ……..

Would it be helpful to have a bilingual interviewer? ☐ Yes ☐ No

If Yes, please indicate the language:

- ○ Urdu
- ○ Punjabi
- ○ Bengali
- ○ Gujarati
- ○ Hindi

☐ **No, please do not contact me again.**

Reply Form version 1 dated 17 March 2004 – RR

Appendix 5 Reply form (Caucasians)

<u>Reply Form</u> <u>for helping the research project</u>

"Acceptance of antihypertensive therapy: effect of ethnicity"

Title:…… Last name……:…… First name:……

☐ **Yes, I would like to help. Please contact me on:**

Telephone number:……..

Postal address: ……

Post Code: ……..

☐ **No, please do not contact me again.**

Reply Form version 1 dated 17 March 2004 – RR

Appendix 6 Consent form

Study Number:
Participant Identification Number for this study:

CONSENT FORM

Title of Project: Acceptance of antihypertensive therapy: effect of ethnicity

Name of Researchers: Dr P. R. Jackson & Dr M. Aarabi

Please initial box

1. I confirm that I have read and understand the information sheet dated ..... (version .....) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

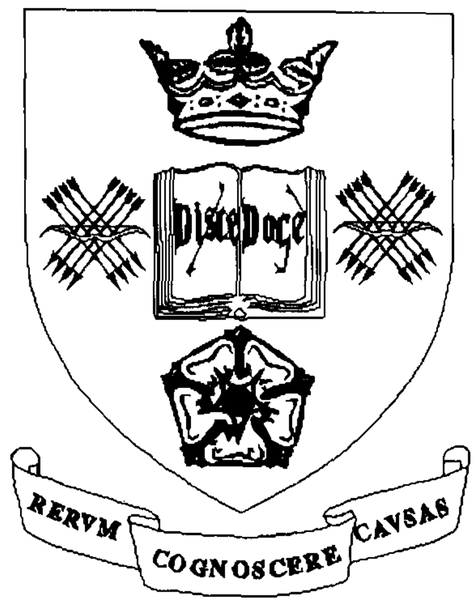
3. I agree to take part in the above study. ☐

Name of Participant Date Signature

Name of Interviewer Date Signature

1 for participant; 1 for researcher; (volunteer study)

Appendix 7 Interview Manual



Acceptance of antihypertensive therapy: effect of ethnicity

Interview manual

Academic Unit of Clinical Pharmacology

Division of Clinical Sciences (South)

University of Sheffield

An introduction for interviewers

This is the manual of operation for the Acceptance of an "Antihypertensive Therapy: effect of ethnicity Study". The complexity of the Study requires that a number of procedures in the interview need to be described in detail.

What is the study trying to find out?

People now want to know more about the drugs they are taking before starting any treatment. We want to find out how keen people are to take tablets to prevent heart disease when they are given the full facts about the tablets including side-effects, the disease, and the likely benefit gained. In particular we are interested in finding whether some ethnic groups are happier to have treatment than others. This is of importance because of the high risk of CHD in some communities e.g. South Asians. This information should help doctors planning health services and in giving advice to individual patients.

What is involved in the study?

The study involves an interviews with selected participants. They are Sheffield residents aged 35-74 years with or without history of cardiovascular disease. Participants have been selected from the Sheffield Population Health Register which holds the names and addresses of all patients who are registered with a Sheffield General Practitioners.

How participants have been chosen?

It is very important when getting views about diseases and their treatments that we do not concentrate on people who are already ill and attending their doctors or the hospital. Because of that we are aiming to speak to a number of people in the community, some of whom may be ill, others who will be perfectly well. A letter will be passed on to randomly selected names by the Primary Care Trust. Their names have not been released to the research group by the Trust and no medical or other information about them has been passed on.

What is involved in the interview?

Interviewers should give information in a way that is far as possible standardized and that participant can understand. The symptoms of some cardiovascular diseases (hypertension, myocardial infarction, and stroke) will be described, what it is like to live with them and all about tablets to help prevent them. The interviewer will then ask the participant to imagine that s/he is a person who is at risk of these diseases and to think about the treatment choices s/he might make. They will show the participant a number of pictures which show how likely s/he is to benefit from treatment and all they ask is that s/he tell the interviewer whether might decide to take treatment or not. We are not suggesting that they have any of these diseases, and are only asking for their opinion.

Questionnaire

The questionnaire has two parts. The first part presents three hypothetical scenarios with different baseline cardiovascular risks. The scenarios detail cardiovascular risks (coronary death and fatal and nonfatal myocardial infarction or stroke) of 10%, 20% and 40% over 10 years.

In the second part, subjects will be asked to provide possible explanatory demographic data including age, sex, ethnicity, educational level, occupation, history of CVD, and receipt of antihypertensive drugs.

Scenarios

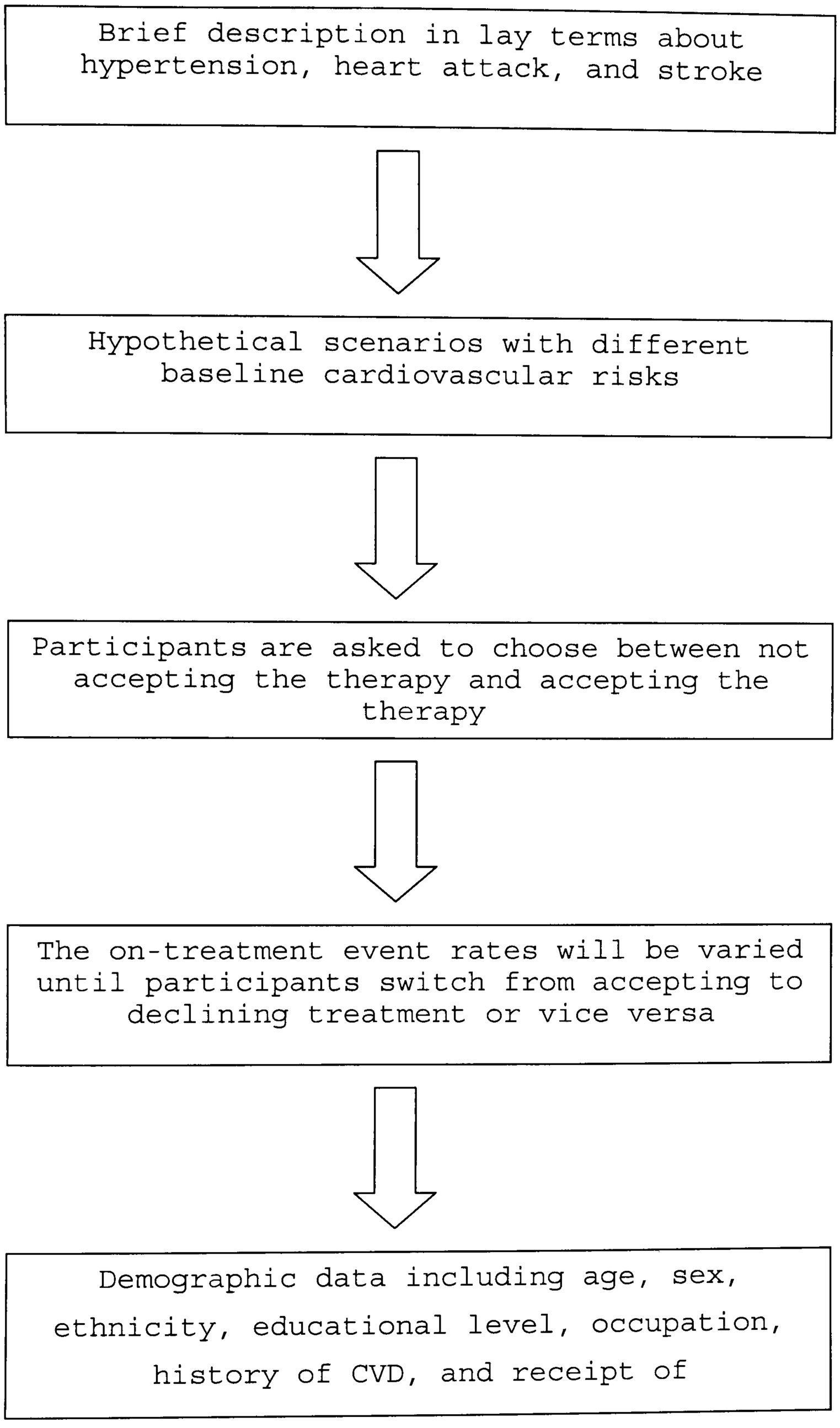
After describing the treatment options (medication and no medication) and the potential outcomes participants are asked to choose between not accepting the therapy (given the baseline risk of an adverse outcome) and accepting the therapy (given a reduced risk of the adverse outcome but also incurring the inconvenience, cost and side effects associated with that therapy). Choices will be presented to subjects both graphically and numerically with risks expressed in positive and negative terms. The graphical presentation will use 100 stick figure icons to show percent frequencies at risk and benefiting from treatment. The event rates will be varied in 1% steps until participants switch from accepting to declining treatment or vice versa. Interviewers must be careful not to influence the participant choice.

Where the interview will take place?

Interviewers will visit participant's home at a time that is convenient to them and the participant. If participants prefer, the interview can be arranged at the Hallamshire Hospital.

If at any stage the participant becomes upset or tired with the questions, the interviewer will leave if s/he asks. If the participant decides not to help it must be stressed that this will not influence his or her treatment by their own doctor or any of the hospitals now or in the future.

Interview flowchart



More details about an interview

The interview can be started by:

"Hello, I am ....."

"We had an arrangement to meet today. "

"Is it still convenient for you to have the meeting?"

The first thing is to tell them what the structure of the meeting will be.

"What I would like to do today is first of all to go through the information sheet. Then if you still happy with the study I would like you to sign a consent form. This is just to ensure that I have been fully honest with you about what the study involves, and if you still happy at that stage we will go on."

"This is simply asking your opinion about the number of different treatments of prevention of heart disease."

"Do you understand all that? Are there any question you want to ask?"

In this stage you can start going through the Information Sheet (bringing out some key points):

"**First**: What is this project about?"

"It is about finding how happy different people are to take tablets to prevent heart disease. It is part of Dr Aarabi's PhD research project but the information will also be useful in developing health services."

"**Next**: What is it actually trying to do?"

"It is trying to find out how keen or enthusiastic people are to take tablets to prevent heart disease when they know the full information about the benefits and risks."

"**Third**: How will we do that?"

"Well it is by a simple interview that is going to take place today. I will ask you to imagine you are the person considering whether or not to take tablets. I will give you three different situations and you must then imagine as that person whether to take treatment or not."

"**Next**: How you have been chosen? "

"I want to reassure you that although you were identified from a list of general practice patients we were not given any information about you and the letters came from the Primary Care Trust not us. You have not been chosen because we think you are at particular risk of heart disease. You have just been chosen by a random selection process from Sheffield residentes."

"**Finally:** It is important for you to know that in helping us with this project you are acting as a volunteer, you really don't need to take part if you prefer not to but obviously we would very much like you to take part and we are grateful if you continue."

"If you have any problems or questions just let me know. If you want any further information you can call Dr Jackson or the research office in the University.

"Do you want to ask me any question?"

"If not then we will begin."

Signing the consent form:

At this stage you now need to consent the interviewee.

"Now I would like you to sign this consent form, what I stress is this is not committing you to anything, it is just to make sure that we have been completely honest in the way we have approached you. What is says is firstly that you had opportunity to read the information sheet, that we have given you, and you had chance to ask questions about it."

"Secondly, you have got to understand that helping us is purely voluntary and if in any time you want to stop you can do that."

"If you are happy to continue can I ask you to tick each of these boxes, then to put your name and to sign it?"

When they have signed that, the interviewers should say:

"Thank you very much for that if you still happy we will continue with the interview."

"The actual interview itself is in three parts. First of all I am going to describe what is like to have high blood pressure and problems that arise because of that and what taking tablets is like. Then I want you to put yourself in a position of somebody who has got high blood pressure deciding whether to take tablets or not. We will do that several times each with slightly different amount of benefit from the tablets. At the end I will ask you one or two question about yourself just to help us understanding answers better."

Background information

At this stage it is important that the information is read word for word from the booklet with checks at several points to ensure understanding.

At the end of background the interviewees need to be asked if they have any questions.

"Do you want to ask any questions about the conditions or the tablets?"

"Do you want me to go over any of things again?"

"If not we will move on and ask your opinion about some imaginary situations."

Scenarios

Now we come to heart of the interview process. At this stage the person who is being interviewed has some information about what is like to have a heart attack or stroke and what is like to have tablets. We now want to put them into a position where they to decide whether to take tablets or not.

We are going to do that for three different scenarios. In each of these there are slightly different starting risks of having a heart attack or stroke. We then adjust the chance of them having a heart attack or stroke when taking tablets until we find a point on which they will just accept the tablets. In other words we would like to find the point at which benefit from taking the tablets is just enough to persuade them that it is worthwhile. The way we do that is with the scenario sheet.

In each scenario there is a brief description at the top outlining the risk of having stroke or heart attack when they are not taking any treatment and then at the bottom there are the two descriptions of what is like not to take medication and to take medication. First of all we explain what is like not to take medication. We remind them no medication means no inconvenience, no side effects, and no costs.

The interviewer can say:

"If you take the medication you have got to do it everyday for ten years. There is the possibility of having side effects and if they pay for their prescription charges it costs them £6.40 each month."

"What is likely to happen to you in this situation if you have no medication is that you have a 10% risk of having a heart attack or stroke. In the stick men diagram that means these people in the top will have a heart attack or stroke (point to the black stick men). These people at the bottom (point to the white stick men) will escape and not have a heart attack or stroke."

You have to remind them the numerical term for each situation.

"This means there is 90% chance that you will not have a heart attack or stroke."

Then for the right side of scenario page you would say:

"What is likely to happen to you in this situation if you have medication is that you have a 5% risk of having a heart attack or stroke. That means these stick men here would have a heart attack or stroke (point to the black stick men) in next ten years and the others would escape having a heart attack or stroke in next ten years." These people at the bottom (point to the white stick men) will escape and not have a heart attack or stroke."

You need to put words as well.

"This means there is a 95% chance that you will not having a heart attack or stroke."

Then you ask them:

"Would you take tablets or not comparing these situations?

Then you follow the instruction at the bottom of page. Based on the answer you have two choices: going to another page or recording the mentioned value. If you are instructed to go to another page you open the booklet 2 at that page and place it over the half right side of the scenario. Then you will explain the new situation using stick men diagram and words, numerically. You can do the recording at the last page of the Interview booklet 1.

It is better at each stage if you remind them of risk of not having the tablets as well as the new risk with tablets.

Once you have completed a record then you move to the next scenario.

For each new scenario you have to remind them that you are presenting a new situation. It is important to emphasize the change in the risk of having heart attack or stroke for example scenario two presents 20% risk in ten years.

You remind them that there is no inconvenience, no side effect, and no cost if they do not take medication. If they do decide to take it daily for ten years they may have side effects and it costs about £6.40 per month if they pay for their prescription.

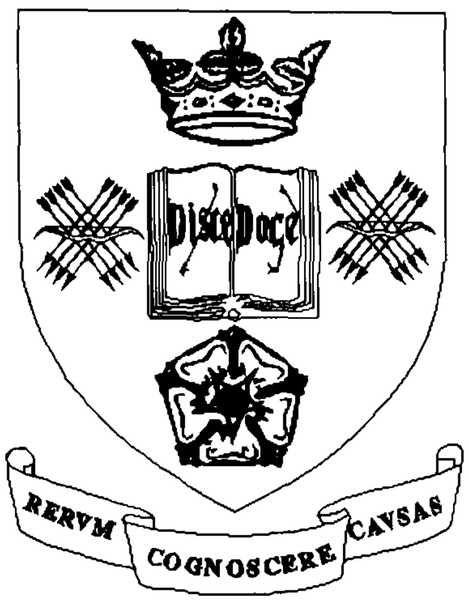
Then explain the outcomes in the next ten years if they take no medication (10% risk of having heart attack or stroke). After that, go to the page that is instructed in the bottom of the page.

At that time you will move to the 3rd scenario. Again you read the top of the page and emphasize the text in bold. The 3rd scenario is in the next ten years but the amount of risk is different from the 1st and 2nd ones. Each time ask the interviewee whether they are still comfortable.

When you finish the 3rd scenario you will ask some questions in the last page of interview booklet 1. Ask the interviewee to provide possible explanatory

demographic data including age, sex, ethnicity, educational level, occupation, history of CVD, and receipt of antihypertensive drugs.

Appendix 8 Interview Booklet



Acceptance of antihypertensive therapy: effect of ethnicity

Interview Booklet (part 1)

Academic Unit of Clinical Pharmacology

Division of Clinical Sciences (South)

University of Sheffield

Interview Booklet 1

Acceptance of antihypertensive therapy: effect of ethnicity

Thank you for participating in this research study. This study is divided into three parts. In the first part, we will describe high blood pressure and how it leads to stroke or heart attack. We will describe what usually happens when someone has a stroke or heart attack, and discuss a medication which can help to prevent strokes or heart attacks in people with high blood pressure.

In the second part, we will describe six situations and ask you to imagine each situation applied to you. Then we will ask your opinion about whether or not you would want to take a blood pressure-lowering medication in each situation.

From this information, we will be able to let doctors know what people think about blood pressure medication.

In the third part, we will ask some questions about you which will allow us to analyze your answers with those of other people similar to yourself.

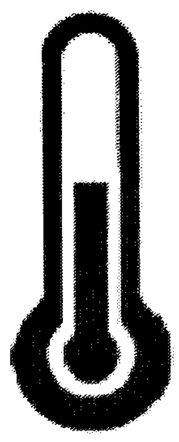
All of your answers will be kept confidential.

BACKGROUND INFORMATION

High Blood Pressure

High blood pressure (also known as "hypertension") is a condition in which a person's blood pressure is higher than normal for someone their age and sex.

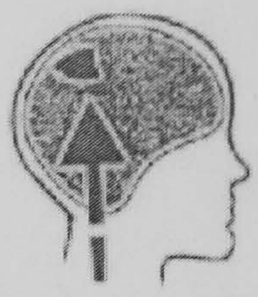
Generally, high blood pressure doesn't cause any symptoms and people do not even know they have it. The only way it can be detected is by measuring the blood pressure with a blood pressure cuff.



High blood pressure is a very important condition as it can cause strokes or heart attacks. In the next page you will learn more about strokes and heart attacks.

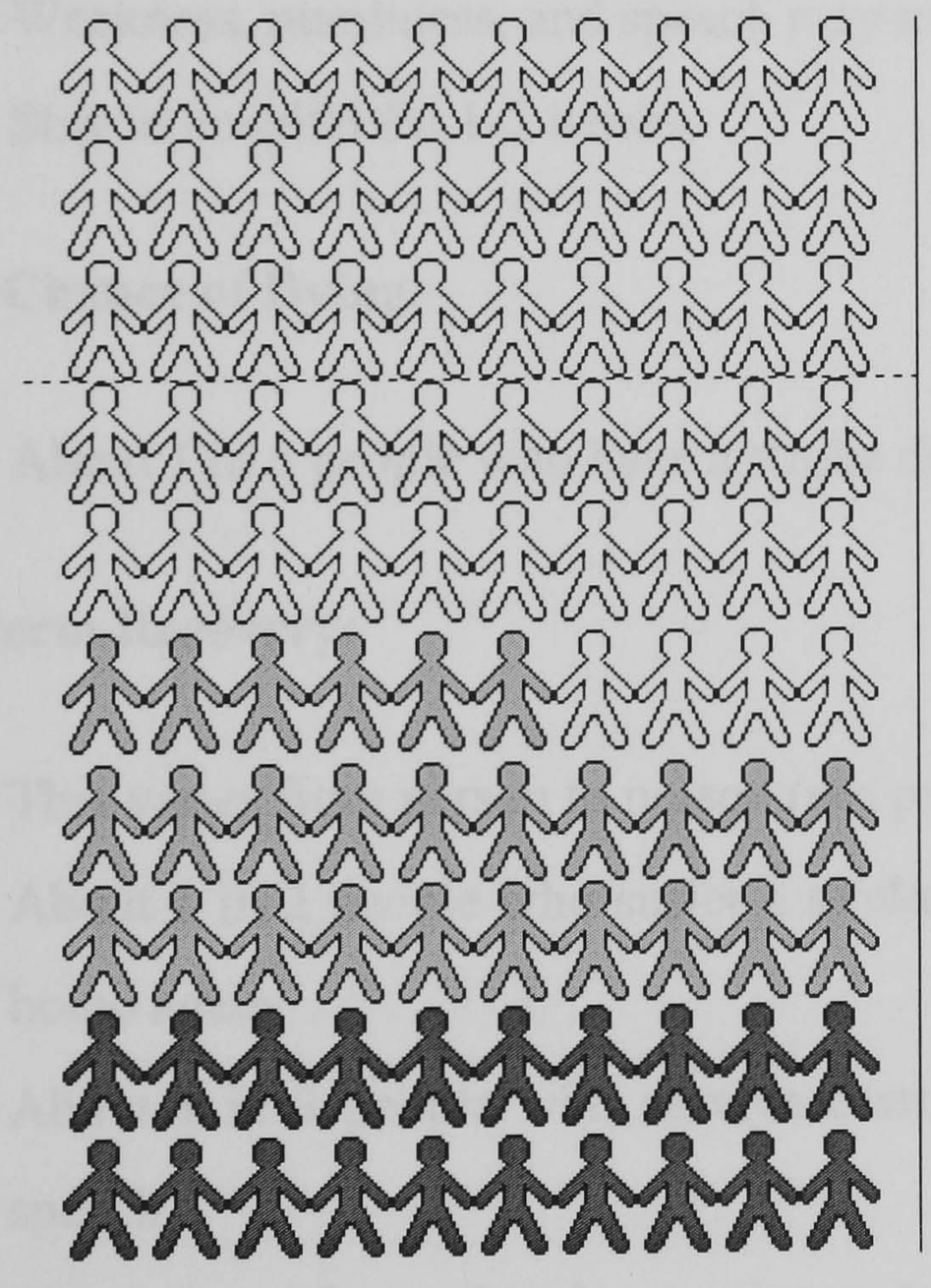
STROKE

A stroke is caused by a blockage in the blood supply to part of the brain.



The effects of a stroke range from being completely normal within a few minutes to being dependent on others for eating, toileting, and movement for the rest of your life. In between these extremes, most people have either minor symptoms or major symptoms.

The stick figures below represent 100 people who have had a stroke. They will be used to show the chances of different things happening. About 1 in every 5 people who have a stroke dies within the first month. Of the survivors, about one third recover completely and are able to return home, one third are able to return home but need some help with walking or talking, and one third need to go to a nursing home as they need help with feeding, toileting, and walking.



Home (independent)

Home (with some help)

Nursing home/long term care

Dead within one month

On the next page, I will describe what a stroke is like.

STROKE

Initial Physical Symptoms:

- Suddenly unable to move or feel your arm and/or leg on one side
- No physical pain
- May not be able to swallow

Initial Mental Symptoms:

- May not be able to fully understand what is being said to you
- May not be able to say what you want to say
- Speech may be slurred and difficult for others to understand

Initial Recovery:

- Will be admitted to hospital
- Weakness, numbness, and speech may improve
- Stay in hospital for 1-2 weeks

Initial Chance of Dying:

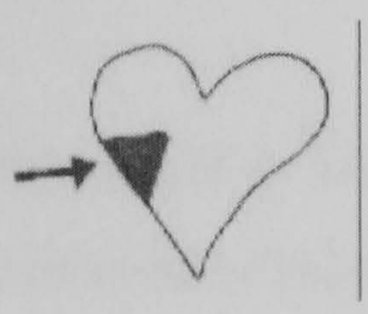
- About 1 in 5 people who have a stroke die within one month

Long-term Recovery:

- This varies from person to person (see previous page)
- About 1 in 2 people who suffer a stroke will recover and be able to return home again
- About 1 in 3 people who survive a stroke will have trouble with slurred speech
- About 1 in 10 people who survive a stroke will be unable to control their bowel or bladder

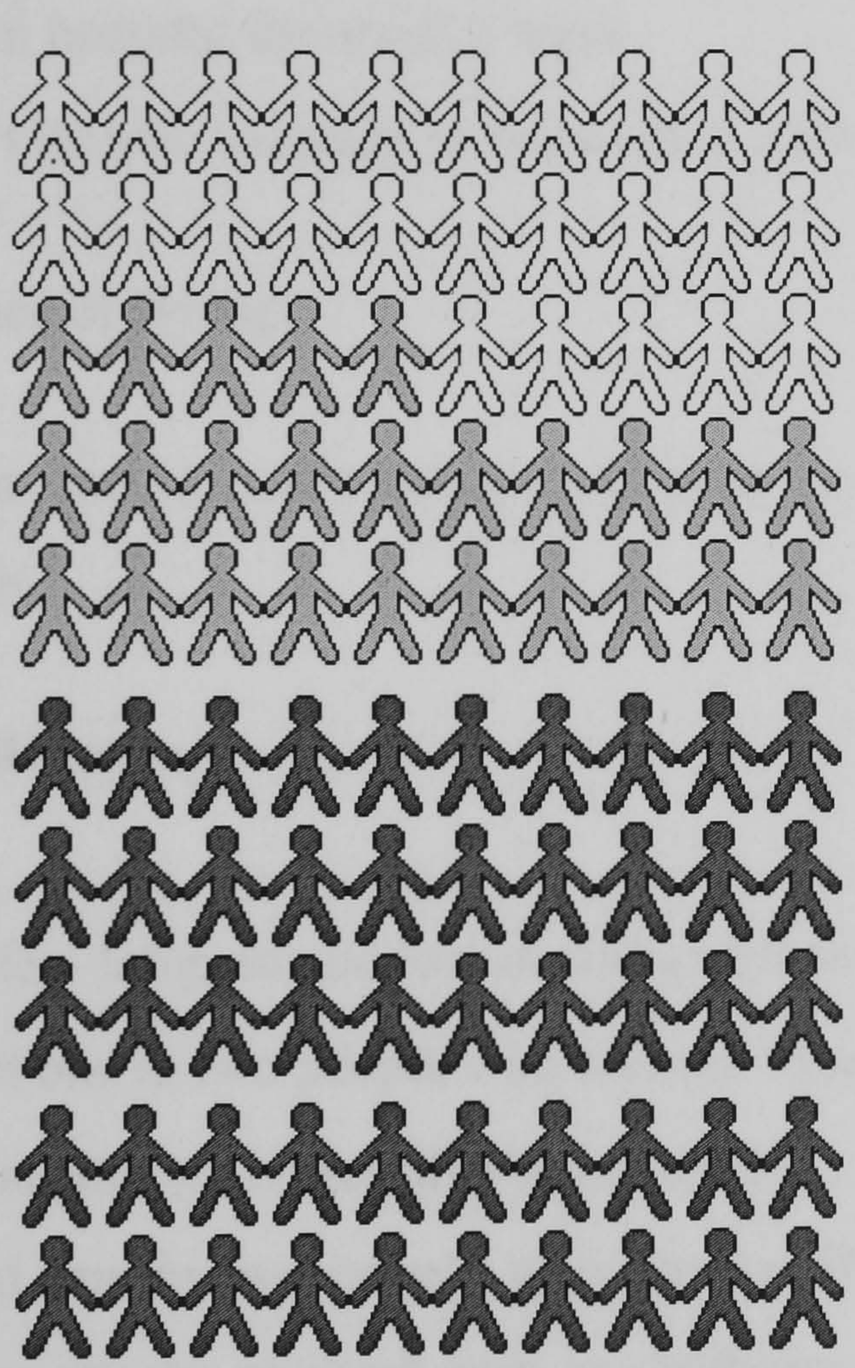
HEART ATTACK

A heart attack is caused by a lack of blood flow to a region of the heart muscle.



The stick figures below represent 100 people who have had a heart attack. They will be used to show the chances of different things happening.

About half of all people who have a heart attack die within one month. Of the people who survive one month, half will recover and be able to resume a normal life and the other half will recover but will have occasional chest pain (angina) or shortness of breath.



Complete recovery

Occasional pain

or shortness of breath

Dead within one month

On the next page, I will describe what a heart attack is like.

HEART ATTACK

Initial Physical Symptoms:

- Suddenly get a heavy feeling or pain in the chest
- May feel dizzy, nauseated, or short of breath

Initial Mental Symptoms:

- May not be able to fully understand what is being said to you

Initial Recovery:

- Will be admitted to hospital
- Chest pain and other symptoms will improve with treatment
- Stay in hospital for about a week
- Won't be able to return to work for at least six weeks

Initial Chance of Dying:

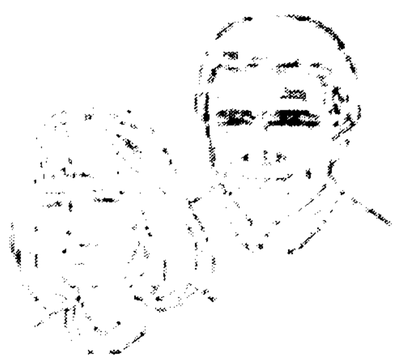
- About one in every two people who have a heart attack die within one month

Long-term Recovery:

- Will feel fatigued and low in energy for several weeks or months after
- About one in two people who recover from a heart attack are able to resume
- their normal activities after a few weeks
- About one in two people who recover from a heart attack are limited by further attacks of chest pain or shortness of breath while doing their usual activities

Treatment with a blood pressure-lowering medication

The goal of treatment with a blood pressure-lowering medication is to prevent a stroke or heart attack in people with high blood pressure. However, the pills are only partially effective and do not prevent strokes or heart attacks in everyone who takes them. This means that some people will benefit from taking the treatment while others will take the treatment without any benefit.



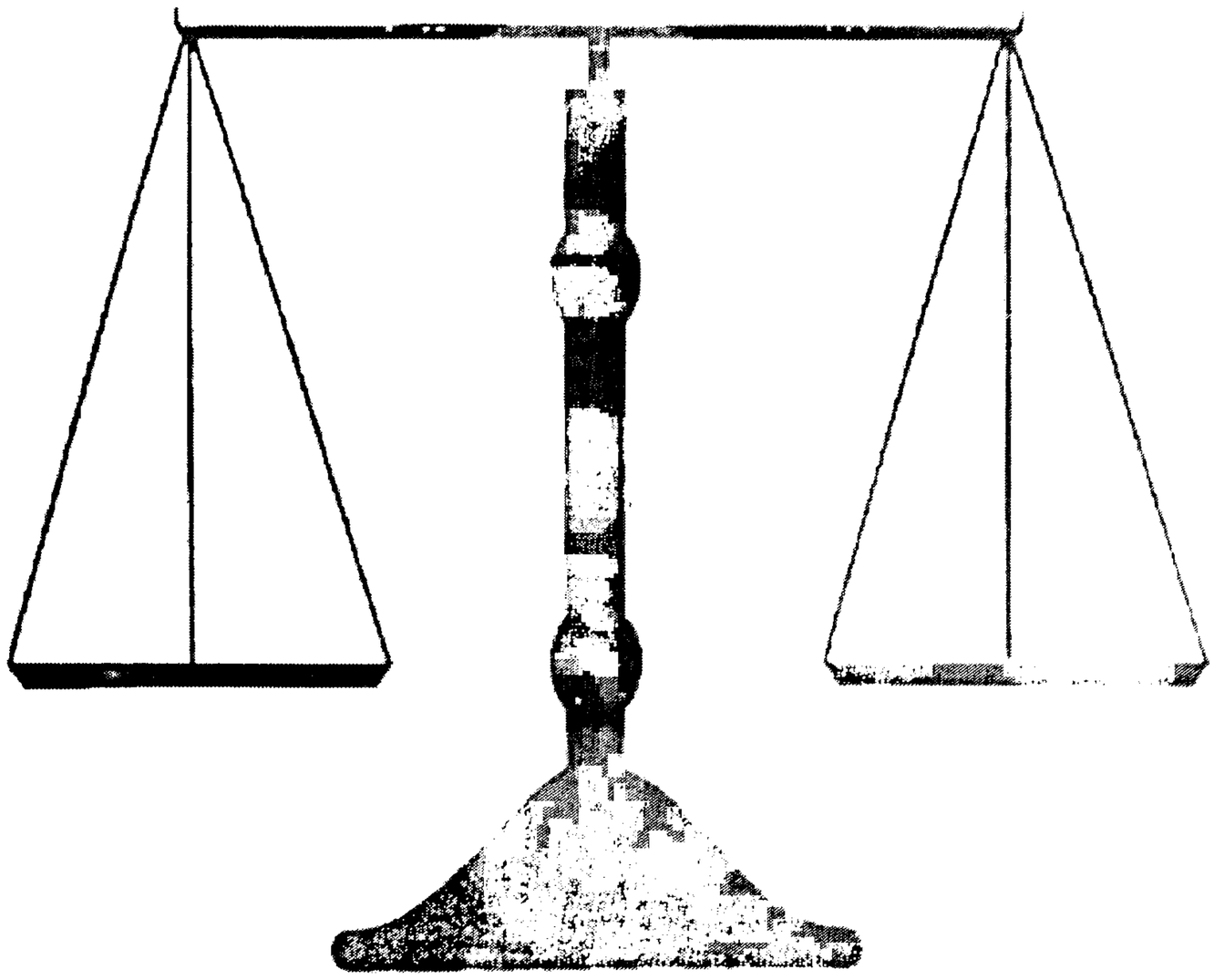
Because high blood pressure is a lifelong condition, most people will have to continue taking these pills for the rest of their life. These pills are usually taken once or twice a day.

Careful studies in thousands of patients have shown that most people don't feel any different when taking the pills and can still do their normal activities.

Of every 100 people who take these pills, 7 have to stop because of side-effects (such as fatigue, difficulty sleeping, impotence, leg cramps, or minor abnormalities in the blood sodium or potassium). The other 93 people do not have any side effects from the pills. These side effects usually disappear within two weeks after stopping the pills. Blood pressure-lowering pills cost about £6.40 per month, but if you don't pay you got it free.

SUMMARY

Taking blood pressure-lowering medication has:



ADVANTAGES	DISADVANTAGES
• reduced chance of stroke or heart attack	• inconvenience (take every day) • side effects • cost

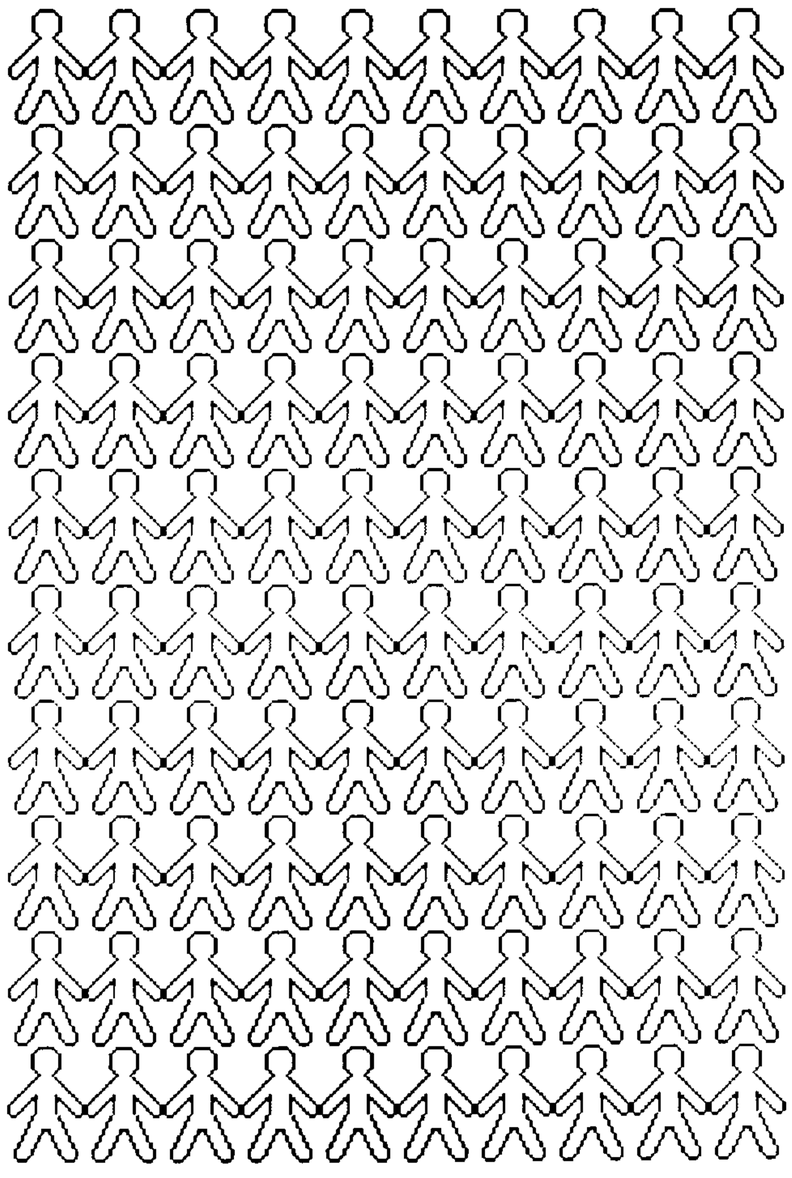
How much benefit you think you would want?

Now its time to consider how much benefit you think you would want before taking the medication every day.

In this section, we will present a series of IMAGINARY situations and ask you to make a choice about whether you would want to take a blood pressure-lowering medication based on its advantages and disadvantages. These situations are imaginary and the same scenarios are being given to all of the people involved in this study.

Remember, this is not a test and there are no right or wrong answers. We are interested in your opinion. You can look at the Information charts from Part 2 and ask the interviewer questions to clarify any points.

We will use 100 stick figures to show the chances of different things happening.

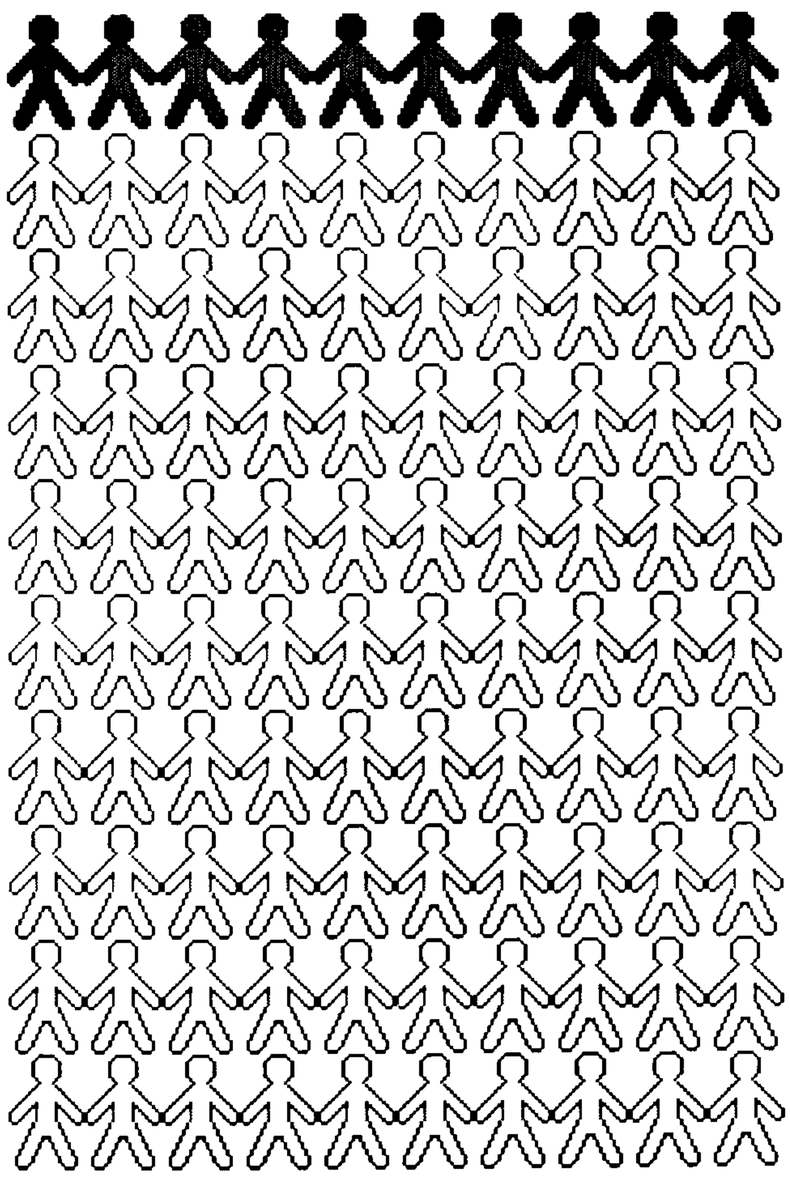
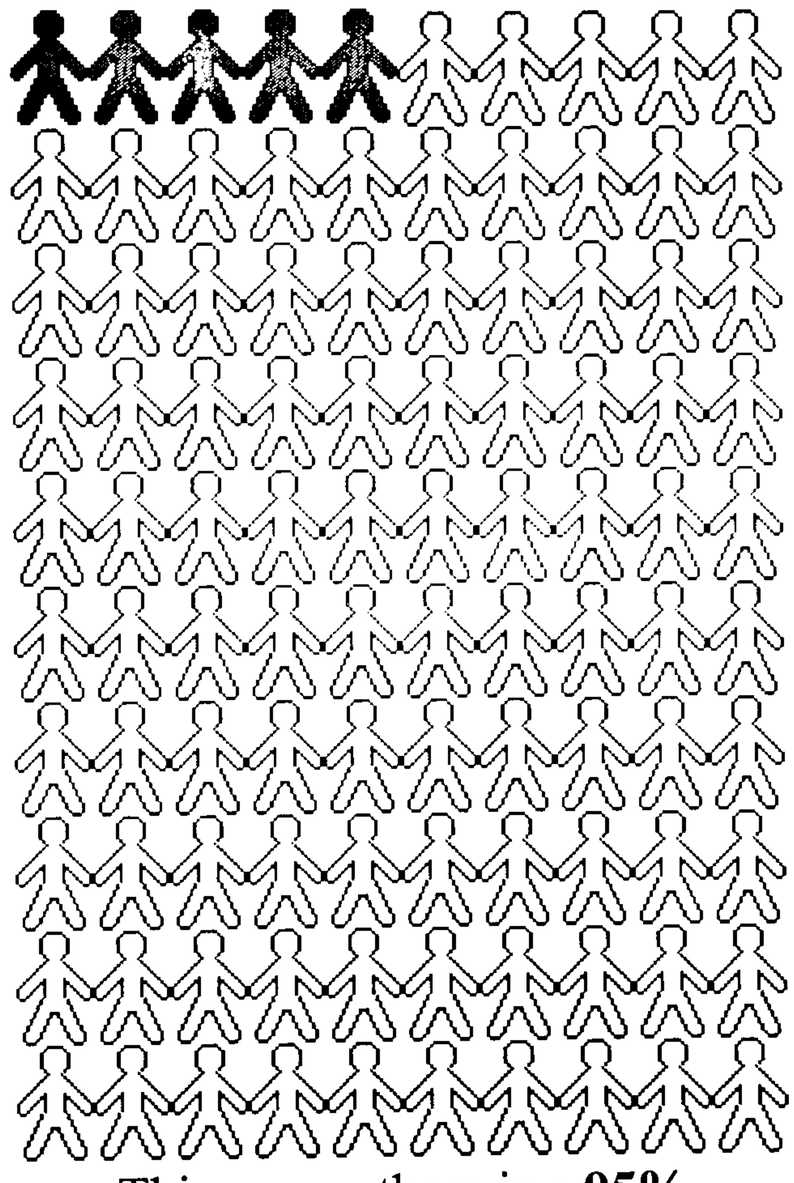


Scenario 1

Now, imagine that your risk of having a heart attack or stroke **in the next ten years is 10%.** If you take a blood pressure-lowering medication every day for **ten years**, you can reduce your chance of having a heart attack or stroke. You have two choices:

NO MEDICATION	**MEDICATION**
No inconvenience No side effects No cost	Take daily for ten year May have side effects Costs about £6.50 per month if you pay for your prescription

OUTCOMES IN NEXT <u>TEN YEARS</u>

NO MEDICATION	**MEDICATION**
You have an **10%** risk of having a heart attack or stroke	You have a **5%** risk of having a heart attack or stroke
	
This means there is a **90%** chance that you will not have a heart attack or stroke	This means there is a **95%** chance that you will not have a heart attack or stroke

WOULD YOU TAKE THE MEDICATION?

If Yes ➔ go to page 9 (booklet 2)
If No ➔ go to page 3 (booklet 2)

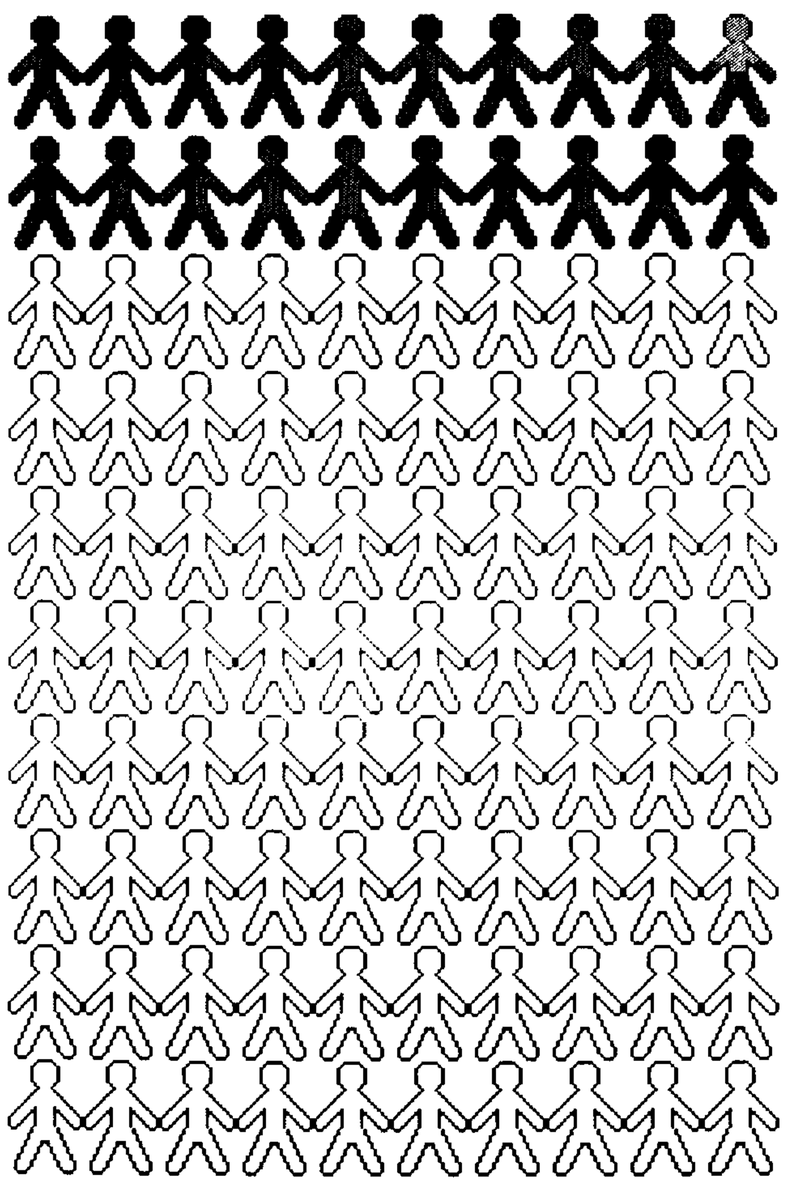
Scenario 2

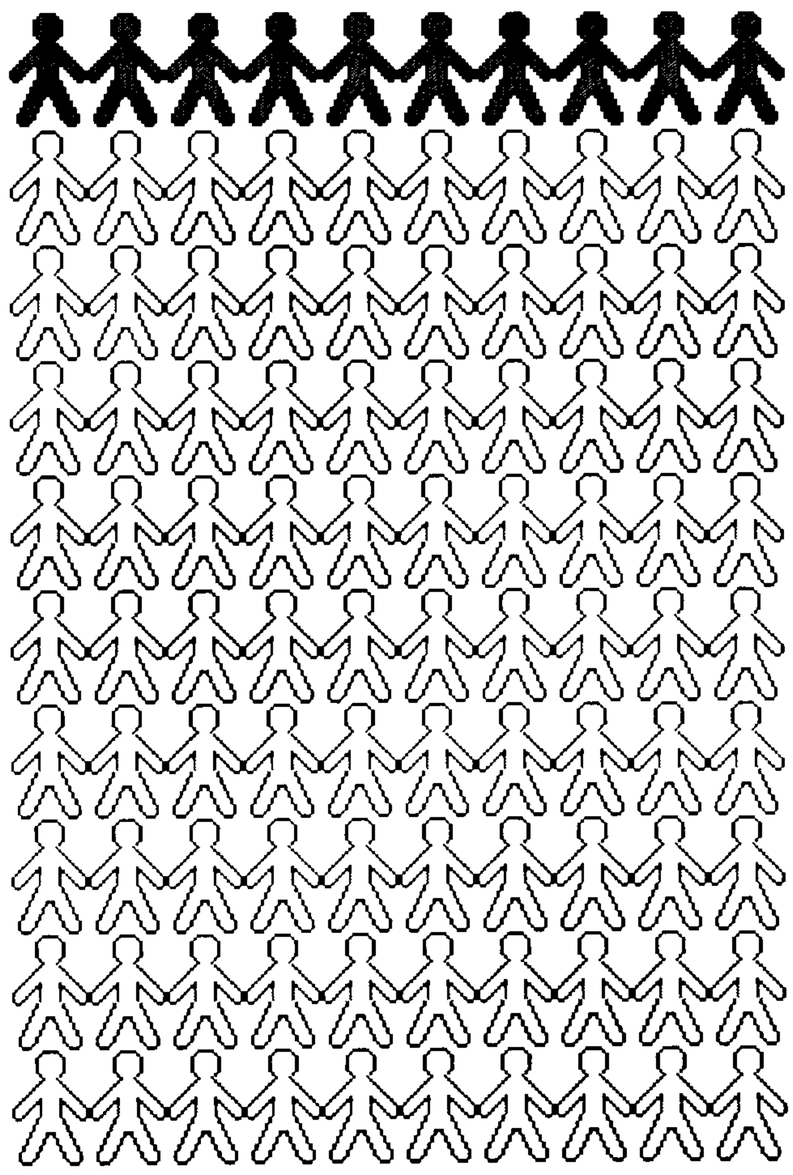
Now, imagine that your risk of having a heart attack or stroke **in the next ten years is 20%.** If you take a blood pressure-lowering medication every day for **ten years**, you can reduce your chance of having a heart attack or stroke. You have two choices:

NO MEDICATION	MEDICATION
No inconvenience	Take daily for ten year
No side effects	May have side effects
No cost	Costs about £6.50 per month if you pay for your prescription

OUTCOMES IN NEXT <u>TEN YEARS</u>

NO MEDICATION	MEDICATION
You have an **20%** risk of having a heart attack or stroke	You have a **10%** risk of having a heart attack or stroke





This means there is a **80%** chance that you will not have a heart attack or stroke	This means there is a **90%** chance that you will not have a heart attack or stroke

WOULD YOU TAKE THE MEDICATION?

If Yes ➔ go to page 16
If No ➔ go to page 6

Scenario 3

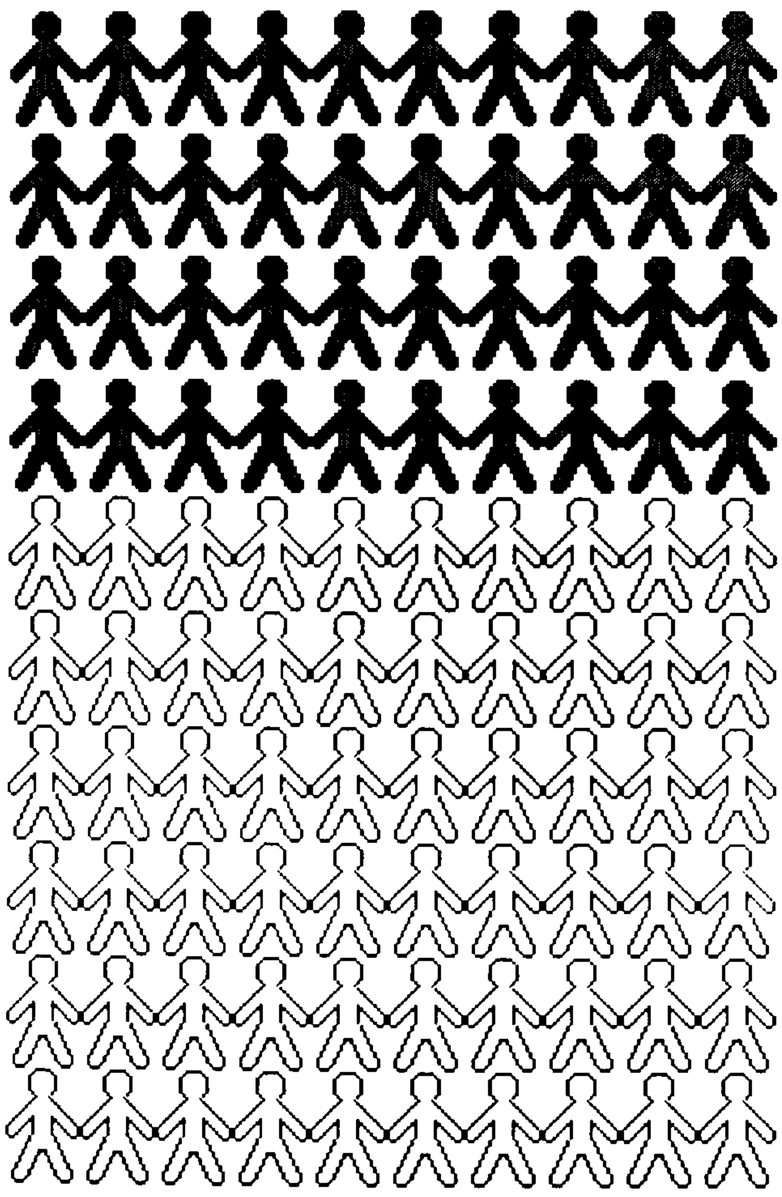
Now, imagine that your risk of having a heart attack or stroke **in the next ten years is 40%.** If you take a blood pressure-lowering medication every day for **ten years**, you can reduce your chance of having a heart attack or stroke. You have two choices:

NO MEDICATION	**MEDICATION**
No inconvenience	Take daily for ten year
No side effects	May have side effects
No cost	Costs about £6.50 per month if you pay for your prescription

OUTCOMES IN NEXT <u>TEN YEARS</u>

NO MEDICATION

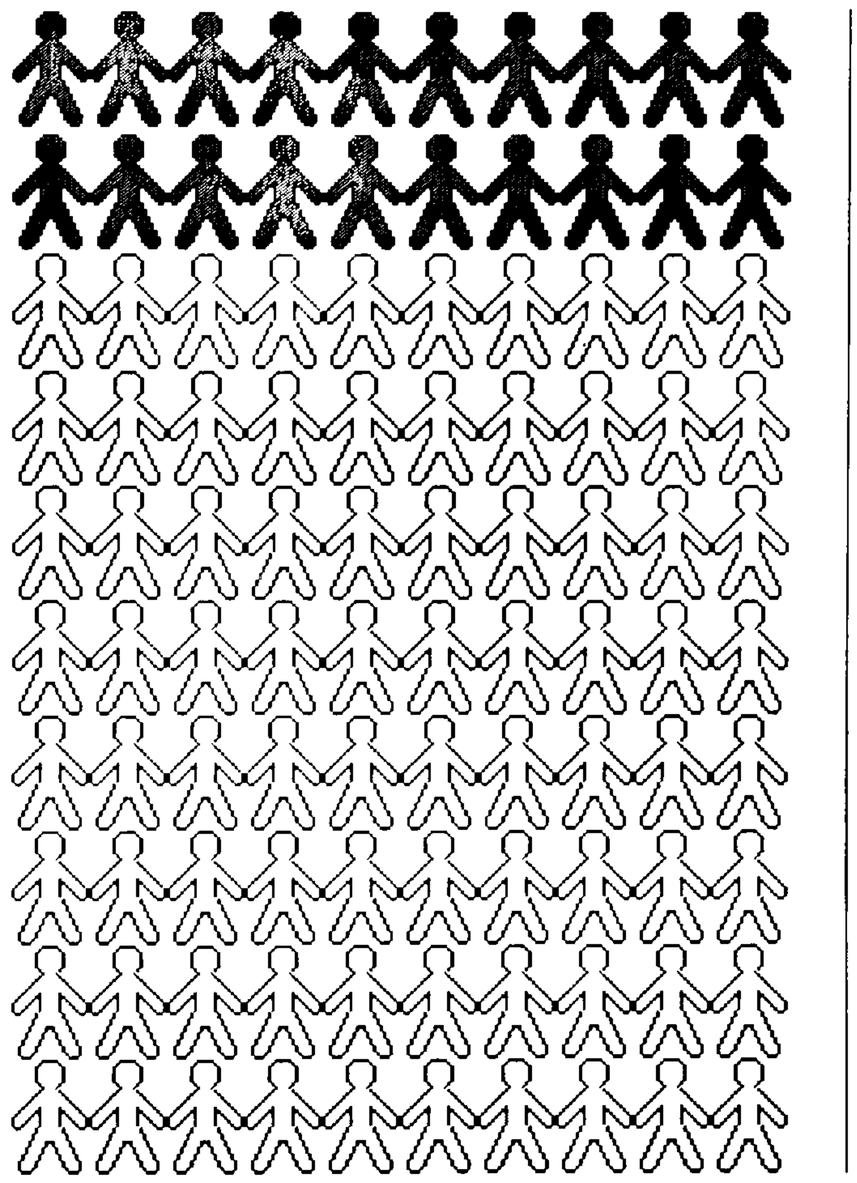
You have an **40%** risk of having a heart attack or stroke



This means there is a **60%** chance that you will not have a heart attack or stroke

MEDICATION

You have a **20%** risk of having a heart attack or stroke



This means there is a **80%** chance that you will not have a heart attack or stroke

WOULD YOU TAKE THE MEDICATION?

If Yes ➔ go to page 31

If No ➔ go to page 11

Some questions about you

Serial number……..

Date of interview	…../…../2005	
Gender	Male	☐
	Female	☐
Month of birthday	……	
Year of birthday	……	
To which group do you belong?	White	☐
	Indian	☐
	Pakistani	☐
	Bangladeshi	☐
	Other……..	☐
Age at leaving full time education:	…… years old	
Occupation	……	
Have you suffered any of the following?	Heart attack	☐
	Angina	☐
	Stroke	☐
Is there any history of cardiovascular disease (heart attack, angina, stroke) in your family (father, mother, brother, sister, children, spouse)?	Yes	☐
	No	☐
Do you use any tablets for high blood pressure?	Yes	☐
	No	☐

Record for Scenarios

Scenario 1: ……%	Scenario 2: ……%	Scenario 3: ……%

Thank you very much for your participation