Epidemiology of Coronary heart disease in ~~South~~ Asians ~~overseas~~ in Britain

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Preface

This thesis describes a programme of work which began in 1984, when I first began to assemble a systematic review of the epidemiology of coronary heart disease in South Asians and to work with Michael Marmot on the analysis of a survey of Gujaratis in north-west London. This led us to plan a study of Bangladeshis in east London which was undertaken during 1985-86. From the results of this study I was able to formulate a new hypothesis at the end of 1986. To test this hypothesis we began planning a larger study in west London. A pilot for this was completed in April and May 1988; the main study began in June 1988 and is still in progress (September 1989). The results of the pilot study, and their application to the final planning of the main study, are described. I have added some preliminary results from the main study to bring the thesis up to date, and closed with a final discussion which draws this material together with other work in the literature. Because it covers not a single study but a continuing programme of work, the thesis does not follow the usual form of review, methods, results and discussion but instead describes the programme as it happened.

Abstract

In countries where people of South Asian origin have settled, unexpectedly high coronary heart disease rates have been recorded in South Asian men and women compared with other ethnic groups. In England high CHD mortality is shared by Gujarati Hindus, Punjabi Sikhs and Muslims from Pakistan and Bangladesh. The high CHD rates in these populations are unexplained by levels of smoking, blood pressure, plasma cholesterol or dietary fat intake.

To test whether disturbances of haemostatic activity, lipoprotein metabolism or carbohydrate metabolism might underlie the high CHD mortality in South Asians, a population study in east London was undertaken. The results confirmed that the high CHD rates in South Asians compared with the native British population cannot be explained by differences in the distributions of blood pressure or plasma cholesterol. The hypothesis of a disturbance of haemostatic activity was not supported. A pattern of low plasma HDL cholesterol and high triglyceride levels, high serum insulin levels after a glucose load and high prevalence of non-insulin-dependent diabetes was identified in Bangladeshis.

On the basis of these findings and a review of other recent work it is suggested that: (i) insulin resistance underlies these disturbances of lipoprotein and carbohydrate metabolism in Bangladeshis; (ii) this tendency to insulin resistance is a general pattern in South Asian populations overseas; and (iii) it is a possible underlying mechanism for the high rates of both CHD and diabetes in these populations. The planning of a large study to test this is described. Preliminary results confirm that a syndrome of metabolic disturbances related to insulin resistance, first identified in Bangladeshis, is present also in Gujaratis and Punjabis. This is associated with a striking tendency to central obesity in South Asians. These findings point to the aetiological role of insulin resistance in CHD and suggest possible strategies for prevention in South Asian communities.

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2 Introduction

Coronary heart disease (CHD) rates have been noted in several parts of the world to be particularly high in people originating from the Indian subcontinent. A basis for preventive strategies in these communities depends upon adequate understanding of the causes of this epidemic. This review examines the evidence of excess CHD rates in South Asians, the extent to which existing knowledge about the pathogenesis of the disease can account for this excess, new hypotheses and possibilities for prevention. In this review the term 'South Asian' is used to denote origin from the Indian subcontinent. Those who migrated before Partition, and their descendants, generally describe themselves as 'Indian'. Migration from India, Pakistan, and Bangladesh to the United Kingdom has occurred mainly since the partition of the subcontinent: in the UK the term 'Asian' is generally used for those originating from this region.

2.1 The Indian diaspora

Indian people have migrated to other lands for many centuries. The modern history of Indian emigration dates from the beginning of the colonial system of indentured labour in 1834[1,2]. This led to the creation of Indian communities in Mauritius (from 1834), the West Indies (from 1838), Natal (from 1860), the Straits Settlements (from 1877), Fiji (from 1879) and East Africa (from 1896). The main agencies responsible for recruiting indentured labourers were in Calcutta and Madras. Indians leaving through Calcutta came mainly from the United Provinces and Bihar, with smaller numbers from Bengal, Orissa, Oudh, Punjab and North-West Provinces. Those emigrating through Madras were mostly Dravidian people from Madras State (now Tamilnadu) and Andhra Pradesh. Hindus exceeded Muslims by about 9 to 1, and many from the South had been converted to Christianity before their departure.

Other Indians travelled through the British Empire on their own initiative, particularly to East and Central Africa. Many of these entrepreneurs and professionals came from Gujarat, Bombay Presidency and Goa. The indentured labour system was banned by the Viceroy in 1917 but

a steady migration of traders, professionals and their families has continued ever since. Indian migrants continued to arrive in East Africa until the enactment of legislative bans in 1954. With independence and subsequent political changes, large numbers of Indians in East Africa were forced to move to India, Europe or North America. Migration to Britain from the Indian subcontinent increased after 1960 and reached a peak around 1966-67, then fell sharply following the introduction of immigration restrictions[3]. Migrants to Britain from Gujarat and Punjab came from rural areas[4]. Most had been agricultural or manual workers but their literacy rate was higher than that of the general population. Migrants from Pakistan and Bangladesh were from poorer circumstances than those from the north of India.

2.2 Coronary heart disease rates in Indians overseas (Table 1)

The earliest report of high CHD rates in Indians compared with other ethnic groups was from Singapore in 1957[5]. Prevalence of CHD - defined in this study as coronary artery disease with myocardial involvement - in a series of all 9568 autopsies undertaken over the years 1950-54 was seven times higher in Indian males than Chinese[5]. Age-standardized CHD death rates in 1954-57 were four times higher in Indians than Chinese. Though CHD mortality in Singapore has more than doubled between 1957 and 1978 in both groups, a threefold excess in Indians compared with Chinese remains[6].

In Uganda 43 percent of deaths among South Asian men in Kampala in the years 1956-58 were certified as due to coronary heart disease while in the African population of Uganda the disease was said to be almost non-existent[7]. In South Africa, CHD mortality in Indian women aged 30-69 was 49 percent above that for women of European descent during 1955-57[8]. Mortality was similar in Indian and European men at this time but over the years 1968-1977 the rate for Indian men aged 15-64 increased to 45 percent above the rate for Europeans[9]: around twice the estimated rates for the USA and UK at this time. In Fiji during 1970-73, myocardial infarction was noted to be much commoner among hospital admissions of men of Indian descent than those of Melanesian descent[10]. National mortality data for 1971-80 showed age-specific mortality from ischaemic heart disease to be about three times higher in Indians than in Melanesians, though only 72% of deaths were medically certified[11].

In Trinidad, where about 30 percent of the population is of Indian descent, the prevalence of coronary heart disease in different ethnic groups was assessed in a survey of a total urban community[12]. The odds ratio for major electrocardiographic Q waves (Minnesota codes 1-1, 1-2) in Indians versus other ethnic groups was 3.8 at ages 35-54 and 1.3 at ages 55-69 years. In a more recent analysis of mortality in this community between 1977 and 1985, age-adjusted relative risk of death from cardiovascular disease (mostly CHD), in comparison with adults of African descent, was 2.6 in Indians, 2.1 in Europeans, and 0.3 in adults of mixed descent, with no significant sex difference in relative risk estimates[13].

In Britain high CHD rates in South Asians were first observed at the time of the 1971 Census. In a community heart attack register in the East London borough of Tower Hamlets, 40 coronary events were recorded over the years 1970-72 in South Asian-born men, predominantly Bangladeshi: the number expected from the rate for all males in the borough was 31[14]. Analysis of national data for England and Wales during the same period showed standardized mortality ratios (SMRs) for CHD in migrants from the Indian subcontinent of 119 for men and 128 for women aged 20-69 years, taking the rates for all men and all women respectively as 100[15]. In contrast migrants from other developing countries had low SMRs for coronary heart disease. Analysis of surnames on death certificates showed that ethnic South Asians born in Africa also had high CHD mortality rates: the proportional mortality ratios (PMRs) were 120 for men and 163 for women, although these ratios were based on small numbers of deaths. The social class gradient of CHD mortality seen in the general population of England and Wales was absent in South Asians.

It is not possible to calculate separate rates for migrants from different regions of South Asia but surnames on death certificates of immigrants from the Indian subcontinent have been used to distinguish Gujaratis, Punjabis, Southerners and Muslims: all four groups had high PMRs for coronary heart disease in the years 1975-77[16]. A 40 to 50 percent excess of myocardial infarctions in South Asians was found in analyses of National Health Service hospital admission data for

Leicester during 1977-78[17] and north-west London during 1980-82[18]. The clinical presentation of CHD and the anatomical distribution of disease at angiography do not differ between South Asian and native British patients except that diabetes is more common in South Asian patients[19,20]. Plasma cholesterol is lower in South Asian than in native British patients[21,22].

National mortality data by country of birth for the period around the 1981 Census are not yet available but data for London boroughs with large South Asian populations show that CHD mortality in 1979-83 was 40 to 60 percent higher among South Asians in each borough than the average for England and Wales (Table 2)[23]. This high mortality is shared by communities originating from Gujarat, Punjab, Bangladesh and Pakistan. Unless the South Asian populations in Table 2 are unrepresentative, mortality from coronary heart disease among South Asians in England and Wales must have increased by about 25 percent over the decade 1971-81. The diminished effects of selection for fitness may account for some of this increase.

The high CHD rates of South Asians in England and Wales in 1970-72 were an unexpected finding in recent immigrants: migrants are usually selected for fitness, although the exodus from East Africa may have been an exception. The high rates seen in certain other migrant groups - those from Scotland, Ireland, Poland, USA and South Africa - correspond to the rates recorded in their countries of origin. It is likely therefore that high rates of coronary heart disease exist in the Indian subcontinent, at least in those sections of the population from which migrants to Britain were drawn.

2.3 Coronary heart disease in the Indian subcontinent

Though Indian clinicians report that CHD is common in urban practice[24] there are no satisfactory population-based data on coronary mortality or incidence in India, Pakistan or Bangladesh. Hospital admission rates for Indian railwaymen between 1958-62 have been reported but only admissions to railway hospitals from electrocardiographically-documented CHD were ascertained and the rates were not standardized for age[25]. Two surveys of CHD prevalence have been conducted in northern India[26,27], and the results have been compared with those of a survey in Tecumseh,

USA[28]. In Chandigarh, capital of Punjab and Haryana, 2030 adults aged 30 years and over were examined, while in rural Haryana a total village community of this age was included for study. The prevalence (rate per 1000) of electrocardiographic Q waves (Minnesota codes 1-1,1-2) in men aged 40-59 years was 38 in Chandigarh (based on 22 cases), 5 in rural Haryana (based on 3 cases), and 26 in Tecumseh (based on 21 cases). The numbers of cases in women were too few for comparison between populations. Despite the small numbers of cases, these findings suggest that CHD rates in urban populations in northern India may have been similar to those in the USA at this time, but that much lower rates exist in rural areas.

2.4 Coronary risk factors in South Asians

Though the explanation of high CHD mortality in South Asians in one community need not necessarily be the same as that in another, the world-wide distribution of increased risk in both sexes from an early age suggests that there may be a common underlying mechanism. Studies which have compared the distribution of known CHD risk factors between South Asians and other ethnic groups with lower CHD rates have been reported from several countries: by reviewing them it was possible to reject several hypotheses and to suggest others.

2.4.1 Smoking

Cigarette smoking is common among South Asian men overseas but unusual in women[13,18,29,30]. In Trinidad the proportion of men who smoked 20 or more cigarettes a day was higher in Indians than in Africans but smoking habit failed to explain the difference in mortality between these two groups[13]. In a survey in Fiji the proportion of men who had ever smoked was less in Indian than Melanesian men[31]. In South Africa during 1975-77 smoking rates were higher in South Asian than European men but much lower in South Asian than European women[32]. National household survey data in Britain show lower smoking rates in South Asian men than in the general population[33].

2.4.2 Hypertension

Hypertension is common in urban and rural populations in the Indian subcontinent[34,35]. In a survey in Durban, South Africa, hypertension was found to be less common in Indians than in Africans or Europeans,

though the design did not control for observer differences[36]. In Guyana, blood pressures were higher in African men and women than in Indians: differences which could be explained by the larger body size of adults of African descent[37]. In Trinidad, adults of Indian descent had a similar prevalence of hypertension to those of European and mixed origin, and lower rates than adults of African descent[38]. Age-adjusted cardiovascular mortality (deaths/1000 person-years) among Trinidadian men with systolic pressures below 130 mmHg was 11.3 in Indians compared with 9.6 in Europeans, 5.1 in Africans and 1.1 in those of mixed descent. In Fiji, mean systolic pressures were similar in Indian and Melanesian men[31]. Higher blood pressures were recorded in Punjabi women who had migrated to England than in the home country[39] but a study of an industrial population in Birmingham found no differences in blood pressure between South Asian and native British workers[40]. Levels of hypertension do not account for the high CHD rates in South Asians overseas.

2.4.3 Serum cholesterol concentration

A high average serum cholesterol, in excess of 5.2 mmol/l, is considered a factor necessary for the occurrence in a population of CHD on a mass scale[41]. Values at or above this level have been reported for urban groups of relatively high socio-economic status in various parts of India, but not in the middle and lower socio-economic groups (Table 3)[42-53]. Comparisons of this type are difficult to interpret since population sampling procedures and laboratory techniques are frequently not comparable. Mean concentrations tend to be higher in Indians overseas than in the subcontinent (Table 4)[7,18,53-55] but not necessarily higher than in other ethnic groups with lower CHD rates.

In the early 1980s mean serum cholesterol for men aged 45-69 years was 5.5 mmol/l in the USA and 6.3 mmol/l in Britain[56,57]. Apart from a 1959 study of South Asian men attending general practitioners in Kampala, Uganda[7], no group originating in the Indian subcontinent has been reported to have a mean serum cholesterol concentration similar to or above that of British men (Table 4). In Trinidad, serum LDL cholesterol concentrations were 0.3 mmol/l higher in Indian than in African men[55] but this did not account for the difference in CHD mortality[13]. In Fiji, plasma total cholesterol levels were 0.3 mmol/l higher in Indian

than in Melanesian men: it is unlikely that a difference of this size could explain the more than twofold difference in CHD mortality between these two ethnic groups. The relatively low average plasma cholesterol of Gujarati men and women in Brent and Harrow[18] is particularly striking since this group has exceptionally high CHD mortality[23].

2.4.4 Dietary fat

If the Keys equation relating diet to average serum cholesterol[58] holds, the relatively low cholesterol levels found in South Asians overseas imply either that saturated fat and cholesterol intakes are low or that polyunsaturated fat intakes are high in comparison with the diets of North European and US populations. The only overseas South Asian populations for which detailed dietary survey data exist are those in Singapore and north-west London. In an assessment of dietary intakes by 24-hour recall in 528 male employees of the Singapore Port Authority, mean total fat intake was highest in Chinese, intermediate in Indians and lowest in Malays[59]. Polyunsaturated fat as a proportion of total fat intake was similar in all three groups. In two studies, one using household food inventories[18] and the other weighed intakes[60], Gujaratis in north-west London were found to have low dietary saturated fat intakes and high polyunsaturated fat intakes compared with the British average. Average plasma cholesterol was close to the value predicted from the Keys formula[18]. Total fat intake was similar to the levels in the British population. Linoleic acid accounted for most of the high polyunsaturated fat intake of Gujaratis. As would be expected in a mainly vegetarian population, dietary intakes and levels in plasma lipids of long-chain polyunsaturated fatty acids of the w3 series were low: these fatty acids are mainly of marine origin and it has been suggested that they protect against atherosclerosis.

Ghee, prepared by heating butter to drive off the water, is traditionally used in North Indian cooking. One analysis has shown that 12 percent of the sterols in ghee obtained from commercial and home-prepared sources were in the form of cholesterol oxides: these compounds were not found in ordinary butter[61]. Since there is evidence from animal studies that cholesterol oxides are more atherogenic than pure cholesterol[62], the presence of these compounds in ghee has been suggested as a possible cause of high CHD rates in South Asians in

Britain and Trinidad[61]. Others have failed to confirm the presence of cholesterol oxidation products in ghee[63]. Use of ghee among Indians in the Trinidad survey was uncommon (GJ Miller, personal communication): it is unlikely therefore that this hypothesis can account for the high CHD rates in South Asians around the world.

Plasma HDL cholesterol and triglyceride levels

Low plasma levels of high-density-lipoprotein (HDL) cholesterol[64,65] and high levels of triglyceride[66-69] are predictors of CHD risk in prospective studies and have been found fairly consistently in South Asians overseas compared with other groups. In urban Trinidad, age-adjusted mean HDL cholesterol concentrations in Indian men (0.9 mmol/l) and women (1.2 mmol/l) were 0.1 mmol/l lower and triglyceride levels were 40 percent higher than in Africans. These differences did not explain fully the excess of CHD deaths in Indian adults in this community[55]. Indian migrants to the United States have also been reported to have lower HDL cholesterol and higher triglyceride levels than the general population[70,71].

There is an inverse association between HDL cholesterol and triglyceride levels[64,72] so that it is difficult to distinguish on the basis of epidemiologic data the extent to which low HDL cholesterol and high triglyceride levels may be separately atherogenic. Both factors are associated with non-insulin-dependent diabetes in European populations[73].

2.4.5 Diabetes and impaired glucose tolerance

Non-insulin-dependent diabetes mellitus is a disease of antiquity in India and has long been recognised as prevalent in the middle-aged, affluent and obese[74,75]. Among overseas Indians the first report of an excess of diabetes in comparison with other ethnic groups was from Saigon in 1913[76]. Similar reports have come more recently from Malaysia[77], Trinidad[78], South Africa[79], Singapore[80], Fiji[81], Surinam[82] and England[83]. Prevalence estimates from published surveys in South Asian populations[13,77,81,84-87] are shown in Table 5 together with data from two British surveys for comparison[88,89]. To allow comparison of recent surveys based on the 1980 WHO Expert Committee's diagnostic criteria[90] with earlier studies using a 50g glucose load, prevalence

figures based on comparable cut-off values for 2-hour blood glucose have been extracted from the earlier studies where sufficient data are given. The low prevalence rates reported in East Pakistan in 1966[77] and in Orissa in 1971[84] are in striking contrast to later findings in urban India and overseas[13,81,86,87]. It is unlikely that this tenfold difference in prevalence can be accounted for by differences in age distribution or diagnostic criteria. Comparison of urban and rural rates in all individuals over 10 years of age is possible from the published Orissa data: 2% in urban Cuttack and 0.5% in rural Badachana were diabetic by the criteria in Table 5. In the Fiji survey the higher prevalence of diabetes in Indian men than Melanesian men was not explained by obesity (measured as triceps skinfold thickness) or physical activity[91].

Preliminary analyses of the follow-up data in the Trinidad study suggested that age- and diabetes- adjusted relative risks of cardiovascular death were similar in men of Indian and European descent, and that diabetes mellitus might explain the difference in CHD rates between these groups[13]. A more recent analysis of cardiovascular morbidity and mortality with longer follow-up failed to confirm this[92]. The European group in this study was small: similar comparisons would be easier to perform in Britain. Diabetes mellitus did not explain more than a small part of the excess risk of CHD in Indians above that of Africans and men of mixed descent in Trinidad: the lowest mortality rates were in men whose fasting glucose was in the range 4.2-4.6 mmol/l and in this stratum age-adjusted cardiovascular mortality (deaths/1000 person-years) was 6.7 in Indians, 3.4 in Africans and 0 in men of mixed descent.

Quantitative consideration of the relationship between glucose intolerance and CHD mortality suggests that markedly elevated CHD risk for an entire population is not easily explained by a high prevalence of glucose intolerance. The relationship between plasma glucose and mortality is non-linear and there appears to be a threshold for elevation of CHD risk, at a 2-hour glucose level approximately equivalent to the WHO criterion for impaired glucose tolerance[93-96]. The largest study to examine this was the Whitehall Study[93,94]: at 10-year follow-up age-adjusted CHD mortality in men in the top 5 percent of

the 2-hour blood glucose distribution, and in a further 1 percent who were known diabetics, was twice that in the rest of the cohort[93]. This implies that the proportion of all CHD deaths which are attributable to glucose intolerance - the aetiologic fraction - is about 6 percent in this population. If this relationship betweeen glucose intolerance and mortality holds across populations then even an exceptionally high prevalence of diabetes and impaired glucose tolerance in South Asians overseas would produce only a modest elevation of total CHD mortality. A 30 percent prevalence of glucose intolerance in middle age, instead of 6 percent as in Whitehall, would double the risk for 30 percent rather than 6 percent of the population but this would yield only a 23 percent excess total mortality, other risk factors being equal. On this basis it is unlikely that a high prevalence of diabetes and impaired glucose tolerance could alone explain a threefold relative risk of CHD death in Indians compared with Chinese in Singapore and in Indians compared with Melanesians in Fiji. In any case the relationship between plasma glucose and CHD mortality is unlikely to be directly causal and it is more likely that both have common underlying determinants[97]. As Jarrett has pointed out, a biological gradient relating plasma glucose to CHD mortality is lacking: impaired glucose tolerance and non-insulin-dependent diabetes carry an equally increased risk of CHD death, and there appears to be no relationship between CHD mortality and the duration of diabetes[97]. The high prevalence of non-insulin-dependent diabetes in South Asians suggests the presence of an underlying disturbance of carbohydrate metabolism.

2.4.6 Socio-economic status

Historically CHD has tended to appear first in the more affluent socio-economic groups, and then to spread into the rest of the population, eventually becoming commonest in those of lowest socio-economic status[98,99]. Some writers have suggested that the high CHD mortality of South Asians in Britain may be partly explained by the association between CHD risk and low socio-economic status[100]. The absence of a social class gradient in CHD mortality among South Asians in England and Wales makes this notion difficult to sustain. It is similarly impossible to explain in terms of economic deprivation the high CHD rates of Indians compared with Melanesians in Fiji, where Indians are the economically dominant group. More relevant to understanding the

high CHD risk in South Asians may be the hypothesis that CHD risk is related to deprivation in early life. For European populations this hypothesis is supported by the relationship of short stature to CHD[101] and by the relationship between the infant mortality and subsequent CHD mortality of different birth cohorts[102]. No similar data for South Asians are available: it would be of interest to examine the relationship between height and cardiovascular mortality in existing datasets. Early deprivation is unlikely to be a sufficient explanation for high CHD rates in South Asians in Britain, since Afro-Caribbeans and others who have migrated from less developed regions have low CHD mortality rates[15].

2.4.7 Psycho-social factors

The failure to account for the excess risk of CHD in South Asians in terms of established risk factors has led to speculation that psychosocial stress may be responsible[100]. Similar ideas have been advanced to explain why smoking, blood pressure and serum cholesterol fail to account for the relationship between acculturation and CHD prevalence in Japanese-Americans[103] and for differences in CHD mortality between employment grades in the civil service[101]. Epidemiologists are often indicted for their reluctance to consider psychosocial explanations[104]: the writer, when presenting the work in this thesis, has been similarly criticized for neglecting this line of inquiry. This section briefly reviews current ideas about psychosocial factors in the aetiology of CHD before examining how these concepts might be applied to explain the high CHD rates in South Asians.

2.4.7.1 The theoretical basis of psychosocial factors

The concepts of psychosocial stress developed by epidemiologists may be classified according to the level of theory embodied in their construction. Low-level constructs are defined operationally and do not depend heavily on theoretical frameworks: examples are Type A behaviour[105], social network scores[106] and the Karasek job strain model[107]. Measurement of these low-level constructs is relatively straightforward but they are usually difficult to apply outside the setting in which they were developed.

Examples of higher-level constructs are quality of social support[108] and learned helplessness[109]. These constructs do not have simple operational definitions and depend to some extent on an underlying theory. High-level constructs are assumed to be generalizable across human and even non-human populations, and to be directly linked to pathophysiologic pathways. It is possible to explain the reversal of predictions based on low-level constructs in terms of higher-level constructs: for instance, high CHD rates in a population with high social network scores can be explained by postulating that the quality of social support is deficient.

2.4.7.2 Type A behaviour

The construct of Type A behaviour - characterized by aggressiveness, competitive drive, preoccupation with deadlines and impatience - was developed to summarize a pattern observed in men in California. Early results of a prospective study showed that the syndrome appeared to predict CHD incidence independently of other risk factors[105]. A subsequent study of the same cohort with longer follow-up failed to confirm this: it appears that the original association was with non-fatal CHD rather than with mortality[110]. Psychosocial factors are likely to affect the chance that CHD will be diagnosed even when they do not influence the natural history of the disease.

2.4.7.3 Social networks and social support

Several prospective studies have shown that a low frequency of social contacts is associated with high mortality[106,111-115]. A few of these reports have mentioned that this association holds with CHD as a separate category and that it is independent of other behavioural risk factors such as smoking[106,111]. The underlying theoretical model is that supportive social relationships buffer the individual against psychosocial stress: proponents have emphasized the need to develop better measures of the high-level construct - quality of social support - which they believe would be more generalizable and predict CHD even more strongly[108]. Review of the prospective studies however discloses a consistent pattern: excess mortality or CHD risk is concentrated in the group with the fewest social contacts, usually the lowest quartile[111,112,114-116]. (In the Gothenburg study the shape of the

relationship between social influences and mortality was not reported[113].) Although the original study in Alameda County demonstrated a dose-response relationship between social networks and mortality[106], the construction of the social network index had been influenced by the mortality results: a subsequent study using the same index failed to confirm the existence of a gradient[114]. If the association is simply between ill-health and social isolation, without a gradient of decreasing mortality with increasing social support, then complex constructs about the quality of social relationships are not necessary to explain it: the group with fewest social contacts is likely to contain many individuals who are in poor health and physically neglected. This does not necessarily mean that social isolation does not cause increased morbidity and mortality, but that the association can be explained at a simpler level than most workers in this field have assumed. This has implications for the application of the social support concept to differences between populations, as argued in Section 1.5.7.6.

2.4.7.4 Work environment

Job dissatisfaction has long been implicated as a possible risk factor for CHD[117,118]. More recently Karasek has proposed that stressful work patterns are those which combine excessive demands and low decision latitude[107]. Three studies have attempted to test this hypothesis in relation to CHD risk. In a nested case-control study of two cohorts of Swedish men based on the national Level of Living Surveys in 1968 and 1974, participants' rating of their jobs as hectic and psychologically demanding was associated with a fourfold relative risk of CHD death after matching for education and current smoking[119]. The relative risks associated with low personal schedule freedom and low intellectual discretion were in the same direction but did not reach significance. Two further studies have used national survey data on the psychosocial characteristics of Swedish occupations to classify the occupational exposures of men in their cohorts[120,121]. Occupations rated as monotonous with few opportunities to learn new things were associated with relative risks of around 1.2 for hospital admission with myocardial infarction. These results are consistent with a modest effect of unsatisfying work environments, though the relationship may not necessarily be as specific as in Karasek's model.

2.4.7.5 Psychosocial factors in South Asians

From the brief review above it appears that the psychosocial exposures most consistently associated with increased CHD risk in European populations are social isolation and job dissatisfaction. Neither of these factors is likely to play a substantial part in explaining high CHD rates in South Asians in Britain. Survey data do not suggest that social isolation is more common in South Asians than in the native British population[122]. The absence in South Asians of a social class gradient in CHD mortality, and the diversity of occupational patterns between groups who share high CHD mortality, make it difficult to construct explanations for the high CHD rates based on work environment. For instance, Gujarati men in north-west London, who work mostly as professionals and self-employed businessmen, have even higher CHD mortality than Bangladeshis in east London, who are predominantly manual workers in the clothing and catering trades.

If South Asians in Britain are experiencing levels of psychosocial stress sufficient to cause excess CHD mortality, we would expect levels of psychological morbidity also to be higher in South Asians than in the native British population. The limited data available do not support this. In a population survey Indian immigrants reported fewer psychological symptoms than native British urban residents[123]; this is consistent with the effects of selection at migration. Psychological symptom scores in Pakistani immigrants were similar to those in the native British population[124]. It is of course possible that standard questionnaires fail to detect psychological morbidity in a different cultural setting from that for which they were originally developed: qualitative studies are needed to resolve this uncertainty.

2.4.7.6 Conclusions about the possible role of psychosocial factors

Pyschosocial explanations of the high CHD rates in South Asians based on applying low-level constructs developed in Western populations, such as social isolation and work environment, do not fit the epidemiological data. It is possible, however, to formulate explanatory hypotheses in terms of higher-level constructs in which South Asians are under greater levels of stress than the native population. Such explanations would

have to specify new low-level constructs of stress specific to South Asians, such as the effects of Indian family structure or of racism. Two such hypotheses, which have been proposed informally, are examined here.

On the assumption that the inverse association between social networks and mortality is related to the quality of emotional support available, it is possible to construct an explanation for high CHD rates in South Asians by postulating that the close family ties in South Asian communities are associated with maladaptive relationships and excessive demands on individuals. If however, as suggested above, the relationship of social support to CHD rates is simply an effect of social isolation, then quality-of-support constructs are irrelevant. In any case, a hypothesis based on the supposed pathological effects of South Asian family ties would predict low CHD rates in first-generation migrants, who escape their responsibilities and duties to the preceding generation.

Emphasis has been placed on the role of psychosocial stress associated with racial tension and adaptation to the host culture in the high CHD risk among South Asians in Britain[100]. The existence of institutionalized racism directed against South Asian immigrants in the UK is not in doubt: however there is no other epidemiological evidence to suggest that racism is generally associated with increased CHD risk. For instance, there is no excess in Afro-Caribbeans compared with the native British population or in Blacks compared with Whites in the United States. Adverse psychosocial effects of adaptation to the host culture may contribute to risk in first-generation South Asian migrants to Britain but these factors cannot account for high CHD rates in long-established Indian communities such as those in the Caribbean and Pacific regions.

I note finally that the inability to explain differences in disease rates in terms of known physiological mediators is a weak basis for assuming that psychosocial factors are responsible: even psychosocial stressors presumably act through physiological mechanisms. The early deprivation hypothesis provides a plausible alternative to psychosocial stress as an explanation for class differences in CHD mortality[102]. A

follow-up study failed to confirm the independent relationship between acculturation and CHD risk found in an earlier cross-sectional study of Japanese-Americans[125]. Further advances in this field may come through studies which relate psychosocial factors to pathophysiological mediators.

2.4.8 Genetic inheritance

Any environmental factor invoked to explain the high rates of the disease in South Asian populations around the world must be common to all the main ethnic groups of the Indian subcontinent, to both sexes and persist several generations after migration. In other migrant groups, such as Japanese in the USA, CHD rates in those settled overseas longest and in their descendants tend to converge to those in the host population[126]. This has led to the view that that between-population differences in CHD rates are environmentally rather than genetically determined. In contrast CHD mortality and diabetes prevalence in communities of Indian descent settled overseas for many generations continue to diverge from the rates in other ethnic groups in the same country, suggesting that in this case genetic factors may be important. Sibling and twin studies in European populations have suggested that non-insulin-dependent diabetes is strongly genetically determined[127,128]. Most reviewers of the epidemiology of non-insulin-dependent diabetes have concluded that the high prevalence in South Asians compared with other groups is unlikely to be explained entirely by environmental factors[129].

One difficulty for genetic explanations is that high diabetes and coronary heart disease rates are shared by populations originating from different regions of South Asia, who are supposed to be genetically dissimilar. European anthropologists of the 19th century assumed that the Indo-European (Aryan) and Dravidian language groups, found in northern and southern India respectively, corresponded to different 'races'[130]: the notion of an Aryan 'race' has subsequently underpinned racist ideologies from Nazi Germany to present-day Sri Lanka. This assumption is not supported by the few studies which have used modern quantitative genetics to compare genetic distances between groups within India with the distances between Indians and other populations[131,132]. Using alleles of the vitamin D binding protein to calculate genetic

distances, populations in Delhi and Madras were found to be genetically close and markedly distinct from other Asian or Pacific populations[131]. A similar study of immunoglobulin allotypes in Punjabis, Sinhalese, Singapore Indians, Malays and Chinese found similarly that the three South Asian groups were genetically close to each other and distant from the east Asian groups[132]. This suggests that the supposed genetic difference between South Asian populations of Aryan and Dravidian linguistic origins has been exaggerated and that both groups originate from a common gene pool.

No specific genetic markers for coronary heart disease (other than those related to hyperlipidaemia) or non-insulin-dependent diabetes have been consistently identified. A selective advantage for the diabetic genotype under conditions of food scarcity has been suggested to explain the high prevalence of the condition in populations exposed to such conditions in earlier generations who have undergone a recent transition to relative affluence[133]. The application of this 'thrifty genotype' explanation to South Asians is considered in more detail in the final section of this thesis. The identification of a genetic basis for the high risk of CHD in South Asians would not of course mean that the condition was not preventable by environmental change.

2.5 Conclusion of review

The evidence reviewed here suggested that levels of dietary fat intake, plasma cholesterol, smoking and blood pressure were unlikely to explain the high CHD rates in South Asians overseas, and that some other mechanism must be responsible for high risk. Three tentative hypotheses for an underlying mechanism were formulated:

(i) a possible disturbance of haemostatic activity: this pathway seemed the strongest contender for an alternative to the lipid hypothesis of atherosclerosis. Fibrinogen and factor VII coagulant activity (VIIc) levels had been found to predict CHD in the Northwick Park Study[134].

(ii) a disturbance of lipoprotein metabolism, causing low HDL cholesterol and elevated triglyceride levels without elevated plasma

cholesterol, suggested on the basis of the findings in Trinidad[12].

(iii) a disturbance of carbohydrate metabolism causing high prevalence of non-insulin-dependent diabetes and increased risk of atherosclerosis.

To test these hypotheses a study of Bangladeshis in East London, described in the next section, was undertaken[29]: a similar study of Gujaratis in Brent was simultaneously undertaken by the Northwick Park group[60]. The results of these studies and other work published since 1985 will be discussed together.

3. Coronary risk factors in Bangladeshis in East London

3.1 Introduction

Since the survey of Gujarati Hindus in north-west London[18] had yielded no clues to the reasons for the high coronary heart disease rates in South Asians we undertook the next investigation in the east London borough of Tower Hamlets, where the South Asian population is made up predominantly of Muslims from the Sylhet region of Bangladesh. High morbidity from coronary heart disease in South Asian-born men compared to the average in this district was first recorded during 1970-72[14]. Mortality data for 1979-83 show an excess of coronary deaths in South Asian men: there were too few South Asian women aged over 40 years in Tower Hamlets for mortality risk in this group to be estimated (Table 2)[23]. The objectives were: first, to determine whether the findings in north-west London could be replicated in a Muslim South Asian population; and second, to investigate whether the high coronary heart disease rate in South Asians in Britain could be explained by other risk factors which were not measured in the earlier study, especially haemostatic activity and glucose intolerance.

3.2 Methods

3.2.1 Sampling

From existing literature[93,134,135] the size of difference in the distribution of each risk factor that would give rise to a 20 percent difference between two populations in male coronary heart disease mortality was estimated. A target sample size sufficient to detect such differences was estimated to be about 80 men in each ethnic group (Table 6). Local ethical approval was obtained.

Fieldwork was undertaken between June 1985 and April 1986. Most South Asian residents of Tower Hamlets live in the western half of the borough (postal districts E1 and E2) and are registered with one of three general practices in this area. The lists of these three practices and of a further two practices with mostly native British patients were chosen as the sampling frame (Figure 1). A sample of men born between 1920 and 1949 was chosen from each practice, excluding residents in hostels for the single homeless and those with mental handicap, recent

psychiatric illness, terminal malignancy or other advanced disease. To minimize the proportion of wrong addresses, those who had not consulted since 1981 or who last attended for immunization before returning to Bangladesh were excluded also, as unlikely to be still resident. The proportions sampled from each practice were adjusted to ensure approximately equal numbers of Asian and non-Asian respondents. In three practices which had age-sex registers the sample was stratified by year of birth to give an even distribution across the age range. In the early stages of the study, women aged over 35 years who were married to South Asian respondents were also invited to take part: because of the age difference between husbands and wives this proved unsatisfactory as a means of sampling older South Asian women. A sample of women was chosen independently from four of the practices in the last four months of fieldwork. In one practice whose list was made up predominantly of Bangladeshi residents, only women born before 1940 were included at this stage. Apart from the exclusions and the stratification by age, sex and practice the sampling procedure was random.

Each eligible subject was sent a letter inviting them to participate. Addresses from which no reply was received were visited to ascertain whether the address was correct and to issue a further invitation. Of the 557 subjects to whom letters were sent, 173 had moved to other addresses either outside the district or unknown, 2 had died and one was in hospital. Of the 381 remaining, 58 refused, 3 were medically unfit to take part and it was not possible to contact 12. 308 interviews were completed: a response rate of 81% from those believed to be resident.

Respondents were interviewed at home with a questionnaire including demographic items, smoking, alcohol consumption and medical history, and invited to attend the London Hospital Medical College for blood pressure measurement and blood sampling. Most Bangladeshi subjects were interviewed in Bengali and most non-Asian subjects in English. Those without a history of diabetes were given a 75g glucose drink and asked to fast overnight before their appointment then to drink it 1½ hours before the time of booking. 253 participants attended for examination, giving a final stage response rate of 66% (Table 8). The target sample size was reached for men but not for women. Age distribution of the respondents is shown in Table 9. There were few Bangladeshi women aged

younger than 45 or older than 54: a result of the unusual demographic structure of the population and the restriction in the later stages of the fieldwork of the Bangladeshi sample to women born before 1940. Blood pressure was measured twice with a random-zero sphygmomanometer after subjects had been sitting quietly for five minutes: all measurements were made by a single observer (PM). A single venous sample was obtained on 247 of the 253 attenders: in those who had been given a glucose load this was timed as nearly as possible to 2 hours after the reported time of consuming it.

3.2.2 Laboratory analyses

EDTA plasma for cholesterol determinations was kept at 4°C for up to 48 hours. High-density lipoprotein was separated by heparin-manganese chloride precipitation; cholesterol in these specimens and in whole plasma was measured enzymatically in a centrifugal analyser. Plasma glucose was measured on a fluoride oxalate specimen by the glucose oxidase method. Fibrinogen concentrations in fresh citrated plasma were measured by a gravimetric method[136]. Citrated plasma samples for factor VII determination were stored in liquid nitrogen, thawed at 37°C and maintained at room temperature to avoid cold activation. Factor VII coagulant activity was assayed by a manual method based on that of Brozovic et al[137] using Immuno AG 100% reference plasma in doubling dilutions from 1/10 to 1/360, 0.025M $CaCl_2$ and 1 in 32 rabbit brain thromboplastin. Factor-VII deficient plasma was prepared from oxalated bovine blood using a modification[137] of the method of Lechnes and Deutsch[138].

Fatty acid composition of plasma lipids was measured by the University of Edinburgh Cardiovascular Research Unit on a random subsample of those seen in the last six months of fieldwork. Lipids were extracted from 1 ml plasma according to Folch's method[139]. Heptadecanoin derivatives of cholesterol ester, phosphatidyl choline and triacylglycerol (Sigma Chemicals) were the internal standards. Lipid classes were separated by thin-layer chromatography. Methyl esters were prepared directly on silica gel using sodium methoxide. Sphingomyelin is excluded since it is not transesterified under the conditions used[140]. Methyl esters were separated (Pye Unicam 204 Gas Chromatograph with temperature programming) on an open packed glass column (4 mm ID x 1.5M) using 10%

SP2330 (Supelco) as stationary phase. Identification was based on retention time with respect to standard methyl ester mixtures (Sigma and Supelco) and confirmed by mass spectrometry and silver nitrate thin-layer chromatography. Peak areas were integrated by a computing integrator (Tribal II, Trevector). A plasma pool was used for quality control and analysed coincidentally with the study samples. In the different lipid classes the coefficients of variation of repeated measurements ranged from 2.0 to 3.6% and from 0.6 to 5.0% for the determination of total fatty acids and percent linoleic acid respectively. Insulin levels in stored serum were measured by a double antibody technique[141].

3.2.3 Statistical analyses

All those of South Asian origin have been included in the group referred to as Bangladeshi and all other participants, including three Afro-Caribbeans, have been assigned to the non-Asian group: this is consistent with the groupings used in analyses of local morbidity and mortality[14,23]. Alcohol consumption categories were defined according to the Quantity-Frequency Index used in the General Household Survey (Table 7)[142]. Participants were classified as diabetic if they had been diagnosed diabetic or their post-load plasma glucose was 11 mmol/l or more. Known diabetics are excluded from the data for plasma insulin and triglycerides since they did not fast or receive a glucose load. In testing for differences between ethnic groups, data have been analysed separately for men and women using a least-squares linear model. Age was treated as a categoric variable with three levels corresponding to the age groups 35-44, 45-54 and 55-69 years. Adjusted means are the values predicted in the model when all covariates are held at their mean values. Other covariates - body mass index, triglycerides and insulin - were treated as continuous variables. Triglyceride and insulin values were log-transformed for these analyses but have been transformed back to SI units for the tabulations. In figures and tables giving means by age group, data for women are given for only two age bands because of small numbers of Bangladeshi women at the extremes of the age range.

3.3 Results

3.3.1 Questionnaires

89 percent of Bangladeshi men and 80 percent of non-Asian men belonged to social classes III manual or IV by the Registrar-General's classification[143]. 17 percent of Bangladeshi men and 64 percent of Bangladeshi women had never received full-time education. 98 percent of Bangladeshi men were married but only two-thirds had their wives living with them in the UK. 53 percent of Bangladeshi men and 20 percent of non-Asian men were unemployed. 97 percent of South Asians were Muslim and 91 percent were from Sylhet. Although most Bangladeshi men were cigarette smokers, only 23 percent of Bangladeshi men smoked more than 15 cigarettes daily compared with 34 percent of non-Asian men (Table 10). 93 percent of Bangladeshi men and all Bangladeshi women were abstainers from alcohol (Table 11). 74 percent of Bangladeshi men but only 2 percent of Bangladeshi women attended the mosque at least once a week. Bangladeshi women appeared to be isolated from social networks outside their own families: 93 percent stated that they had no social contact with a close friend in an average week.

3.3.2 Clinical and laboratory findings (Tables 12-27, Figures 2 and 3)

Average systolic blood pressures were 10 mmHg lower in Bangladeshis than in non-Asians. Adjusting for body mass index accounted for about half of this difference. The most striking differences in plasma lipids were the low high-density lipoprotein cholesterol and high triglycerides in Bangladeshi men and women compared with non-Asians. The percentage of total plasma cholesterol as HDL was also lower in Bangladeshis than in non-Asians (Table 24). The relationship between age and several of the variables measured was less marked in Bangladeshis than in non-Asians: this was true for body mass index (Table 15), systolic blood pressure (Table 16), plasma cholesterol (Figure 2), plasma triglycerides (Figure 2) and serum insulin (Figure 3). The proportion of essential fatty acids of the w6 series (predominantly linoleic acid) and the polyunsaturated/saturated ratio in plasma lipids were lower in Bangladeshis than in non-Asians (Table 20). Levels of fatty acids of the w3 series were slightly higher in Bangladeshis, consistent with the use of fish in Bangladeshi cooking. Fibrinogen levels did not differ between ethnic groups and factor VII coagulant activity (VIIc) was

markedly lower in Bangladeshi than in non-Asian men (Tables 18 and 19). VIIc levels were correlated with plasma cholesterol but in a regression analysis plasma cholesterol did not explain fully the ethnic difference in VIIc levels.

Prevalence of diabetes exceeded 20 percent in Bangladeshi men and women: three times higher than the rate in non-Asians (Table 21). Two-thirds of diabetics were already diagnosed: this proportion did not differ between ethnic groups. Serum insulin levels after a glucose load were about twice as high in Bangladeshis as in non-Asians (Figure 2). This difference persists after controlling for time of sampling (Table 23). The insulin/glucose ratio was also higher in Bangladeshis than in non-Asians (Table 22). Insulin levels were correlated with body mass index within each ethnic group (Tables 25 and 26). Insulin and triglyceride levels were correlated with each other and inversely correlated with high-density lipoprotein cholesterol: some of the difference in high-density lipoprotein cholesterol between Bangladeshis and non-Asians was accounted for by the differences in insulin and triglycerides.

3.4 Discussion

3.4.1 Cholesterol, clotting, smoking and dietary fatty acid intakes

This study confirms that the excess of coronary heart disease among South Asians in Britain is not explained by elevated plasma cholesterol. A similar difference in average serum cholesterol between South Asian and European men was found in the study of Gujaratis in Brent[60]. According to the Keys equation[58], the average serum cholesterol of a population is linearly related to (2S-P), where S and P are the percentages of total dietary energy obtained from saturated and polyunsturated fats respectively. If the Keys equation holds in both South Asian and European populations, the value of (2S-P) must be lower in Bangladeshis than in non-Asians to account for the relatively low plasma total cholesterol in Bangladeshis. Though no direct dietary measurements were made in this study, the low polyunsaturated/saturated ratio in plasma lipids implies that dietary P/S ratios are also low in Bangladeshis. If average values of (2S-P) and the ratio P/S are lower in Bangladeshis than in non-Asians, it follows that average dietary

saturated fat intake (S) must also be lower in Bangladeshis. The relatively high plasma cholesterol of Bangladeshi men aged under 45 years suggests that this group may be following a less traditional diet.

These conclusions about the diets of Bangladeshis, based on plasma lipid analyses, are directly opposite to those of an earlier report, based on one-day recording of the diets of 12 Bangladeshi men in east London[144]. Total fat intakes and P/S ratios were reported to be unusually high in this group compared with the native British population. There are several reasons for doubting the validity of these findings: the men were selected on the basis of their ability to speak English which may have biased the sample; and their mean energy intake was estimated as 3400 kcal/day, an unlikely level for sedentary individuals.

Differences in haemostatic activity also fail to explain the high coronary heart disease rates in South Asians. The haemostatic varables most strongly implicated as risk factors for CHD are fibrinogen and factor VIIc: they were measured by similar techniques in Brent[60] and in this study. Fibrinogen levels did not differ between South Asians and Europeans in either study. Factor VIIc activity was similar in Gujaratis and Europeans, and markedly lower in Bangladeshi men than European men.

The high proportion of smokers among Bangladeshi men differs from the low smoking rates of Asian men recorded in north-west London[18] and in a nationally representative sample[33]. The low levels of polyunsaturated fatty acids of the w6 series in plasma lipids of Bangladeshis contrast with the very high levels in Hindus in north-west London. While smoking and a low dietary polyunsaturated/saturated ratio may contribute to the high coronary heart disease rate of Bangladeshi men in east London, they cannot explain the national mortality pattern which includes other South Asian groups.

3.4.2 Evidence for insulin resistance in Bangladeshis

The associations between non-insulin-dependent diabetes, hyperinsulinaemia following a glucose load, high plasma triglyceride and low high-density lipoprotein cholesterol in Bangladeshis suggest that these factors are manifestations of a single metabolic disturbance.

These associations have also been reported in other populations[145-147]: hyperinsulinaemia increases VLDL triglyceride synthesis[145,148] and this appears to lower HDL cholesterol levels by a mechanism that is still poorly understood[72]. One hypothesis is that increased transfer of triglyceride from VLDL to HDL particles results in the formation of triglyceride-rich HDL_2 which is rapidly removed by hepatic lipase[149]. Definitive demonstration of insulin resistance requires steady-state measurements of glucose disposal and insulin levels but the parallel findings of elevated insulin/glucose ratio and high diabetes prevalence in Bangladeshis make it reasonable to infer that insulin resistance underlies the elevation of insulin levels. Although the high insulin levels in Bangladeshis were not explained by differences in body mass index, which were in the opposite direction, this index may be inappropriate for comparing adiposity between groups different in average frame size[150]. In other populations insulin levels are more closely related to upper body fat deposition, not measured in this study, than to body mass index[151].

3.4.3 Similar findings in other South Asian populations

The combination of high prevalence of non-insulin-dependent diabetes, hyperinsulinaemia, high plasma triglyceride and low HDL cholesterol in Bangladeshis appears to be part of a general pattern in South Asians overseas. The 22 percent prevalence of diabetes in this small sample is similar to the figure reported for other overseas South Asian populations[13,81,86] but much higher than the 1.3 percent reported in a comparable survey in East Pakistan in 1964[77].

Triglycerides and HDL cholesterol

High triglycerides and low HDL cholesterol in South Asians compared with Europeans have also been reported in Trinidad[12] and the United States[70,71]. More recent studies show a similar pattern. In Fiji plasma triglyceride levels were 30 percent higher in Indians than in Melanesians: plasma HDL cholesterol levels were not measured[31]. In Singapore levels of HDL cholesterol, apolipoprotein A-I and apoplipoprotein A-II were lower in Indian than in Chinese men attending for pre-employment medical screening[152]. In Brent, HDL cholesterol levels were 0.1 mmol/l lower in South Asian (mainly Gujarati) than in European men but the ratio of HDL to total cholesterol did not differ

significantly between these groups[60]. Triglyceride levels were not higher in South Asian than in European men in the Brent study, in contrast with findings in other populations.

In the study reported here there was no sex difference in high-density lipoprotein cholesterol levels in either the Asian or the non-Asian groups: while this has been reported in other South Asian populations[18,43,52] the absence of the usual sex difference of about 0.3 mmol/l in the non-Asian group is puzzling since the 95% confidence interval for the difference (-0.15 to +0.15 mmol/l) is less than this. It is therefore unlikely to be explained entirely by chance or random measurement error.

Insulin

In South Africa, insulin levels after a glucose load were higher in students[153], children[154] and nurses[155] of Indian origin than in those of European origin. Similarly high post-load insulin levels in Indians compared with Europeans have been reported for hospital outpatients in West London[156] and for vegetarians in Washington, DC[157].

3.4.4 Possible mechanism for high coronary heart disease rates

Although the evidence relating a high-fat diet, plasma cholesterol, hypertension and smoking to the occurrence of coronary heart disease is strong, these factors do not account for the high disease rates in South Asians overseas: any attempt at explanation must therefore invoke less well-established risk factors. Pathological and epidemiological evidence support the view that the combination of elevated plasma insulin, elevated triglycerides, and low high-density lipoprotein cholesterol is atherogenic[64,158,159]. Elevated plasma insulin has been found to be an independent predictor of CHD in three prospective studies[160-162]: it may exert atherogenic effects either directly or through disturbances of lipoprotein metabolism[158]. Some of the association of hypertension and non-insulin-dependent diabetes with CHD risk may also be mediated by hyperinsulinaemia.

On the basis of these findings we suggested a unitary hypothesis for the mechanism of high rates of coronary heart disease and diabetes in South Asians overseas[29]: insulin resistance may be responsible for

hyperinsulinaemia, secondary disturbances of lipoprotein metabolism and a high prevalence of non-insulin-dependent diabetes. This metabolic pattern might lead to accelerated atherogenesis either through a direct effect of insulin upon the arterial wall or as a result of disturbances in lipoprotein metabolism. If the hypothesis is correct then measures to reduce insulin resistance, such as weight reduction and increased exercise, may be the most effective means of preventing coronary heart disease in South Asians: this is considered further in Sections 4 and 7.

4. Discussion of methodological issues in the East London Study

The account of the methods of the East London Study in the previous section concentrated on describing material directly relevant to the interpretation of the results. However the problems encountered in the project raise some wider issues relevant to the planning of future work. This section discusses these problems and the possibilities for resolving them.

4.1 Why study the health of of migrants and ethnic minorities?

The term 'ethnic' is used here to denote groupings to which people identify themselves as belonging on the basis of shared physical and cultural characteristics. Ethnic differences in health, like class differences, provide a model in which to generate and test aetiological hypotheses. Apart from this fundamental purpose, studies of social and cultural variation are also useful for defining high-risk groups, identifying pathways for intervention, and planning of services.

Migrant studies have specific uses[163]. Studies of first-generation migrants can be used to validate international differences in disease rates: for instance, the low coronary mortality of French and Italian immigrants to England and Wales supports the view that the low rates reported in their country of origin are real and not just a result of different death certification practice[15]. Comparison of disease rates in migrants with rates in their countries of origin can help to elucidate the contribution of environment to these international differences: thus studies of Japanese migrants to the United States have demonstrated that differences between these countries in cancer and ischaemic heart disease rates are of environmental rather than genetic origin[126,164,165]. By examining disease rates according to age at migration the age at which risk of disease in later life is 'set' can be determined. For instance, low rates of multiple sclerosis have been reported in those who migrated from Europe to South Africa before age 15 compared with those who migrated at later ages[166]: it has been inferred that the disease is a consequence of exposures in childhood.

The post-war influx of immigrants to Britain presents unrivalled

opportunities for research into the health of different groups in the population. In the United States such research is hampered by the lack of a comprehensive health service covering the most disadvantaged groups, while Scandinavian countries which have such coverage do not have large immigrant communities. To take full advantage of these opportunities it is necessary to study first-generation migrants as well as their British-born offspring. Between these two generations disease rates are likely to change markedly. The young adults who formed the majority of migrants to the UK in the 1950s and 60s are now entering middle age when the conditions which make up the leading causes of death become common.

Accurate and meaningful routinely collected health data are fundamental to epidemiological research and to the practice of community medicine. It is, for instance, difficult to evaluate the performance of a local health service in preventing strokes or deaths related to diabetes without standardizing for ethnic origin. Access to statistics on housing, employment and health by ethnic group is also of direct value to ethnic minority communities in identifying discrimination. Without Census denominators these statistics cannot be compiled: only in perinatal data is it possible to calculate rates from a built-in denominator. At present the only published Census statistics giving ethnic breakdowns at small area level relate to OPCS's category of 'New Commonwealth and Pakistan (NCWP) ethnic origin' based on country of birth of heads of household. This is intended to be a measure of the 'non-white' population though it includes Cypriots and Maltese who in the Labour Force Survey normally describe themselves as 'white'[167]. Attempts to include a question on ethnic origin in the 1981 Census were abandoned: the results of a pilot study for the 1991 Census, which included an ethnic question, are awaited.

Other government surveys of the British population have devised their own systems: for instance the OPCS General Household Survey classifies people as either 'white' or 'coloured' whereas the Department of the Environment's National Dwelling and Housing Survey asks individuals to assign themselves to one of seven 'racial groups'. A similar system is used for the OPCS Labour Force Survey. None of these surveys use a large enough sample for accurate breakdown by age at small area level.

The construction of a standard classification for recording ethnicity in the Census, death registration and the National Health Service would be of considerable value: this is unlikely to happen without a clear lead from researchers and other professionals.

4.2 Uses of metabolic measurements in epidemiology

This study concentrated on measuring metabolic and physiological factors which were likely to predict CHD incidence and mortality, rather than attempting to study causes directly. The purpose was to identify possible mechanisms for high CHD rates in South Asians so as to direct further studies of the underlying causes. This emphasis on pathophysiologic mechanisms has been widely adopted in cardiovascular epidemiology, sometimes to the point where study of possible causal factors in the social environment is excluded. One reason is that the measurement of long-term environmental exposures such as diet is difficult. The understanding of the relation between diet and CHD rests on a hypothetical causal chain: dietary fat intake causes elevated plasma cholesterol which causes the disease. Direct evidence for this is scarce. It is difficult to detect an association between diet and CHD within populations: the variation of dietary fat intake between individuals is of similar order to the variation between measurements on the same individual on different occasions: in consequence the statistical power to detect an association between diet and disease risk is low unless there are repeated measurements or the population is heterogeneous. The ability of dietary fat intake to explain variation in CHD rates between populations, the experimental demonstration that increasing dietary fat increases plasma cholesterol, and the observational evidence that plasma cholesterol predicts CHD provide indirect evidence for this central dogma of cardiovascular epidemiology. We considered a diet survey as part of this study but decided it would be too difficult: the low literacy rate would have made it difficult to obtain weighed diet records or household food inventories without more resources than were available to us.

4.3 Choice of study design

A case-control design for investigating the aetiology of CHD in South Asians was considered at an early stage but eventually rejected, for two reasons. First, it would have answered the wrong question. We are

seeking to explain the difference in CHD rates between populations whereas case-control methods are used for investigating factors associated with disease within populations. Second, the exposures we are interested in - blood pressure, metabolic measurements, diet, psychosocial factors - are affected by the onset of symptoms and past exposure cannot be assessed in a manner free from bias. For this reason case-control studies have been used in cardiovascular epidemiology only to study easily quantifiable past exposures such as use of oral contraceptives or stable characteristics such as genotype. One innovation has been the measurement of composition of subcutaneous fat samples, which are not affected by disease of recent onset, to assess the relationship between past dietary intake of essential fatty acids and the risk of myocardial infarction[168]. This design was considered but the results from north-west London[18] suggested that deficiency of dietary linoleic acid was unlikely to explain the excess CHD risk in South Asians.

The cost of mounting a large cross-sectional or cohort study made it out of the question until more preliminary work had been done. The design chosen was the simplest one available to test hypotheses about the reasons for the high rate in South Asians: a correlational study comparing risk factor levels between two populations having different disease rates. A model for this was provided by the Edinburgh-Stockholm Study, designed to investigate reasons for the differences between Scotland and Sweden in CHD mortality rates[169]. By comparing the distributions of risk factors in relatively small samples of men randomly chosen from the populations of each of the two cities, it was possible to reject an explanation based on serum cholesterol levels and and to suggest several new ones: disturbances of lipoprotein metabolism, deficiency of essential fatty acids, insulin resistance, short stature, and low physical fitness.

One limitation of this type of study is that any comparison of a large number of variables in two populations is likely to uncover numerous differences in possible risk factors to which the difference in disease rates can then be attributed. Comparisons between South Asians and the native British population are exceptional in that several of the established risk factors for coronary heart disease - smoking, plasma

cholesterol, blood pressure and haemostatic activity - differ in the opposite direction to the difference in CHD rates. The effect is to break the confounding of these factors with other exposures, and to isolate for study whatever risk factors are higher in South Asians than Europeans. Another limitation is the possibility of 'ecological fallacy': the false inference that assumption that associations at the population level apply to individuals. An association between national suicide rates and national income per capita, for instance, would not necessarily mean that within each country those with higher incomes were more likely to commit suicide. In cardiovascular epidemiology the risk factors which predict CHD within populations are fairly well characterized: when such factors are found to differ between populations there is therefore some basis for hypothesizing an explanatory role.

4.4 Problems in East London and lessons learnt

This study presented a number of special problems: social deprivation affecting the study population, use of an appropriate sampling frame, gaining acceptance from the community and an adequate response rate, and conducting fieldwork under conditions of racial tension in an inner-city area.

4.4.1 The Bangladeshi community in Tower Hamlets

Men from the Sylhet region of East Pakistan were recruited as seamen on British vessels and began to settle in England in the mid-1950s. In London they found work in the catering trade and garment manufacture. From the mid 1960s they began to bring their families to join them in Britain: this process is still continuing, often delayed by immigration control procedures. The Sylheti dialect is sufficiently different from standard Bengali for a Sylheti speaker to have difficulty understanding a Bengali interpreter and it has no written form. Most Bangladeshis in Britain are not literate in any language.

Bangladeshis are the most disadvantaged of all the main ethnic minorities in Britain: the difficulties they face have been reviewed in a recent report from the House of Commons Committee on Home Affairs[170]. The Committee identified three underlying causes of the Bangladeshis' problems: recent arrival from the rural peasant society of Sylhet to a metropolitan country, poor command of English, and discrimination. It

noted the consequent restriction of employment opportunities, poor housing and educational difficulties. In Tower Hamlets especially the scale of migration to the borough and the rapid growth of the Bengali population, compounded with the neglect of the housing stock, has created an exceptional housing problem. Competition between different communities for scarce housing has fomented racial hatred.

4.4.2 Sampling frame

Since the validity of the study rested on comparison of South Asians and non-Asians resident in Tower Hamlets the ideal sampling frame would have been a complete population register of the borough. However the technique we were recommended to use for measurement of plasma fibrinogen necessitated taking the blood samples at a site with immediate access to laboratory facilities. To minimize distances between the base at the London Hospital and participants' homes it was decided to limit the sample to those resident in postal districts E1 and E2, the western half of the borough in which the hospital lies and which contains most of the South Asian population. Native British residents who have remained in ghettos predominantly inhabited by immigrants are likely to be less economically active and less healthy than those who leave for the suburbs. Most of the native British in the sample were however resident in Wapping, which has a stable population with few non-Europeans. At the time of the fieldwork the colonization of this area by high-income professionals was just beginning and only a few turned up in the sample.

The use of general practitioners' lists has several advantages. In theory it is a near-complete population register, an approach to subjects can be made by a personal invitation from the GP, subjects ineligible because of other health problems can be excluded in advance, and follow-up is possible. In this study it was a source of serious difficulties. The absence of age-sex registers in two of the practices made it necessary to conduct a manual sampling procedure directly from the record cabinets, in one practice under cramped conditions. To ensure that the sample was not biased towards those who consulted frequently and therefore had thicker envelopes, a two-stage procedure was adopted. From each row of envelopes in each drawer of the filing cabinet a folder was selected as follows: digit (m) was selected from a

random number table, the distance (m/10 x length of drawer) was measured from the front of the drawer, and the envelope at this point lifted. The next digit (n) between 5 and 9 was selected from the random number table and a further n envelopes were counted from the lifted envelope towards the back of the cabinet, The first eligible subject in the row from this point onwards was chosen.

This was time-consuming and it was difficult to stratify the sample evenly between age groups, especially when sampling Bangladeshi women. Many subjects were uncertain of their dates of birth though most were certain of at least the year in which they were born. Even in those practices which had compiled age-sex registers it proved necessary to check each address in the register against the clinical record envelope. Outside Wapping, fewer than one-third of addresses in practice records were correct. Use of postcode directories to add full postcodes helped to correct mistakes in the recording of addresses and to exclude some which no longer existed.

Inner-city populations are generally mobile but the inaccuracy of address records in Tower Hamlets has been exacerbated by the movement of the native British population to the suburbs and the chaotic state of the borough's housing: it is common for two or three Bangladeshi families to share a single flat as sub-tenants and when subsequently homeless to to be placed in hotels in other parts of London. Extended visits to Bangladesh were another reason for absence. After the extent of the problem became clear, subjects who had not consulted since 1982 or whose last attendance was for cholera and typhoid immunization were excluded: this reduced the proportion of incorrect addresses.

Many respondents stated that they had not received the letter of invitation. In some blocks of flats we discovered that the Post Office had placed notices to inform residents that letters would no longer be delivered because of obstruction of the stairwells by refuse. Sending out invitations by recorded delivery would have been one way of ensuring that all letters were delivered and letters to those no longer resident were returned: in future surveys in other populations we plan to do this. In this study the language barrier between Bangladeshi householders and postmen might have made it less useful. The recording

of patients' phone numbers would have saved considerable work: only one practice had done this.

We hope that in future work it will not be necessary to study populations living in such unstable conditions as in this study. If it were to be necessary we would seriously consider taking a separate census first in a small area and basing the sample on it rather than on any extraneous population register such as GP lists. The transfer of Family Practitioner Committee records to computers, now in progress, may help to improve the accuracy of address records, if duplicates are removed and annual checks made by recorded delivery letters.

4.4.3 Community acceptance and response rate

Difficulties in obtaining a satisfactory response rate were anticipated and the initial advice of other workers who had attempted to conduct research in the Bangladeshi community was not to attempt this study. Success in field surveys depends upon recruiting fieldworkers who are acceptable to the community and obtaining the help of key individuals whose endorsement will help to reassure doubtful respondents[171]. Clergy in the local mosque helped with announcements at prayer meetings and displaying posters. Few Bangladeshi subjects returned their appointment slips, the problem being that they could not read either English or Bengali. The response rate in this group depended on house-to-house calls. Our Bengali-speaking interviewer was accompanied by the writer on most of these visits since it would have been unacceptable in this community for a Muslim woman on her own to visit all-male households. To make house-to house calls easier the addresses were indexed by postcode and invitations were sent out in batches grouped by postcode sector. Finding addresses on council estates was difficult: many blocks of flats were no longer identifiable by lettering on the walls of the buildings. Maps at the entrances to the estates had faded to illegibility.

The final stage response rate of 66% did not differ between Bangladeshis and non-Asians. In practice Bangladeshis seldom refused at the interview stage but frequently failed to turn up to their clinic appointments: native British subjects were more likely to refuse at the

interview stage but seldom failed to make their appointments. Attendance of Bangladeshi women was particularly low: husbands were sometimes reluctant for their wives to take part. The original plan had been to invite spouse pairs, since in this community it is not customary for women to go out without their husbands and there are very few single women so that this would not have biased the sample. In the early part of the study 13 wives of Bangladeshi respondents were interviewed, of whom 8 attended the clinic. The age difference between wives and husbands made it necessary to choose the rest of the Bangladeshi female sample directly from general practitioners' lists: 51 were interviewed and 37 attended. A circular from the local mosque endorsing the study was sent to all non-attenders and their husbands but produced little improvement. Bangladeshi men were frequently concerned about the quantity of blood to be taken and this sometimes necessitated lengthy reassurance: Bangladeshi women, accustomed to antenatal clinics, were less concerned. Several respondents expressed bewilderment at the number of research projects conducted on their community by social scientists.

4.4.4 Racial tension

Racial tension in East London is well-documented and racial attacks are common[172]. Native British respondents in conversation frequently expressed resentment of the local Bangladeshi population, sometimes in violent terms. To have publicized the study in the general population as an investigation of heart disease in Bangladeshis would have made it difficult to obtain cooperation and for this reason the objective of examining ethnic differences was not mentioned in the initial invitation to non-Asian subjects though it was discussed later with respondents who expressed interest in the purpose of the study. We also considered it inadvisable for our Bangladeshi fieldworker to conduct any interviews with native British respondents, though it was possible for the other two members of the team to interview those few South Asians who were fluent in English. This confounding of group comparisons with interviewer differences is of course a methodologic weakness but in the circumstances there was no alternative. Physical safety of the field staff was a particular concern as it was necessary to conduct visits in the evenings. Additional difficulties were encountered with police roadblocks during the disturbances resulting from a newspaper dispute in

Wapping at this time. In further residence-based surveys we plan to concentrate the fieldwork in the summer months so that it can be completed in daylight.

4.5 Future plans

Including the time of all those who worked on this study, the cost per subject was about £150. For large studies to be feasible it is necessary to reduce this unit cost. Using an occupational sampling frame or studying a more stable population with a high proportion of owner-occupiers will help. If literacy had not been such a problem we could have used a self-administered questionnaire in this study, with consequent saving of interviewer time and particularly less necessity for working unsocial hours. The use of a mobile trailer which parked close to the immediate area of study could have helped to improve response rates: however equipping such units with adequate space, heating, running water, and power supplies to run a centrifuge is not cheap. Lack of suitable premises close to the study area has continued to cause difficulties in our current investigation.

5. Insulin resistance and risk of coronary heart disease in South Asians and Europeans - the Diabetes and Coronary Risk Study

5.1 Background of the project

5.1.1 The insulin resistance hypothesis

On the basis of our findings in East London we formulated a specific hypothesis: insulin resistance is responsible both for high rates of diabetes in South Asians and, by causing hyperinsulinaemia and secondary lipoprotein disturbances, for high rates of CHD. The only possible design to test this hypothesis definitively is a large prospective study including both South Asians and a comparison group. Initial test of the hypothesis will be available from cross-sectional analyses and more definitive results will be available at follow-up.

A secondary objective is to find the cause of insulin resistance in South Asians, or at least to identify how to prevent it, since if the high CHD rates are related to insulin resistance, environmental influences upon this pathway offer the best chance for prevention of CHD in South Asians. There has been relatively little research on this even in European populations: existing data point to the importance of body fat pattern, physical activity and dietary carbohydrate.

5.1.2 Central obesity and insulin resistance

The best characterized determinant of insulin resistance is body fat pattern[151,173,174]. Central obesity is strongly associated with insulin resistance and predicts both CHD[174-176] and diabetes[177]. In planning the new study it was necessary to review this work in detail.

Modern interest in regional adiposity dates back to the clinical observations of Jean Vague from 1947 onwards, who reported that an 'android' pattern of obesity - fat deposition mainly on the upper part of the body - was associated with coronary heart disease, hypertension and non-insulin-dependent diabetes[178]. This was contrasted with 'gynoid' obesity - fat deposition mainly on the hips and thighs - which was associated only with 'mechanical' circulatory disorders such as varicose veins. These observations lacked statistical analysis and were

ignored for many years: reports of more formal investigations in this field began appearing from 1982 onwards. Clinical studies of the relationship between central obesity and metabolism were reported by Kissebah's group in Milwaukee, Wisconsin[174,179]. Cohort studies were reported from Gothenburg and Paris relating body fat pattern to increased risk of diabetes[177] and cardiovascular death[176,180,181].

Current understanding of the relationships between regional adiposity, metabolism and cardiovasular disease risk is summarized below:-

(i) The associations of metabolic disturbance and cardiovascular disease with obesity are specific to a pattern of fat deposition affecting the abdomen and upper half of the body: fat deposited predominantly on the hips and thighs is not associated with increased risk of coronary heart disease, hypertension or diabetes[176,177,181].

(ii) This pattern of central obesity can be measured by the waist-hip circumference ratio[176,180], waist-thigh ratio[182], or by trunk skinfold thicknesses[181]. Waist-hip ratio correlates strongly with radiographic estimates of the proportion of total body fat sited intra-abdominally[183,184].

(iii) Insulin resistance appears to underlie many of the metabolic disturbances associated with central obesity: glucose intolerance, hyperinsulinaemia, elevated triglyceride and low HDL cholesterol[179,185].

(iv) Sex differences in cardiovascular disease risk may be explicable on the basis of sex differences in body fat pattern: women with high waist-hip ratio are at increased risk of coronary heart disease[176].

(vi) The mechanism of the association between central obesity and insulin resistance is unknown. A direct causal relationship has been postulated, in which free fatty acids released from visceral fat cells into the portal vein cause decreased insulin extraction by the liver or impaired glucose uptake in skeletal muscle[186]. Alternatively the association may be indirect, with central obesity and insulin resistance both resulting from a developmental aberration or a disturbance of sex hormone levels[187].

(vi) The factors determining body fat pattern are unknown. Genetic factors are important but no specific genetic markers have been identified[188]. Sex differences are presumably determined by exposure to sex hormones, not necessarily in adult life. Elevated androgen levels are associated with central obesity and insulin resistance in women but apparently not in men[189].

5.1.3 Physical activity and insulin resistance

Increasing physical activity appears to have two effects: a short-term effect on insulin levels, which lasts for only a few days after returning to previous activity levels[190], and a long-term effect in mobilizing central fat and reducing central obesity which also reduces insulin levels[191].

5.1.4 Diet and insulin resistance

Dietary experiments on subjects with hyperinsulinaemia suggest that the quantity and type of dietary carbohydrate may be more important in determining insulin levels than dietary fat[192,193]: dietary sucrose appears to elevate insulin levels more than equivalent quantities of starch[193].

5.2 Objectives

The specific hypotheses to be tested are:-

(i) that hyperinsulinaemia and glucose intolerance are responsible for high rates of CHD in South Asians compared with Europeans.

(ii) that the high insulin levels, in turn, are related to central obesity, body fat patterning, elevated plasma free fatty acid levels, physical inactivity, and excess dietary sucrose.

5.3 Planning of the sampling protocol

5.3.1 Sample size

To keep the sample size to a minimum the main study will include only men: in this age group the prevalence of CHD in women is low. 'Prevalent CHD' is defined by the presence of at least one of the following three criteria: electrocardiographic signs of 'probable CHD' (Section 4.3.3), positive angina questionnaire or a medical diagnosis of myocardial infarction. The sample size of 3000 men will have 90 percent power to detect at a 5 percent level of significance the difference between a 7.7 percent prevalence of CHD in Asian men and 5 percent in non-Asian men: a relative risk of 1.54 (calculation shown in Appendix C)[194]. From local mortality data for Ealing[23] the crude relative risk is about 1.4 but adjusting for risk factors on which Asians score lower - smoking, blood pressure and plasma cholesterol - in a multivariate analysis is expected to yield an estimate of the effect associated with ethnicity equivalent to a relative risk of 1.6 or more, assuming that the relative risk for prevalent disease parallels that for mortality.

5.3.2 Sampling frame

An occupation-based sampling frame has practical advantages: the relative ease of obtaining fasting and 2-hour specimens and the easier access to a population on a few sites. Although those in employment are likely to be healthier than the general population, this does not necessarily bias comparisons of prevalence of risk factors and their relationship to disease.

The initial plan was therefore to conduct the entire study in industrial populations. As a result of lengthy enquiries four large workforces containing a high proportion of middle-aged South Asian men were identified in West London: British Airways Catering, Nestle, Lyons Tetley and Quaker Oats. Together these workforces contained about 1500 men aged 40-64, of whom about half were South Asian. No other suitable large workforces were found: expense and logistic difficulties precluded looking outside Greater London.

Allowing for a 70 percent response rate, this leaves us with only about

1000 participants available from an industrial sample. Accordingly we decided to add a residential sample from general practices in Southall, where most of the South Asians employed in the four participating companies live. An additional sample from Greenford will make up sufficient numbers of native British participants comparable in socio-economic status to South Asians in Southall.

5.3.3 Planning the data collection protocol

Glucose tolerance test

The use of a residential sample presents a serious difficulty: if participants have to attend for a fasting and 2-hour sample, they will be away from work for about 2½ hours plus travelling time. Even those booked for 7.30 am will not be able to leave for work until 10 am, since blood pressure and ECG recordings cannot be made immediately after a glucose load.

Several options were considered:-

(i) omitting the fasting sample and collecting only a 2-hour sample following a glucose load taken at home, as in the East London study.

(ii) collecting the fasting sample at the first visit and the 2-hour sample on another day following a glucose load taken at home, so that there are two visits but each one is relatively brief.

(iii) running screening sessions at weekends for those unable to take time off on weekdays. This necessitates having sufficient resources to be able to allow staff who have worked at weekends time off in lieu.

By basing the field station within a few minutes' walk of participants' homes, and holding occasional evening sessions for those who could not attend in the morning but were prepared to fast from breakfast-time, it proved possible to attain an acceptable response rate with a protocol including both fasting and 2-hour samples. Most participants return home in the intervening period.

Questionnaire items

The self-administered questionnaire was designed to include the usual items covering demographic background, medical history, smoking, alcohol, and occupation. We wished to obtain data on two other possible risk factors not usually measured in cardiovascular field surveys[102,103]: the degree of acculturation of South Asian participants; and socio-economic status in childhood.

Items developed to measure acculturation were frequencies of eating typical Indian and typical English foods, neighbourhood of residence, use of first language rather than English at home, and frequencies of religious observance at home and at places of worship. To assess socio-economic status at age twelve years, questions about father's occupation, housing tenure, number of people per room at home, and availability of baths or running water at home were included.

Anthropometry

The design required measurements that were quick. reproducible and valid as indices of total adiposity, regional fat pattern, and metabolc disturbance. The development of these measurements was a principal objective of the pilot study.

Devices currently available for ultrasonic measurements of subcutaneous fat were evaluated and rejected as too slow to use under field conditions. Waist and hip circumferences were essential but no agreed anatomic definitions of waist and hip levels exist: two different waist measurements were therefore included, as described in the pilot study. The choice of skinfold measurements was based on the results of the Paris Prospective Study, in which the best predictions of CHD from anthropometric measurements were obtained with ratios of trunk to thigh skinfolds[181]. Since it has been suggested that it is the metabolic activity of intra-abdominal fat that causes the association between central obesity and insulin resistance[186], we chose to include sagittal abdominal diameter in the supine position, on the basis of radiographic studies which show this measurement to be highly correlated with intra-abdominal fat mass[183].

Diet survey

We plan to obtain 7-day weighed diet records from subsamples of the participants in this study, specifically to examine the relationship of insulin resistance to energy intake, percent of energy from fat and carbohydrate, and type of carbohydrate consumed. A random subsample of 30 South Asian and 30 European men without known diabetes, together with a further 25 from the lowest and 25 from the highest quintiles of the distribution of serum insulin in each group will be invited to complete 7-day weighed diet records under the supervision of a nutritionist. This sample size will have 90 percent power to detect at a 5 percent level of significance a 15 percent difference in total carbohydrate intake or an 18 percent difference in total fat intake between any two groups.

Coding and analysis

As in the Whitehall Study[93], 'positive ECG' is defined by the presence of one or more of the following Minnesota codes:

1.1 - 1.3	Q/QS waves
4.1 - 4.4	S-T depression
5.1 - 5.3	T wave inversion or flattening
7.1	Left bundle branch block

ECG criteria for 'probable CHD' are more restrictive: major Q waves (1.1 or 1.2) or left bundle branch block (7.1).

Analysis of the cross-sectional data will include:-

(i) the difference in prevalence of probable CHD between South Asians and Europeans.

(ii) in a multivariate analysis, the extent to which this difference can be accounted for by factors associated with insulin resistance.

(iii) the relationship of insulin resistance to central obesity, elevated free fatty acid levels, self-reported physical activity and diet.

Including South Asian populations at low risk of CHD and diabetes is crucial to identifying possibilities for prevention. We are collaborating with Dr K S Reddy and his colleagues at the All-India Institute of Medical Sciences who are planning a similar survey of urban and rural populations in Delhi, supported by the Indian Council for Medical Research. Use of standardized methods will allow comparison between our results.

6. Pilot study in Finchley

6.1 Objectives

The objectives of the pilot study were:

(i) to test the practicability of the protocol to be used in the main study and in particular to develop accurate and reproducible techniques for the measurement of body fat pattern

(ii) to determine whether the hyperinsulinaemia identified in Bangladeshis was present in other South Asian groups

(iii) to determine the validity, compared with fasting measurements, of measuring plasma total cholesterol, HDL cholesterol and triglyceride levels at 2 hours after a glucose load.

6.2 Methods

6.2.1 Data collection

All men aged over 40 years in an engineering factory in North London were invited to take part: 60 of the 323 names were South Asian. There were 226 participants: a response rate of 70 percent. 47 of the respondents were of South Asian origin: of these 42 spoke Gujarati as their first language and 35 were Hindu. Participants completed a self-administered questionnaire and attended for screening between 7.30 and 10.30 a.m. after an overnight fast.

The self-administered questionnaire included:

Medical history:	history of diabetes, hypertension and CHD including the WHO chest pain questionnaire
Diet:	frequency of eating different animal products, typical Asian foods and typical English foods
Smoking:	cigarettes, handrolled tobacco, pipe and cigar smoking
Alcohol:	based on General Household Survey
Exercise:	frequency of activities grouped into three lists as light exercise, moderate exercise, and vigorous exercise on the basis of calorimetric measurements in the literature[195], supplemented with a question about sweat-inducing activity[196]
Demographic items:	including country of birth of respondent and both parents, first language
Occupation:	sufficient details to allow coding of social class, together with Karasek scale of job demands and job control
Economic status at age twelve years:	father's occupation, housing and land tenure, number of persons per room.

On arrival at the field station the questionnaire was checked and written consent obtained.

After resting quietly for five minutes sitting blood pressure was measured twice with a random-zero sphygomanometer. A 12-lead electrocardiograph was recorded according to the Minnesota protocol. Skinfolds were measured at the following sites: biceps, triceps, subscapular, supra-iliac, and anterior mid-thigh. A Holtain caliper was

used, with readings taken 3 seconds after releasing the jaws. Sagittal diameter of the abdomen at the level of the iliac crests was measured in the supine position with a Holtain anthropometer. Waist circumference was measured (i) as the smallest circumference between the costal margin and the iliac crest, and (ii) as the circumference at a level halfway between the costal margin and the iliac crest in the mid-axillary line. Hip circumference was measured at the level of the greater trochanters. A tape measure 1.5 cm wide was used, drawn to a tension of 600g. Thigh circumference was measured in the standing position at the level of the gluteal fold.

After a fasting blood sample had been taken the participant was given a drink containing 75g anhydrous dextrose to drink under supervision over 5 minutes and instructed to return for a second blood sample 2 hours after starting to drink it.

6.2.2 Laboratory analyses and data processing

Plasma from the fluoride specimens and the EDTA specimens were separated immediately. The clotted specimen was left for at least 1 hour to allow the clot to form before separating the serum. One EDTA specimen was frozen on dry ice and the other specimens were kept at 4°C. All specimens were transferred to the Unit for Metabolic Medicine at Guy's Hospital at the end of the screening session. Plasma glucose was measured in a COBAS analyser by the hexokinase method and serum insulin by radioimmunoassay. HDL cholesterol was separated by heparin/$MnCl_2$ precipitation. Cholesterol was measured by the cholesterol oxidase method in a centrifugal analyser. Plasma for free fatty acids and LDL cholesterol determinations were stored at -70°C: measurements were undertaken at the General Clinical Research Center, Stanford University School of Medicine.

6.2.3 Statistical analysis

Age distribution of participants by ethnic group is shown in Table 27: 40 percent of the participants were aged under 50 years but among South Asian participants this proportion was 66 percent. To control for age the sample was stratified into two age groups: 40-49 and 50-64 years. Waist-hip ratio has been calculated from the average of the two waist measurements except when these two measurements were specifically

compared. Known diabetics are excluded from the analyses of lipid and insulin levels since they did not fast or receive a glucose load. Body mass index, skinfolds,blood pressure, serum insulin, plasma triglycerides, plasma glucose and plasma free fatty acid levels were log-transformed, adding a constant term where necessary to eliminate skewness. The values in the tables have been transformed back to the original units.

Differences between South Asians and Europeans were tested for significance by analysis of variance in least-squares linear models, with age group and ethnicity as categoric variables, and other measurements as continuous variables. To control for the effect of body size relative to the 75g glucose load, the post-load insulin levels have been adjusted for height.

A principal component analysis was used to examine the intercorrelations between the metabolic measurements: this technique is useful for summarizing multivariate data but is not intended to distinguish causal relationships.

6.3 Results

6.3.1 Anthropometry (Table 28)

South Asian men were on average 5 cm shorter and 6 kg lighter than European men: mean body mass index was not significantly different between the two ethnic groups. Three measures of central obesity - subscapular skinfold, suprailiac skinfold and the ratio of sagittal abdominal diameter to hip circumference - were higher in South Asian than European men: the relationship of these differences to metabolism is examined in Section 6.3.4. Differences between groups in waist-hip circumference ratios were not significant. Anterior thigh skinfold thicknesses were greater in South Asian men but arm skinfolds were not different between groups. Average systolic and diastolic blood pressures did not differ between South Asians and Europeans (Table 28).

6.3.2 Lipids (Table 29)

Fasting plasma total cholesterol, HDL cholesterol and triglycerides were

not significantly different between South Asians and Europeans in this small sample. Between fasting and 2 hours, the average change in plasma total cholesterol was a 3% fall: the size and direction of this change did not differ between ethnic groups. Over the same period plasma triglycerides fell on average by 5% in Europeans but rose by 3% in South Asians: this difference was highly significant. The change in triglycerides in response to a glucose load correlated positively with fasting insulin levels, waist-hip ratio and trunk skinfolds but negatively with fasting free fatty acid levels. In a regression model, inclusion of fasting insulin and fasting free fatty acid levels as dependent variables explained about one-third of the ethnic difference in triglyceride response.

6.3.3 Glucose and insulin (Table 29)

Fasting glucose levels were not different between ethnic groups but 2-hour levels were higher in South Asians. Fasting insulin levels were 22% higher and 2-hour insulin levels were 79% higher in South Asians than Europeans. Fasting insulin was not significantly related to height but 2-hour insulin was inversely associated with height: the slope of the regression line was a 3% decrement in predicted serum insulin with each 1 cm increment in height. Adjusting for height reduced the ethnic difference in 2-hour insulin levels from 79% to 56%. Inclusion of waist-hip ratio and trunk skinfolds in the models reduced the ethnic difference in fasting and 2-hour insulin levels to 16% and 49% respectively, but these differences remained significant.

6.3.4 Obesity and insulin levels (Tables 30 and 31)

Waist-hip ratio and trunk skinfolds were the strongest predictors of fasting and 2-hour serum insulin levels, compared with less direct measures of central obesity, such as arm skinfolds and body mass index. Three measures of relative intra-abdominal adiposity were compared for their ability to predict insulin levels: smallest waist circumference, circumference at L3-L4 level and sagittal abdominal diameter at L4 level, each expressed as ratio to hip circumference. The two waist measures were about equally strongly associated with insulin levels. Ratios with hip circumference as denominator were more strongly related to insulin levels than ratios with thigh circumference as denominator. Sagittal abdominal diameter was weaker than waist circumferences as a

predictor of fasting insulin levels but stronger than waist circumferences in its relationship to 2-hour insulin levels.

6.3.5 Free fatty acids (Table 29)

Fasting plasma free fatty acid levels were slightly lower and 2-hour levels were slightly higher in South Asians than Europeans. These differences were not significant but the ratio of 2-hour to fasting free fatty acid levels was significantly higher in South Asians.

The relationship of free fatty acid levels to other metabolic and anthropometric measurements was examined in a correlation matrix (Table 32). Fasting and 2-hour free fatty acids were correlated with each other and with fasting and 2-hour glucose levels. Fasting free fatty acids were correlated with 2-hour insulin levels, fall in triglyceride after a glucose load, and systolic blood pressure. 2-hour free fatty acid levels were correlated with fasting insulin, triglycerides and measures of central obesity. These correlations were equally strong when the European group was considered separately (Table 33).

The correlations were examined in a principal component analysis including all ethnic groups (Table 34). The first two eigenvectors accounted for 43 percent of the variation. Scores on the first factor, which loaded on central obesity and serum insulin, were markedly higher in South Asians: scores on the second factor, which loaded on fasting free fatty acid levels and hyperglycaemia, did not differ between ethnic groups. The third factor loaded mainly on blood pressure.

6.4 Discussion of results of pilot study

These preliminary data on ethnic differences should be interpreted with caution: (i) the South Asian sample was small; (ii) the socio-economic status and degree of acculturation of the Gujarati men in this workforce were not typical of Gujaratis in London, who generally work in non-manual occupations. A serious problem with studies in employed populations is selection for fitness: this selection process may differ between ethnic groups. The factory at which this investigation was conducted was about to close and many skilled employees were leaving to work elsewhere. Native British workers still employed there at the time

of this study are likely to have been older and less fit than those who had left: immigrant workers, having fewer opportunities for mobility, may have been less affected by this reverse 'healthy worker effect'. Since physical fitness is associated with greater insulin sensitivity, such differential selection would have been expected to lessen the metabolic differences between groups.

The results confirm that the tendency to hyperinsulinaemia after a glucose load, first identified in Bangladeshis, is present also in Gujaratis. Although the sample was too small for comparisons of the prevalence of diabetes, and differences in HDL cholesterol and fasting triglycerides did not reach significance, the results are consistent with our hypothesis that a pattern of metabolic disturbances related to insulin resistance occurs generally in South Asians overseas.

The results also suggest that insulin resistance is associated with a tendency to central obesity in South Asians. The failure of differences in body fat pattern to explain more than a small part of the ethnic difference in 2-hour insulin levels in this small sample suggests that either central obesity is not the cause of the metabolic disturbance in South Asians or the techniques used to measure body fat pattern are too inaccurate and too indirect. As an index for comparing central obesity between ethnic groups, waist-hip ratio is open to the same criticism as body mass index: it may confound body fat distribution with body frame type. Skinfold thicknesses measure adiposity more directly but are notoriously inaccurate: studies using computed tomography may be needed to give a definitive answer to the extent to which ethnic differences in insulin resistance may be explained by the relative proportion of body fat sited intra-abdominally.

Waist-hip ratio and the sum of the two trunk skinfolds were the strongest predictors of insulin levels in this dataset, displacing body mass index, arm skinfolds and alternative measures of central obesity such as waist-thigh ratio. It is possible that sagittal abdominal diameter measurements may be better than waist circumference for predicting 2-hour insulin levels. Comparisons of body mass index fail to detect the differences in adiposity between South Asians and Europeans: this index is clearly inappropriate for studies comparing

obesity between ethnic groups, as others have pointed out[60].

Although plasma free fatty acid levels are highly labile and not usually measured outside the metabolic ward, in this dataset they correlate with glucose, triglyceride and blood pressure measurements, with coefficients up to 0.38. This suggests that even under the conditions of field surveys free fatty acid measurements may have sufficient predictive power to be useful in cardiovascular epidemiology.

In laboratory studies elevated free fatty acid levels have been associated with obesity and insulin resistance[197,198]. Two hypotheses to account for this association have been advanced. One is that that insulin resistance is caused by elevated levels of free fatty acids in the systemic circulation blocking glucose uptake by skeletal muscle[186,199]. The other explanation is that both the effect of insulin upon glucose disposal and the suppression of lipolysis in response to insulin are diminished in insulin-resistant individuals[197,198].

In this dataset the absence of an ethnic difference in fasting free fatty acid levels accompanying the difference in fasting insulin is evidence against the hypothesis that elevated free fatty acids cause insulin resistance and hyperinsulinaemia. The alternative hypothesis that insulin resistance affects both pathways is consistent with the smaller percentage fall in free fatty acid levels between fasting and 2 hours in South Asians than Europeans, despite markedly higher 2-hour insulin levels in South Asians.

If these findings are confirmed in the main study they will constitute compelling evidence against the hypothesis that elevated free fatty acids in the systemic circulation are responsible for the insulin resistance which accompanies central obesity: in this case other explanations for the association between central obesity and insulin resistance must be sought.

No population survey including free fatty acid measurements together with other metabolic and clinical measurements has been reported before and there were some unexpected findings. 2-hour insulin levels correlated with fasting rather than 2-hour free fatty acid levels, and

fasting insulin levels with 2-hour rather than fasting free fatty acids. Systolic blood pressure was more strongly associated with fasting free fatty acid levels than with any other variable apart from diastolic pressure: the lipolytic effects of sympathetic nervous activity may underlie this association. It is clear from inspection of the correlation matrix that the associations between free fatty acids, insulin, glucose, triglyceride, HDL cholesterol and obesity cannot all be accounted for in terms of a single common factor. Elevated plasma free fatty acids 2 hours after a glucose load are associated with central obesity, hyperinsulinaemia, hypertriglyceridaemia, low HDL cholesterol, and a rise in triglycerides between fasting and 2 hours. On the other hand, elevated fasting free fatty acids are associated with hyperglycaemia and a tendency for triglycerides to fall after a glucose load. Principal component analysis confirms that at least two factors are needed to summarize the data.

This suggests that there may be two distinct underlying metabolic disturbances:-

(i) a tendency to insulin resistance associated with central obesity, with rise in triglycerides in response to a glucose load, and weakly associated with elevated 2-hour free fatty acids,

(ii) a tendency to hyperglycaemia strongly associated with elevated fasting free fatty acids, and with fall of triglycerides in response to a glucose load. Insulin deficiency may be the underlying mechanism of this second disturbance.

This suggestion, though developed independently, is consistent with Reaven's suggestion[200] that the relationship between insulin resistance and glucose intolerance is mediated by changes in free fatty acid levels. When insulin resistance leads to failure to suppress plasma free fatty acids, hepatic glucose production increases leading to hyperglycemia. In this dataset hyperglycaemia appears to be associated with more strongly with fasting than 2-hour free fatty acids. The principal component analysis suggests that it is only insulin resistance that differs between South Asians and Europeans: the second component, loading on hyperglycaemia and free fatty acid levels, does not differ

between ethnic groups. This hypothesis will be tested in more detail when free fatty acid results are available for the main dataset. The effect of hyperinsulinaemia upon VLDL triglyceride synthesis[145] may explain the tendency of triglycerides to rise after a glucose load in South Asians.

The appropriate adjustment to make for body size when comparing the effects of a standard glucose load between individuals and groups is not clear. Adjustment for body weight confounds the effects of obesity with the effect of body size relative to the glucose load. The rationale for using height to adjust 2-hour insulin levels in this analysis is that since height is uncorrelated with fasting insulin, the inverse association with post-load insulin levels measures only the effect of relative body size.

6.5 Modifications to the protocol for the main study

The unexpected finding of ethnic differences in the triglyceride response to a glucose load have led us to continue measuring triglycerides and cholesterol both at fasting and 2 hours for the main study.

6.5.1 Questionnaire design

Items on the frequency of eating typical Indian foods failed to discriminate between westernized and traditional South Asians: for instance, all Indians in this sample ate dhal almost every day. Initial plans to use a supplementary questionnaire for South Asian respondents were abandoned as this caused difficulties with the rest of the workforce. Questions about residence in a neighbourhood inhabited mainly by others of the same ethnic group were also difficult to use without causing mistrust. Items about use of first language rather than English with spouse and with children appeared to be acceptable and could be used to split the South Asian participants into two approximately equal-sized groups.

Questions about frequency of light, moderate and vigorous exercise were found to be too vague and replaced by more specific questions about physical activity at work, other leisure time and sport. modified from the Baecke questionnaire[201]. The Karasek scale was poorly filled in and time-consuming to check with participants: for the main study it was shortened to three items. Questions about socio-economic conditions at age twelve years sometimes caused offence but were found to be useful in distinguishing those from poorer backgrounds from those who had been relatively affluent during childhood. Many participants were unwilling to describe their living conditions during childhood; explanation of the underlying objectives was necessary.

6.5.2 Anthropometry

It was necessary to use an anthropometrist of the same sex as the participant: the most efficient method was for this fieldworker to dictate the measurements into a tape recorder with remote switch, leaving both hands free.

Accurate positioning of the forearm was essential to reproducibility of biceps and triceps skinfold measurements. The midline of the triceps was found difficult to define with the palm held forwards and for the main study a semi-prone position of the forearm was adopted.

The size of fold grasped was difficult to standardize: the rule adopted was that the fold should be large enough to include subcutaneous tissue not just dermis, but not more than this: where two observers disagreed in duplicate measurements, the observer whose reading had been higher repeated the measurement taking a smaller fold. This training eventually resulted in close agreement between observers. Use of a 5-second rather than a 3-second delay after release of the calipers was adopted for recording skinfolds: this gives better agreement with radiographic estimates of subcutaneous fat (Peter Jones, unpublished).

Since trunk skinfolds were better than arm skinfolds as predictors of insulin levels the biceps skinfold measurement was dropped from the protocol to save time. Lateral, medial and posterior thigh skinfold measurements were also abandoned. Though these measurements were

obtained successfully on policemen in the Paris Prospective Study[181], we found it difficult to obtain them without causing discomfort. The anterior thigh measurement was obtained without difficulties, and a lateral supra-patellar skinfold was added as an extra measure of lower limb fat.

Positioning the tape to measure thigh circumference at the level of the gluteal fold in the standing position was found to be awkward. For the main study the Stanford protocol was used instead: maximal thigh circumference with the foot resting on a chair so as to bend both hip and knee to a right angle.

7. Preliminary results of the Diabetes and Coronary Risk study

This section presents preliminary analyses of the clinical findings on the first 714 men examined in the main study in west London.

7.1 Methods

Field methods have been described in detail in the previous section. The sample was based on three industrial workforces in west London: Quaker Oats, Lyons Tetley, and British Airways Catering. All 1013 men aged over 40 on these sites were invited to participate and 714 were examined, giving a response rate of 70 percent. The response rate did not differ between those with South Asian and those with non-Asian names. Punjabi was the first language for 64 percent of the South Asian participants: 77 percent of Punjabi-speakers were Sikhs. Plasma total cholesterol and triglyceride were measured on both fasting and 2-hour samples: HDL cholesterol was measured on the 2-hour sample only. The strength of association between waist-hip ratio, body mass index and other variables was estimated separately within each ethnic group. For each dependent variable a regression analysis was performed with 10-year age group as a categoric variable. The residuals from this analysis were then entered as the dependent variable in a further regression analysis with linear and quadratic terms in the independent variables. This method ensures: first, that the associations detected are independent of age; and second, that the effects of non-linearity are allowed for when using the percentage of variance explained to compare the strength of associations. The percent variance explained by adding linear and quadratic terms in each variable has been computed first for each variable separately, and second when one variable is added after the other.

7.2 Results

7.2.1 Anthropometry (Tables 36 and 37)

As in the pilot study, mean body mass index was not significantly different between the two ethnic groups. South Asian men showed a striking tendency to central obesity: trunk skinfolds, waist-hip ratio, waist-thigh ratio and abdominal diameter-hip ratio were markedly higher than in European men. Comparison of mean skinfold thicknesses in the

two ethnic groups shows clearly the different distribution of body fat in the two ethnic groups: subscapular and supra-iliac skinfolds were thicker in South Asians, triceps and anterior thigh skinfolds did not differ between groups, and supra-patellar skinfolds were thicker in Europeans. The difference in waist-hip ratio amounted to almost one standard deviation (Figure 4). Average systolic blood pressure was 4 mmHg higher and diastolic pressure was 3 mmHg higher in South Asian than in European men: adjusting for waist-hip ratio and trunk skinfolds in a regression model reduced these differences to 1 mmHg and 2 mmHg respectively. The proportion of manual workers was higher in the South Asian group than in the European group but in neither ethnic group were there any significant differences between manual and non-manual workers in blood pressure, body mass index or waist-hip ratio (Table 39).

7.2.2 Plasma lipids (Table 38)

Plasma total cholesterol was 0.2 mmol/l lower in South Asians than in Europeans (Table 38). Plasma HDL cholesterol was 0.1 mmol/l lower in South Asians: there was no significant ethnic difference in the percent of total cholesterol as HDL. Mean fasting triglyceride was 8 percent higher and mean 2-hour triglyceride was 17% higher in South Asians than in Europeans. As in the pilot study, the effect of a glucose load on plasma triglyceride was different in the two ethnic groups. Between fasting and 2 hours, the mean triglyceride level fell by 5% in European men: in South Asians there was a 2% rise. This change in triglycerides was correlated with fasting insulin levels.

7.2.3 Glucose and insulin (Tables 39-41)

Age-standardized diabetes prevalence was 14.5% in South Asians and 4.7% in Europeans (Table 41). Prevalence of impaired glucose tolerance was also higher in South Asians than Europeans: 8.7% compared with 4.1%. Fasting insulin levels were 20% higher and 2-hour insulin levels were 66% higher in South Asians than Europeans (Table 38). Neither fasting nor 2-hour insulin was significantly related to height or age in either ethnic group.

7.2.4 Relationship of obesity to insulin levels and glucose intolerance (Tables 42-45, Figure 5)

The relationship of insulin levels to waist-hip ratio within each ethnic

group is shown in Figure 5. Inclusion of waist-hip ratio and trunk skinfolds as dependent variables in regression models reduced the ethnic differences in fasting and 2-hour insulin levels to 16% and 49% respectively. Waist-hip ratio was stronger than body mass index as a predictor of triglyceride levels in both ethnic groups: only in South Asians was waist-hip ratio more strongly associated than body mass index with serum insulin levels. Among South Asian men the highest tertile of waist-hip ratio identified individuals with glucose intolerance (diabetes or impaired glucose tolerance) with a sensitivity of 58 percent and specificity of 73 percent (Table 45). By comparison the highest tertile of body mass index identified glucose intolerance with 45 percent sensitivity and 70 percent specificity. In European men this difference in predictive value between waist-hip ratio and body mass index was less striking.

7.3 Discussion of preliminary results of main study

Although at this stage the sample size is too small to analyse for relationships with prevalent coronary heart disease, it is adequate to draw some preliminary conclusions about risk factor distributions.

(i) The syndrome of metabolic disturbances associated with insulin resistance, first identified in Bangladeshis, is present also in Punjabis and Gujaratis. The metabolic pattern includes hyperinsulinaemia, high plasma triglyceride, low HDL cholesterol, and high rates of non-insulin-dependent diabetes. Hypertension is another feature of the syndrome.

(ii) This syndrome is associated with a striking tendency to central obesity in South Asians. In contrast to other ethnic groups with obesity and a high prevalence of diabetes, such as Pimas, this difference in body fat distribution occurs in a group who are not overweight by comparison with Europeans.

(iii) Weight-for-height indices are inappropriate for identifying South Asians at risk of the metabolic consequences of central obesity. More direct measures of central body fat, such as girth ratios or skinfold

thicknesses, are essential in research and clinical practice.

(iv) It is unlikely that the differences of 0.1 mmol/l in mean HDL cholesterol and 0.2 mmol/l in mean triglyceride could explain more than a small part of the 50 percent excess CHD mortality in South Asians compared with Europeans in west London. If insulin resistance underlies the high CHD mortality in South Asians compared with other groups, pathways other than the levels of these lipid fractions must mediate the association between insulin resistance and CHD risk.

8. Conclusion: the insulin resistance syndrome in epidemiological perspective

8.1 The concept of an insulin resistance syndrome

The interpretation proposed in this thesis aligns the writer with an emerging view that non-insulin-dependent diabetes is but one complication of a syndrome of metabolic disturbances caused by insulin resistance and that this syndrome is associated with increased cardiovascular disease risk even in those whose glucose tolerance is normal[200].

Himsworth (1936) first demonstrated that injection of insulin failed to suppress the hyperglycaemic response to a glucose load in maturity-onset diabetics, in contrast to juvenile-onset diabetics or healthy volunteers in whom hyperglycaemia was suppressed[202]. He concluded that a relative insensitivity to the action of insulin existed in maturity-onset diabetics and speculated that a circulating antagonist to insulin might be present. Subsequent work confirmed that insulin-mediated glucose disposal was impaired not only in maturity-onset diabetics but also in impaired glucose tolerance and in many obese or hypertensive individuals with normal glucose tolerance[203,204]. With the development of radioimmunoassays for insulin in the 1950s it became possible to study the relationship between insulin levels and glucose disposal without injecting insulin: population studies were then feasible. The intercorrelations of obesity, blood pressure, glucose intolerance, insulin, triglyceride and HDL cholesterol in population surveys led to the idea of a common underlying disturbance[147,205,206]. Metabolic and physiological studies suggested that hyperinsulinaemia could affect lipoprotein metabolism and blood pressure, and pointed to insulin resistance as the fundamental process. Hyperinsulinaemia is a more consistent finding in impaired glucose tolerance than in non-insulin-dependent diabetes: this is consistent with the view that non-insulin-dependent diabetes represents a late stage in which hyperinsulinaemia and hyperglycaemia leads to islet-cell failure[207]. Reaven has tentatively given the name 'syndrome X' to the associations of glucose intolerance, hyperinsulinaemia, hypertension, hypertriglyceridaemia and low HDL cholesterol with resistance to insulin-stimulated glucose uptake[200]: other writers would include central obesity on this list.

The association of insulin resistance with non-insulin-dependent diabetes and obesity led to the idea that elevated insulin levels might be responsible for the increased CHD risk associated with these conditions. Early studies comparing myocardial infarction survivors with controls found that insulin levels were higher in cases than in controls[208-210]. There are obvious possibilities for bias in case-control studies based on metabolic measurements after the onset of disease. Three prospective studies of the relationship between insulin levels and CHD risk have been reported[95,96,211]. The Busselton study[211] lacked adequate statistical power: at 13-year follow up of the 577 men aged 40-59 there were only 19 CHD deaths. The other two studies were much larger: the Paris Prospective Study, with 126 CHD deaths at ten-year follow-up[95]; and the Helsinki Policemen Study, with 63 new CHD cases at 9½-year follow-up[96]. In both Helsinki and Paris fasting and 2-hour insulin levels were predictors of CHD and the association was non-linear, with most of the excess risk in the highest quintile of insulin levels. These associations were independent of glucose, triglyceride, body mass index, physical activity and blood pressure. HDL cholesterol was not measured in either study. The limitations of multivariate analyses of this kind are discussed later in this chapter.

8.2 Pathophysiology of insulin resistance

The causes of insulin resistance and the mechanism by which it is associated with obesity and lipoprotein disturbances are still poorly understood. Any explanation must account for the association between insulin resistance and central obesity, and for the evidence that correcting obesity by diet or exercise leads to increased insulin sensitivity. This implies that the path of causation runs from obesity to insulin resistance. Most glucose disposal takes place in skeletal muscle rather than in the liver[212] and any postulated mechanism for insulin resistance must therefore involve effects on glucose uptake by muscle. One possible explanation for the association between insulin resistance and obesity is the glucose-fatty-acid cycle[199,213]. In the fasting state free fatty acids, derived from lipolysis in adipose tissue, are the main fuel for skeletal muscle. Free fatty acids block glucose uptake by skeletal muscle: in the fasting state this spares

glucose for other tissues which depend on it. The rise in glucose levels after a meal causes a rise in insulin levels which suppresses lipolysis and accelerates glucose uptake by skeletal muscle. Failure to suppress free fatty acids would cause resistance to insulin-stimulated glucose uptake. In support of this hypothesis, several studies have shown that free fatty acid levels are raised in diabetics even in the presence of normal or raised insulin concentrations[198,213,214]. Obesity is also associated with failure to suppress free fatty acid levels in response to exogenous insulin[215]. Omental fat cells are less sensitive than subcutaneous fat cells to the antilipolytic action of insulin[216]. The association between central obesity and insulin resistance could be explained either by the high lipolytic activity of abdominal fat cells or by the effects of high free fatty acid levels in the portal vein[186]. An alternative explanation for the association between insulin resistance and elevated free fatty acid levels is that resistance to the action of insulin affects both stimulation of glucose uptake and suppression of lipolysis[200].

8.2.1 Effects of insulin resistance on blood pressure

Associations between glucose, insulin and blood pressure have been demonstrated in several population studies[206,217-219]. Steady state infusion studies have demonstrated that hypertensive patients are more insulin resistant than controls[220,221]. Experimental evidence of a cause and effect relationship is available from animal studies: feeding rats with fructose produces insulin resistance, hyperinsulinaemia and a rise in blood pressure[200]. Two possible mechanisms for an effect of insulin on blood pressure have been suggested: stimulation of sympathetic nervous activity; and promotion of sodium reabsorption in the kidney. For the purposes of this discussion it is sufficient to note that, unlike the association with lipoprotein disturbances, the association between insulin resistance and hypertension is probably mediated by a direct effect of insulin.

8.2.2 Effects of insulin resistance on lipoprotein metabolism

Transfer of lipids from the liver to peripheral tissues is accomplished by lipoprotein particles. Triglyceride-rich VLDL particles are synthesized by the liver and catabolized in peripheral tissues by lipoprotein lipase to intermediate-density (Sf 12-60) and low-density

lipoprotein particles: in this process triglyceride is delivered to the tissues. The low-density lipoprotein fraction is heterogeneous and distinct subclasses of particles have been identified in normal individuals[222]. The cholesterol-rich LDL particles are taken up by specific receptors: this process delivers cholesterol to cells. Atherogenesis does not appear to depend on receptor-mediated uptake of LDL since individuals with LDL receptor deficiency are at high risk of CHD.

Insulin has two main actions on lipoprotein metabolism: it affects VLDL triglyceride synthesis, and it increases lipoprotein lipase activity. It is the effect on VLDL synthesis that is believed to underlie the association between insulin and triglyceride levels[145]. Several lines of evidence indicate that hyperinsulinaemia alone does not stimulate VLDL triglyceride synthesis. Insulin inhibits VLDL triglyceride by cultured rat hepatocytes when glucose alone is supplied as the substrate[223,224]. Euglycaemic insulin infusions lower triglyceride levels in normal individuals[225]. Insulinoma patients have extremely low triglyceride levels. The principal substrate for hepatic triglyceride synthesis is free fatty acid[226] and it appears that the combination of elevated insulin and free fatty acid levels does cause hepatic synthesis of VLDL triglyceride[145,227]. If insulin-resistant individuals respond to a carbohydrate load with hyperinsulinaemia and also fail to suppress free fatty acid levels to the same extent as insulin-sensitive individuals, increased VLDL triglyceride synthesis would occur.

Elevated VLDL triglyceride levels in the insulin resistance syndrome are accompanied by effects on the lipoprotein fractions produced by catabolism of VLDL: IDL and LDL. The precise mechanisms of these associations are not understood. VLDL triglyceride and IDL levels are highly correlated and increased levels of the IDL fraction are present in diabetics[228]. In non-diabetic individuals IDL levels are associated with central obesity[229]. An LDL subclass pattern characterized by a preponderance of small, dense LDL particles is strongly associated with central obesity, elevated VLDL triglyceride, low HDL cholesterol, and elevated IDL levels[230,231]. These small dense LDL particles contain less cholesterol than the other main LDL subclasses so that the presence of this pattern is associated with elevation of the ratio of apoprotein

B to cholesterol in the LDL fraction. It is suggested that these small dense LDL particles are produced from VLDL and IDL particles by repeated cycles of triglyceride enrichment and lipolysis[222].

An inverse association between triglycerides and HDL levels is a consistent finding in population surveys and clinical studies. The association appears to be specifically with the HDL_2 subfraction. Several possible mechanisms have been suggested: the most plausible is that triglyceride is transferred from VLDL to HDL particles by the action of lipid transfer protein[149,232]. The triglyceride-enriched HDL_2 articles produced in this process are rapidly catabolized by hepatic lipase, depleting HDL levels. Another possible effect of elevated triglyceride levels is on fibrinolytic activity: elevated triglyceride levels are associated with elevated plasminogen activator inhibitor levels[233]. This may explain earlier observation of associations between obesity and prolonged clot lysis times[234].

8.3 How could the insulin resistance syndrome cause coronary heart disease?

Based on the pathophysiological relationships outlined above, the insulin resistance syndrome may be considered as a group of disturbances resulting from a single perturbation in a system. This model is summarized in Figure 6. The relationship between central obesity and insulin resistance is the least well-understood of the causal pathways in this model: otherwise there is reasonable evidence for most of the relationships shown. The relationship of this syndrome to cardiovascular risk may be interpreted in two ways. In Reaven's formulation, it is the presence of a 'cluster' of coronary risk factors - hypertension, lipoprotein disturbances and glucose intolerance - in individuals with the insulin resistance syndrome that leads to cardiovascular disease[200]. The assumption is that insulin resistance exerts effects on atherogenesis by several different mechanisms, including effects on insulin, glucose tolerance, blood pressure, triglyceride and HDL cholesterol. An alternative and more plausible explanation is that the insulin resistance syndrome exerts effects on atherogenesis through a single pathway, and that other features of the syndrome predict coronary disease because they are markers for this

process. To justify this radical hypothesis it is necessary to examine the validity of the methods used to identify 'independent' risk factors.

Results of cohort studies of cardiovascular disease are usually analysed as logistic regression models. When all factors are included in the regression model, those which still predict disease significantly are considered to be 'independent' risk factors. Evidence of causal relationships rests on the demonstration of these 'independent' associations. When the measurements included in the model are intercorrelated and labile, this assumption that independent association implies causation is not valid unless repeat measurements have been obtained and the analysis corrected for the effects of within-individual variation. The problem is that the strongest predictive relationships are not necessarily with those factors that are causal but rather with those that can be most reliably characterized by a single measurement. This is because the effect of error in the measurement of the independent variable upon the results of a regression analysis is to bias towards zero the estimate of the slope of the relationship.

An example of this situation in cardiovascular epidemiology is the relationship of plasma triglyceride and HDL cholesterol levels to CHD risk. In multivariate analyses low HDL is a consistent 'independent' predictor of CHD whereas elevated triglyceride is not an independent predictor (at least in men). This has been interpreted as evidence that the relationship of HDL to CHD risk is causal and the relationship of triglyceride to CHD is not[235]. This does not take account of the differences between HDL and triglyceride in within-individual variability. Plasma triglyceride is highly labile whereas HDL cholesterol levels are relatively stable within individuals. It is possible that HDL cholesterol predicts CHD simply because it is better than a single measurement of fasting triglyceride as a marker for the long-term plasma triglyceride.

It is suggested that this misinterpretation of multivariate analyses has seriously hampered the understanding of the aetiology of cardiovascular disease and led to the identification of spurious 'independent' risk factors, which predict not because they are truly causal but because they are associated with other risk factors which cannot be reliably

measured. Of the many 'independent' risk factors identified, it is likely that only a few are truly causal. This argument applies especially to the labile and intercorrelated disturbances of body fat pattern, metabolism and haemodynamics that comprise the insulin resistance syndrome. We cannot rely on multivariate analyses to distinguish causal pathways between the syndrome and disease. Two alternative approaches can help to break these associations: clinical studies of single defects of lipid metabolism, and epidemiological studies of different groups.

A unique contribution of comparisons between South Asians and Europeans is the ability to isolate the effects of the insulin resistance syndrome for study. The contrast between these two groups breaks the confounding of this syndrome with other established coronary risk factors such as elevated serum cholesterol and hypertension. Comparison of different groups from South Asia helps to break the confounding further: for instance the very low HDL cholesterol found in Bangladeshi Muslims is not seen in Punjabi Sikhs and yet both groups share the same elevated CHD risk. Whatever factors underlie the association between the insulin resistance syndrome and CHD must be unfavourably distributed in all the high-risk South Asian populations.

8.3.1 Possible direct effects of insulin upon atherogenesis

Although there is some evidence from experimental studies that insulin may be directly atherogenic, there are also powerful objections to this as an explanation for the effects of the insulin resistance syndrome[236]. The prospective studies suggest that, as with plasma glucose, the relationship of insulin to CHD risk is non-linear with a threshold of elevated risk at the 80th or 90th centile of post-load insulin level[95,96]. This absence of a dose-response effect suggests that the association may not be directly causal. Insulin is one of the few putative cardiovascular risk factors to have been subjected to a randomized controlled trial: the University Group Diabetes Program. In this study cardiovascular mortality was not higher in the groups treated with insulin than in the group treated with placebo[237]. As reviewed later in this chapter, it is not insulin levels but the associated lipoprotein patterns that differ between men and women. If the insulin

resistance syndrome does have something to do with sex differences in cardiovascular disease risk, the mechanism of action cannot be a direct effect of insulin.

8.3.2 Effects on blood pressure

It is unlikely that the association with blood pressure can be the main mechanism of the effect of its effect on atherogenesis. Randomized trials have failed to yield convincing evidence that treatment of hypertension reduces CHD morbidity and mortality[238,239]. Earlier in this thesis it was demonstrated that differences in blood pressure between some South Asian groups and Europeans are in the wrong direction to explain the differences in CHD risk.

8.3.3 Effects on lipoproteins as a possible mechanism for atherogenesis

The insulin resistance syndrome is associated with disturbances of the concentration or composition of all four main lipoprotein fractions: elevated VLDL, low HDL, elevated IDL and altered composition and size of the LDL particles. In considering which, if any, of these effects could mediate the association between the insulin resistance syndrome and atherogenesis, it is useful to examine the clinical syndromes caused by single defects in lipoprotein metabolism. The most compelling evidence for a direct causal relationship between LDL and atherogenesis is the increased risk in patients with familial hypercholesterolaemia caused by LDL receptor deficiency. In heterozyous familial hypercholesterolaemia LDL levels are markedly elevated but VLDL and IDL levels are normal. In contrast, deficiency of lipoprotein lipase or apo CII (on which the lipase depends) leads to elevated chylomicrons and VLDL triglyceride with low HDL levels and low or normal LDL levels. In these conditions CHD risk is not elevated, although other complications such as pancreatitis occur[240]. Subjects with hepatic lipase deficiency have high levels of VLDL, IDL, triglyceride-enriched LDL and triglyceride-enriched HDL_2. This condition is associated with peripheral vascular disease rather than coronary disease[240].

This clinical evidence strongly implicates the LDL particle in atherogenesis. It also indicates that VLDL particles are unlikely to be directly atherogenic (unless atherogenesis is itself dependent on the action of lipoprotein lipase as Zilversmit[241] suggested). The possible

role of IDLs remains an open question. The compelling evidence relating LDL to atherogenesis directs attention to the effects of insulin resistance on the composition of the LDL particle as a possible mechanism by which the insulin resistance syndrome is related to cardiovascular risk. This has the additional advantage of being the most parsimonious hypothesis: the LDL particle would then be a final common pathway for both the dietary fat-lipid model and the insulin resistance model.

There is some preliminary evidence for the presence of small dense LDL particles, high in apoprotein B but low in cholesterol, as a risk factor for CHD. In a study of angiography patients in Australia, several lipid lipid measurements were compared for their strength of association with coronary disease[242]. The strongest association was with apoprotein B levels in the LDL fraction, rather than with LDL cholesterol or total cholesterol. This finding was not confirmed in another angiography-based study from the same city[243]. More impressive evidence comes from a formal population-based case-control study in Boston, which was specifically designed to test the hypothesis[230]. The presence of an LDL subclass pattern characterized by a preponderance of small dense LDL particles was associated with a relative risk of 3 for myocardial infarction[230]. Similar evidence implicates elevated IDL levels[243-245]. IDL mass predicted the progression of coronary artery disease in hypercholesterolaemic patients participating in an intervention trial[244]. In a study of angiography patients, IDL apoprotein B and IDL triglyceride levels were more strongly associated with coronary artery disease than with levels of the HDL, VLDL or LDL fractions[245]. As emphasized earlier, since these disturbances are highly intercorrelated, multivariate analyses are not necessarily helpful.

8.4 Implications for the understanding of coronary heart disease: how much of the epidemiology of the disease could the insulin resistance syndrome explain?

The arguments above have suggested that the insulin resistance syndrome may provide a unifying explanation for the relationships of obesity, hypertension, glucose intolerance, low HDL and elevated triglyceride to CHD risk. A review of findings in other populations suggests the

possibility that this mechanism may explain not only the high CHD risk in South Asians but also other ethnic differences in CHD rates, such as the low risk among Black American and Afro-Caribbean men.

8.4.1 Relevance to Africans, Afro-Caribbeans and Black Americans

Although no prevalence studies have been reported, mortality data and clinical experience suggest that non-insulin-dependent diabetes is commoner in Afro-Caribbeans in the UK than in the native British population. In Afro-Caribbeans in Trinidad[13] and in Black Americans[246] surveys of diabetes prevalence have been undertaken and the results reported according to modern diagnostic criteria. In African men and women aged 35-69 in urban Trinidad in 1978 the prevalence of diabetes, adjusted to WHO criteria, was 11 percent[13]. In native British men in the UK the prevalence in this age range is about 5 percent[88]. In the United States Health and Nutrition Examination Survey during 1976-80, diabetes prevalence by WHO criteria was 18% in Blacks aged 40-64 and 10% in Whites[246].

If insulin resistance underlies the high rates of non-insulin-dependent diabetes in Afro-Caribbeans and Black Americans, then the hypothesis proposed in this thesis predicts that, other risk factors being equal, these populations would also have high CHD mortality. Data from the UK and the USA suggest that in Afro-Caribbean and Black men the opposite is the case. In England and Wales in 1970-72 the standardized mortality ratio for CHD was 45 in Caribbean-born men and 88 in Caribbean-born women aged 20-69 (England and Wales = 100)[15]. This low CHD mortality rate in Afro-Caribbean men is consistent with morbidity data from a coronary heart attack registry in London[14].

Interpretation of differentials in CHD mortality rates in Blacks and Whites in the United States is difficult because of the social inequalities between Blacks and Whites, reflected in markedly higher all-cause mortality rates among Blacks[247]. Another complication is that most published mortality data do not distinguish Blacks from other non-White groups. In 1977 the ratio of CHD mortality in US Blacks to that in Whites was 0.93 in men and 1.28 in women[248]. High all-cause mortality in deprived inner-city Black communities contributes to this relatively high risk. In Washington DC, which contains an exceptionally

deprived Black population together with a privileged White population, the ratio of CHD mortality in Blacks to that in Whites in 1975 exceeded 2 in men and 3 in women[249]. Three cohort studies of CHD mortality in the USA have included sufficient numbers of Blacks for a comparison with Whites[250-252]. The American Cancer Society cohort was large but based on selection of respondents by volunteers[251]; at 12 years the ratio of CHD mortality in Black men to that in White men was 0.78 (95% confidence interval 0.72 - 0.84). In women the ratio was 1.07 (95% confidence interval 0.98 - 1.17). The MRFIT study was also based on volunteers[250]: at 5 years the relative risk of CHD death in Black versus White men was 0.89, not significantly different from unity. The Evans County Study is the only cohort study of CHD in Blacks to have been based on a population sample but it contained only 866 men aged 40-64[252]. At 20-year follow up the ratio of CHD mortality in Black men to that in White men was 0.86 but this ratio was based on only 31 deaths in Black men.

These data are consistent with the general conclusion that when the effects of social deprivation are discounted, CHD risk is lower in both Afro-Caribbean and Black American men than in the general population of the UK and USA, despite the high prevalence of hypertension in the Black groups. This relative immunity to CHD is not shared by Black women in either country.

There are no published studies comparing the insulin response to a glucose load in Afro-Caribbeans or Black Americans with that in Europeans. In a recent large study of men and women aged 18-30 years in the United States, fasting insulin levels were 13 percent higher in Black than in White men and 45 percent higher in Black than in White women[253]. In men waist-hip ratio was lower in Blacks than Whites (0.82 versus 0.84) but in women waist-hip ratio was higher in Blacks (0.75 versus 0.73). Studies of body fat pattern or insulin levels in older age groups have not been reported. Triglyceride levels are consistently lower and HDL cholesterol levels consistently higher in Afro-Caribbeans or Black American men than in men of European descent(Table 47)[253-258]. In women this difference between Blacks and Whites is not seen, possibly because Black women tend to be more obese than White women[259].

These findings indicate that although diabetes and hypertension are

common in Afro-Caribbeans and Black Americans the other features of the insulin resistance syndrome - central obesity, high triglyceride and low HDL - are not unfavourably distributed in Black men. The differences in lipoprotein pattern between Black and White men are in the opposite direction to that which would be expected if insulin resistance and central obesity were more prevalent in Black men. In women the differences between Blacks and Whites in triglyceride and and HDL cholesterol are less evident. These differences in lipoprotein pattern parallel the differences in CHD risk. The low CHD rates in Black American and Afro-Caribbean men are therefore not inconsistent with the hypothesis proposed here. However the dissociation of glucose intolerance and lipoprotein disturbances in the contrast between Black and White men is puzzling. If insulin resistance does not explain the high rates of diabetes in Afro-Caribbeans and Black Americans, what does? One small study in South Africa suggested that beta-cell secretory capacity in response to a maximal stimulus was less in people of African descent than in Europeans[260]. Even if Blacks are not more insulin-resistant than Whites, this does not explain why triglyceride should be so much lower and HDL so much higher in Black than in White men. A possible explanation is discussed later in the section on sex differences.

8.4.2 Relevance to Pimas and Mexican-Americans

Certain United States populations of Native American origin appear to have a similar metabolic pattern to that found in South Asians but appear to be at low risk for coronary heart disease. Criticism of the hypothesis proposed in this thesis has been based on the apparent dissociation of insulin resistance and CHD risk in Pimas and in Mexican-Americans[236]. The evidence is examined below.

Some of the highest recorded prevalence rates of non-insulin-dependent diabetes occur in Pimas, a Native American group living in Arizona. Prevalence by WHO criteria in Pimas aged 35-64 in 1965-75 was 37 percent in men and 47 percent in women[261]. Pimas are exceptionally obese and the median body mass index in men and women aged 35-44 exceeds 30 kg m^{-2}. No data on waist-hip ratio or other fat distribution measurements have been reported. In a study of volunteers, 2-hour serum insulin

levels were more than twice as high in Pimas as in Europeans, and steady-state metabolic studies have confirmed that glucose disposal in Pimas is resistant to the action of insulin[262]. Results of a survey of plasma lipids in Pimas during 1979-82 have been compared with data for US Whites from the Lipid Research Clinics Prevalence Study[263]. Laboratory measurements were standardized between the studies. Compared with the LRC data, triglyceride levels were higher in Pima men up to age 45 and higher in Pima women up to age 55. HDL cholesterol levels were slightly lower in Pima men and markedly lower in Pima women than in the corresponding White groups.

These data suggest that Pimas share with South Asians the metabolic features of the insulin resistance syndrome: high diabetes prevalence, hyperinsulinaemia after a glucose load. high triglyceride and low HDL cholesterol. One study has suggested that there may also be something unusual about VLDL catabolism in Pimas compared with Europeans: in Pimas a higher proportion of VLDL is catabolized without conversion to LDL[264]. This may account for the relatively low plasma total cholesterol and LDL cholesterol levels in Pimas[263] despite levels of dietary fat intakes which are similar to those of the general population of the US[265].

CHD mortality or incidence rates in Pimas have not been reported, presumably because of unreliable death certification data. Attempts to assess CHD rates in this group were made in a post-mortem series and in a population survey[266]. In a review of 120 necropsy records for Pima men and women aged 40 years and over in 1965-73, 15 cases of myocardial infarction were identified: although the age-standardized prevalence was lower in this series than that reported in a series of autopsies on US Whites, there are obvious difficulties in making comparisons from a retrospective review of autopsy findings. In a population survey reported in 1976, major electrocardiographic Q waves were found in 9 of 351 men aged over 40 years: the age-standardized prevalence was lower than in reported surveys of US White populations but but the difference was not statistically significant. Total mortality in Pimas during 1965-75 was not associated with body mass index except in those with body mass index greater than 40 kg m^{-2}, and in men diabetes did not predict mortality[267]. These findings have been used to argue against a causal relationship between insulin resistance and CHD risk[236].

However, as with inner-city US Blacks, mortality data for deprived groups living on the margin of society cannot be interpreted in the same manner as rates for more cohesive populations. Comparison of the mortality of the Pima cohort during 1965-75 with data for US Whites in 1970 shows that age-specific mortality rates are about three times higher in Pimas than in US Whites (Table 48)[267]. If Pimas die from causes such as respiratory disease, alcoholism and violence then it is not surprising that diabetes and obesity do not predict mortality, or that the prevalence of myocardial infarction at post-mortem is relatively low. Only 240 Pima men aged 40-59 remained on the reservation by 1975[266]. This number is too small for CHD prevalence or incidence to be reliably determined and the true rates of CHD in this group will probably never be known. If CHD rates in Pimas was indeed relatively low, as the electrocardiographic prevalence data suggested, one possible explanation may lie in the differences in VLDL catabolism mentioned earlier.

Prevalence of non-insulin-dependent diabetes in Mexicans in the southern United States is about three times higher than in Anglos (non-Hispanic Whites)[268]. Diabetes prevalence is highest in low-income Mexican groups but these groups also have the lowest skin reflectance values and presumably the highest proportions of Native American genetic admixture[269]. Fasting and post-load insulin levels are higher in Mexican-Americans than in Anglos but may not be as high as in South Asians in the UK. In the San Antonio study the insulin area (area under the insulin curve during a glucose tolerance test) in Mexicans compared with Anglos was 26% higher in men and 31% higher in women (Table 47)[268,270]. Compared with Anglo women, Mexican women had higher body mass index, higher waist-hip ratio, higher serum triglyceride and lower HDL cholesterol levels[268]. Mexican men had higher triglyceride levels but did not differ on the other measures. Plasma total cholesterol levels in Mexican-Americans and Anglos were similar[268].

CHD mortality in Mexican-Americans appears to be lower than the average for US Whites, at least in men. The most recent published data on CHD mortality in Mexican-Americans and Anglos (non-Hispanic Whites) are for Texas, where in 1980 the ratio of CHD mortality in Mexicans to that in Anglos aged 35-64 was 0.81 in men and 1.06 in women[271]. For all-cause

mortality the ratios were 0.97 and 1.00 respectively. Even lower mortality rates were recorded for metropolitan Chicago in 1979-81, where the SMRs for all heart disease in those aged 15-74 were 33 and 58 in Mexican-born men and women respectively (Anglos = 100). Mortality from ischaemic heart disease as a separate category was not reported in this study[272]. The all-cause SMR was 51 for Mexican-born men and 68 for Mexican-born women. Most Mexicans in Illinois had migrated during the previous decade, and selection for fitness in this group may account for the exceptionally low mortality rates.

Similarities and differences between the Mexican/Anglo comparisons in Texas and South Asian/native British contrasts in London are summarized below:-

(i) Prevalence of diabetes is high in both South Asians and Mexicans but the differences between Mexicans and Anglos in the insulin response to a glucose load are smaller than the differences between South Asians and native British.

(ii) Differences between Mexicans and Anglos in waist-hip ratio, HDL cholesterol and triglyceride in Mexicans are seen clearly only in women. When South Asians are compared with the native British population, these differences are seen in both sexes.

(iv) South Asian men have high waist-hip ratio but are no more overweight than in native British men. This dissociation of body fat distribution from overweight is not seen in Mexicans.

(iii) Comparison of CHD mortality in Mexicans and Anglos suggests low rates in Mexican men but high rates in Mexican women. In South Asians CHD mortality is high in both men and women compared with the native British population.

There are several possible explanations for the relatively low CHD rates in Mexicans despite metabolic patterns indicating insulin resistance. One possibility is that the disturbances are quantitatively less than in South Asians: the insulin data suggest that insulin resistance may not

be as extreme in Mexicans as in South Asians, where post-load insulin values are up to twice as high as in the native British population. Another explanation could be that the underlying syndrome in Mexicans is qualitatively different from that in South Asians: Mexicans tend to have generalized obesity, unlike South Asians who have an extreme form of central obesity but are no more overweight than the native British population.

Even if these considerations can explain why the excess CHD risk seen in South Asians does not affect Mexican-Americans to the same extent, they do not explain why the CHD mortality rates in Mexican men should be so much lower than the US average, despite similar average plasma cholesterol levels in Mexicans and Anglos. One possibility is that Mexicans may have been exposed to fewer atherogenic influences during childhood than Anglos. Selection for fitness at migration may also have been important: most Mexican-Americans are recent migrants who have been employed in physically demanding jobs such as farm work. It may also be relevant that Mexican-Americans are of mixed European and Native American descent, unlike South Asians or Anglos who may be more genetically homogeneous. The results of the Trinidad study suggest that mixed genetic origin may confer considerable protection from cardiovascular disease[92]; the biological phenomenon of hybrid vigour is a possible basis for this.

8.4.3 Relevance to other populations at high risk of CHD

Similar findings in other populations at high risk of CHD may be relevant. Edinburgh men in early middle age have a threefold higher from ischaemic heart disease than men in Stockholm: a study of healthy men in these two cities found that the Scottish men had lower HDL cholesterol, higher triglyceride levels and higher levels of insulin after a glucose load than the Swedish men[169]. Aboriginal Australians have exceptionally high prevalence of non-insulin-dependent diabetes[273,274] and also have higher prevalence rates of ischaemic electrocardiographic signs than Australians of European origin[275,276]. However as emphasized earlier it is difficult to interpret CHD rates in extremely deprived populations.

8.4.4 Relation to sex differences

Sex differences in body fat pattern and metabolism

Although the proportion of body weight made up by fat is generally higher in women than in men after puberty, men have a higher proportion of body fat on the trunk and abdomen. Although a central distribution of body fat is associated with hyperinsulinaemia and glucose intolerance in both men and women, there is no obvious sex difference in the insulin response to a glucose load. In population surveys fasting and post-load insulin levels either do not differ between the sexes[277] or are slightly higher in women than men[278]. Similarly there are no consistent sex differences in the prevalence of diabetes and impaired glucose tolerance. In contrast the lipoprotein disturbances associated with the insulin resistance syndrome - plasma triglyceride, plasma HDL cholesterol, and the composition of LDL particles - display consistent sex differences, at least in European populations, consistent with the relative immunity of women from CHD. The correlation of triglyceride with glucose and insulin levels is weaker in women than in men[205].

This raises two questions for the insulin resistance hypothesis. First, if central obesity causes resistance to the action of insulin on glucose uptake, why are there no sex differences in fasting and post-load plasma insulin? Second, if sex differences in body fat pattern are responsible for sex differences in lipoprotein levels, how does this happen in the absence of a difference in insulin levels?

The absence of sex differences in the insulin response to a glucose load may be explained by the existence of two equal and opposing factors: greater insulin sensitivity of skeletal muscle in women but a greater mass of skeletal muscle available to dispose of a glucose load in men. When obese men and women were matched for the proportion of body weight made up by fat, fasting and post-load insulin were higher in men than in women[151]. Levels of insulin, triglyceride and blood pressure in men at each level of body fat mass were equivalent to those of women with 20 kg more body fat. In a small study measuring steady-state glucose disposal directly in 11 men and 13 women in Finland, the rate of glucose disposal maintained by an insulin infusion was equal in men and women[279]. However in the women fat accounted for a higher proportion of body

weight than in the men, so that the rate of glucose disposal per kilogram of muscle tissue was estimated to be 45% higher in women than men.

A possible explanation to link sex differences in body fat pattern with sex differences in lipoprotein levels is a sex difference in the ability of insulin to suppress free fatty acids. The metabolic studies discussed earlier indicate that the combination of hyperinsulinaemia and failure to suppress free fatty acid levels stimulates VLDL triglyceride synthesis, and that central obesity may be associated with failure to suppress free fatty acids as well as resistance to insulin-mediated glucose disposal. The higher VLDL triglyceride levels in men than in women could therefore be explained by higher post-load free fatty acid levels, in turn caused by the more central distribution of body fat in men. This hypothesis depends on demonstrating that post-load free fatty acid levels are lower in women than in men. No large studies of this in adults have been reported; one study of 12 volunteers found that free fatty acid levels were significantly lower in women than men after a standard breakfast[280]. A similar dissociation between the action of insulin upon glucose disposal and the ability to suppress free fatty acids could explain the relatively favourable lipoprotein pattern in US Black and Afro-Caribbean men despite high prevalence of diabetes in these groups.

Central obesity, glucose intolerance, triglyceride and HDL as CHD risk factors in men and women

Although only a few prospective studies of CHD contain sufficient numbers of women for comparison between sexes of the strength of association of CHD risk factors, it appears that risk factors associated with the insulin resistance syndrome, such as central obesity, glucose intolerance and low HDL cholesterol, are especially powerful predictors of CHD in women. Prospective studies of waist-hip ratio and CHD have been reported from Gothenburg[176,180]. CHD incidence was examined at 13-year follow-up of a cohort of 792 men aged 54 years [180] and myocardial infarction incidence was examined at 12-year follow up of a cohort of 1462 women aged 38-60[176]. The analyses were based on small

numbers of events (91 new CHD cases in the men and 29 first myocardial infarctions in the women). From the published data it is possible to calculate for each study a ratio for incidence rates in two groups: those whose waist-hip ratios were in the highest 40 percent of the distribution, and those whose waist-hip ratios were in the lowest 40 percent of the distribution. This ratio was 1.4 in Gothenburg men and 7.1 in Gothenburg women[176,180]. Although the numbers are small and the measurement techniques and end points were different in the two studies, this suggests that central obesity may be a more powerful risk factor in women than in men.

In the Framingham Study the relative risk for CHD in diabetics compared with non-diabetics was 2.4 in men and 5.1 in women at 18-year follow-up[281]. Lipoprotein fractions were measured on 2815 men and women in Framingham in 1969-71: analyses of the relation of CHD incidence to lipoprotein levels in each sex have been reported but the number of cases and length of follow-up in this subset of the original cohort are not given[282]. In univariate logistic regression analyses HDL cholesterol, triglyceride, and relative weight were stronger predictors of CHD risk in women than in men; the strength of association between LDL cholesterol and CHD risk was about equal in men and women (Table 48)[282]. The only other large prospective study of the relation of HDL cholesterol to coronary risk in both men and women is the Donolo-Tel Aviv study, with 291 events in men and 86 events in women[283]; a direct comparison between men and women of the strength of association of HDL with CHD risk has not been reported for this dataset. A study of coronary angiography patients also found that plasma triglyceride was more strongly correlated with severity of disease in women than in men[243].

These results suggests that high waist-hip ratio, diabetes, high triglyceride and low HDL cholesterol are asociated with higher relative risks for CHD in women than in men. The effects of central obesity or diabetes are sufficient to abolish the sex difference in CHD risk. This suggests that the insulin resistance syndrome may be the principal cause of sex differences in CHD risk. This hypothesis is supported by examination of the patterns of sex differences in CHD risk in South Asians and Blacks. In both these groups sex differences in triglyceride

and HDL levels tend to be less than in Europeans. In effect, Black men have the lipoprotein pattern of European women, while South Asian women have a lipoprotein pattern resembling that of European men. This attenuation of sex differences in lipoproteins in Blacks and South Asians parallels the attenuation of sex differences in CHD risk.

8.5 Evolutionary considerations

In Section 1 brief reference was made to the 'thrifty genotype' hypothesis first developed by Neel[133]. Although his original suggestion for a pathophysiological mechanism has been abandoned, the general idea remains plausible: genes which confer high risk of non-insulin-dependent diabetes in developed countries may have been selected for under conditions of food scarcity and high physical activity levels. It is possible to reformulate this hypothesis to explain the development of the insulin resistance syndrome. A tendency to develop obesity when food was abundant would have obvious advantages for surviving food scarcity. Central body fat, being more metabolically active and causing less interference with locomotion than peripheral fat, would allow energy to be mobilized quickly. Under conditions of starvation, resistance to the action of insulin in suppressing lipolysis and stimulating glucose uptake by muscle would ensure that free fatty acids rather than glucose were used to fuel physical exertion: this would spare glucose for the brain, minimizing the need for ketogenesis or gluconeogenesis from protein.

Selective pressure may have operated against the expression of these traits in women, since insulin resistance would have predisposed to gestational diabetes which in the absence of medical care is associated with high perinatal mortality. The requirements of childbearing would have led to selection for fat storage in extra-abdominal rather than intra-abdominal depots. This would have led to the emergence of sex differences in susceptibility to central obesity and insulin resistance.

In isolated populations such as Pimas and Aboriginal Australians, whose survival depended on long desert journeys, it is possible to imagine that selection for the ability to survive starvation would have been powerful. Similar selection pressure may have acted upon the group that

first settled South Asia, perhaps before arrival in the subcontinent. Subsequent urbanization and economic development would be associated with less physical activity and with the availability of a high energy intake in the form of fat and refined carbohydrates: diabetes would have appeared first in the affluent, and later spread through urban populations as energy expenditures fell and intakes rose.

8.6 Implications for prevention in South Asians

The rarity of CHD in rural India indicates that the disease is no less preventable in Indian than in European populations. Strategies for CHD prevention depend on identifying risk factors which are amenable to intervention and which account for a large aetiological fraction of cases. Current strategies for CHD prevention in the UK emphasize avoidance of smoking and reduction of dietary fat and plasma cholesterol. The distribution of these factors, and the possibilities for intervention, in South Asians are reviewed below.

8.6.1 Smoking

Several surveys have shown that South Asian men are less likely to smoke than native British men[18,33,60] and this is also the case for patients with myocardial infarction[22]. The lowest smoking rates are in Sikhs, where a powerful religious prohibition exists: only 3 percent of Sikh men studied in our current survey in west London are smokers. In our survey in north-west London in 1982 34 percent of Gujarati Hindu men were smokers compared with 38 percent of men in the general population. Only in Bangladeshi men (a relatively small group) are smoking rates higher than in the native population[29]. Smoking remains uncommon in all groups of South Asian women, at least in the first-generation migrants among whom CHD is now occurring. Although the association between smoking and CHD risk is not in doubt, since smoking rates are already low in most South Asian communities it follows that policies to control smoking can have only a modest effect on CHD rates in these groups. The epidemiological evidence indicates that high CHD rates in South Asians occur in both sexes and are common to Gujarati Hindus, Punjabi Sikhs and Muslims from Pakistan and Bangladesh. Among Sikhs and among women of all South Asian groups smoking rates are already so low that the effect of smoking control on total CHD rates will be negligible.

8.6.2 Diet and plasma cholesterol

The 1984 report of the Committee on Medical Aspects of Food Policy (COMA) recommended that the average dietary saturated fat intake of the UK population should be reduced from 20 percent of total energy intake (excluding alcohol) to 15 percent, and that the P/S ratio should be allowed to increase from 0.23 to 0.45[284]. The relationships of dietary saturated and polyunsaturated fat to plasma cholesterol, and the relationship of plasma cholesterol to CHD risk underpinned the scientific basis of these recommendations and similar advice from other sources[284-286]. The Committee did not give a target level for the average plasma cholesterol of the UK population but it may be estimated from standard formulae[58] that implementing these dietary changes would have lowered the average plasma cholesterol of the UK population from about 6.1 mmol/l to 5.6 mmol/l in middle age.

There have been two population surveys of dietary intake in South Asian adults in the UK, both in north-west London where Gujarati Hindus make up most of the South Asian population[18,60]. In 1982, saturated fat accounted for 12% of total energy intake in South Asians compared with a national average of 18%[18]. The P/S ratio was 0.85 compared with 0.28 in the UK population. A second survey by another group of investigators in 1985 confirmed the higher dietary P/S ratio in this group: separate data for saturated fat intake were not given.

The relationship of dietary fat to cholesterol levels underpinned the COMA recommendations and all similar advice on dietary prevention of CHD. Table 47 shows that, in all groups except Sikhs, average cholesterol levels in South Asians are already below the levels that would be achieved if the COMA recommendations were implemented.

Although diet survey data are available only for Gujaratis, the relatively low average plasma cholesterol levels in Bangladeshis compared with the native British population imply that average saturated fat intakes are low in this group also, if the standard relationship[58] holds. This is not to dispute the COMA recommendations for the native British population but only to point out that they are not necessarily applicable to South Asians, since at least in some groups average dietary saturated fat intakes and plasma cholesterol are already at or

below the levels recommended for the UK population. The Committee specifically stated that its recommendations were not intended to apply to ethnic minorities who already consumed a diet low in saturated fatty acids[284]. Adoption by Gujaratis of the COMA recommendation that saturated fatty acids should account for 15 percent of energy intake would mean an increase of average saturated fat consumption from the present level of 12 percent in this group. For effective CHD prevention in South Asians it will be necessary either to set more radical dietary guidelines aimed at reducing the average plasma cholesterol still further, or to identify other pathways amenable to intervention.

8.6.3 Conclusion

While smoking and plasma cholesterol may well predict CHD risk within the South Asian population, they do not explain the excess rates in South Asians compared with other groups. It is possible that dietary intervention aimed at reducing still further the average plasma cholesterol in South Asians would be effective, but the data for Gujarati women suggest that even lowering the average plasma cholesterol to less than 5.0 mmol/l may not be sufficient. If the high risk of CHD in South Asians overseas is mediated by a syndrome of metabolic disturbances associated with insulin resistance, as this thesis suggests, then for those at risk ameliorative measures such as increased physical activity and control of obesity may be the most effective means of preventing CHD. Further studies are required to define the efficacy of these measures in South Asian populations at risk. Understanding attitudes to factors such as obesity and physical activity in South Asian communities may also be necessary for effective intervention strategies.

Appendix A

Table 1 - CHD mortality in South Asians overseas

Country	Period of study	Groups contrasted	Age range	Sex	Rate ratio (age-adjusted)
Singapore	1957-78	Indians/Chinese	20-69	M&F	3
South Africa	1957-77	Indians/Europeans	30-69	M&F	1.5
Uganda	1956-58	S Asians/Africans	30-	M	not given
England	1970-72	S Asians/UK-born	20-69	M&F	1.2 (M), 1.3 (F)
Fiji	1971-80	Indians/Melanesians	20-	M&F	3
Trinidad	1977-85	Indians/Africans	35-69	M	2.6

Table 2 - Mortality from coronary heart disease among South Asians aged 20-64 in London boroughs, 1979-83

(a) Standardized to the average for each borough

	Number of deaths	Standardized mortality ratio (%) and 95% CI		Proportional mortality ratio (%)
Males				
Brent & Harrow (Gujarati)	177	163	138-187	146
Ealing (Punjabi)	118	136	111-161	122
Tower Hamlets (Bangladeshi)	49	118	85-151	132
Waltham Forest (Pakistani)	36	180	121-239	121
Females				
Brent & Harrow (Gujarati)	33	157	103-211	145
Ealing (Punjabi)	30	173	111-235	158
Tower Hamlets (Bangladeshi)	2	(106)	-	(136)
Waltham Forest (Pakistani)	7	(318)	-	(268)

(b) Standardized to the average for England and Wales

	Standardized mortality ratio (%)	95% confidence interval
Males		
Brent & Harrow (Gujarati)	160	136-183
Ealing (Punjabi)	147	120-173
Tower Hamlets (Bangladeshi)	141	102-180
Waltham Forest (Pakistani)	156	105-207
Females		
Brent & Harrow (Gujarati)	160	105-215
Ealing (Punjabi)	206	132-280
Tower Hamlets (Bangladeshi)	(108)	-
Waltham Forest (Pakistani)	(217)	-

Appendix A

Table 3 - Surveys of serum cholesterol in India and Pakistan

Year	Ref.	Place	Population sampled	Age	Mean serum cholesterol (mmol/1) Males	Females
1969	42	Delhi	high-income group		6.2	
			industrial workers	30-59	4.5	
			rural workers		4.8	
1982	43	Delhi	middle to moderate income	31-50	4.5*	4.2*
1959	44	Uttar Pradesh (Agra)	higher socioeconomic		5.3	
			middle income	31-60	4.8	
			lower income		4.5	
1971	45	Uttar Pradesh (Aligarh)	voluntary blood donors	55-	4.7	
			paid blood donors		4.0	
1966	46	Bihar (Patna)	economically privileged	"Adults"	4.9	
1972	47	Bihar (Ranchi)	industrial employees:			
			upper social classes	35-	5.9	
			lower social classes		4.5	
1976	48	Rajasthan (Bikaner)	academics	36-51	5.6*	
			low income		5.1*	
1978	49	Punjab (Jullundur)	hospital outpatients:			
			higher social classes	30-	5.7	
			middle/lower classes		4.4	4.4
1980	50	Andhra Pradesh (Kakinada)	middle & low income groups	31-60	4.6	4.3
1956	51	Tamilnadu (Coonoor)	high socioeconomic	40-49	4.4	
			low socioeconomic		3.3	
1983	52	Tamilnadu	Not stated	30-39	5.7*	5.4*
1982	53	Pakistan (Peshawar)	manual workers	33-48	4.8	

* estimations on plasma or whole blood

Appendix A

Table 4 - Surveys of serum cholesterol in South Asians overseas

Year	Ref No	Place	Population sampled	Age range	Mean serum cholesterol (mmol/1) Males	Females
1959	[7]	Uganda (Kampala)	GP attenders	40-	6.6	
1968	[54]	Guyana (Annandale)	Lower socio-economic	35-54	5.0	5.3
1977	[55]	Trinidad (Port-of-Spain)	Middle and lower socio-economic	35-69	5.9	6.0
1980	[53]	Surinam (Nickerie)	Lower socio-economic	33-48	5.3	
1985	[31]	Fiji	Urban and rural residents	30-69	4.8*	
1987	[152]	Singapore	Pre-employment screening	18-56	4.8	
1982	[18]	England (NW London)	Urban residents	25-65	5.0*	4.3*
1988	[60]	England (NW London)	Urban residents	45-54	5.4	
1988	[29]	England (East London)	Urban residents	35-69	5.5*	5.4*

* estimations on plasma

Table 5 - Surveys of diabetes prevalence in South Asians

Year	Ref. no	Place	Population sampled	2-hour sample cut-off value (mmol/l)	Sex	Age range	Prevalence
<u>Using a 50g glucose load</u>							
1966	77	East Pakistan	Urban and rural residents	Whole blood glucose > 9.5	M & F	30-	1%
1971	84	Orissa	Urban and rural residents	Whole blood glucose > 9.5	M & F	30-	2%
1973	85	Calcutta	low-income outpatients	Whole blood glucose > 10.5 or > 7.8	M & F	30-	5-15%*
1977	13	Trinidad	urban residents	Whole blood glucose > 8.9	M F	35-69	19% 22%
<u>Using a 75g glucose load and 2-hour plasma glucose > 11.0 mmol/l</u>							
1983	81	Fiji	urban and rural residents		M F	35-	25% 22%
1985	86	Durban	residents		M & F	30-	22%
1988	87	Karnatka	urban residents		M & F	35-44 45-64	9% 29%
1988	29	London	Bangladeshis		M & F	35-69	23%
1989	89	Coventry	mainly Punjabis		M & F	40-59	10%
<u>For comparison:</u>							
1985	88	London	mainly European sample		M & F	40-	5%
1989	89	Coventry	Europeans		M & F	40-59	4%

* An interval is given since break-points in the original table lie either side of the cut-off value that would be equivalent to 1980 WHO criteria.

Table 6 - Sample size estimates for East London Study

Risk factor	Hypothetical difference estimated to give 20 percent higher mortality in Asians	Sample size (no. in each group) for $\alpha=\beta=0.05$
Smoking	66 percent of Asians current smokers compared with 38 percent of British men (assuming smoking to carry a relative risk of 2	77
Elevated serum total cholesterol	Mean serum cholesterol 0.8 mmol/l higher in Asian men than British men (Framingham[135])	39
Hypertension	9 mmHg difference in mean blood pressure (Whitehall Study, unpublished data)	82
Glucose intolerance	27 percent prevalence compared with 6 percent in British men (Whitehall Study[93])	49
Elevated clotting factor levels	0.26 g/l difference in mean plasma fibrinogen (Northwick Park Study[134])	140

Table 7: Definitions of drinking categories in the Quantity-Frequency Index[142]

	Number of units on a typical occasion			
Frequency of drinking	1-2	3-4	5-6	7 or more
Most days				
	FREQUENT		MOD-	HEAVIER
Three or four times a week	LIGHT		ERATE	
Once or twice a week				
Once or twice a month	INFREQUENT LIGHT			MODERATE
Once or twice in six months				
			OCCASIONAL	
Once or twice in the year				

Table 8 - Response rate in the East London Study

	No	(Percent)
Attended clinic	253	(66)
Interviewed,		
non-attender	55	(14)
Refused interview	58	(15)
Unfit / in hospital	4	(1)
Not at home	12	(3)

Total resident	382	(100)
Moved away	173	
Dead	2	

Total	557	

TABLE 9 - Numbers attending field station by age, sex and ethnic category

	Male		Female	
Age	Asian	Non-Asian	Asian	Non-Asian
35-44 yr	17	22	3	12
45-54	35	35	38	11
55-64	22	31	4	18
65-69	2	2	.	1
All	76	90	45	42

Table 10 - Daily cigarettes smoked by sex and ethnic category

FREQUENCY (PERCENT)	Male		Female	
	Asian	Non-Asian	Asian	Non-Asian
Non-smoker	17 (18)	54 (55)	50 (78)	28 (61)
1-15/day	55 (59)	11 (11)	14 (22)	7 (15)
16 or more	22 (23)	34 (34)	0 (0)	11 (24)
TOTAL	94	99	64	46

Table 11 - Alcohol consumption pattern by sex and ethnic category, classified as in the General Household Survey[142]

FREQUENCY (PERCENT)	Male		Female	
	Asian	Non-Asian	Asian	Non-Asian
Abstainer	88 (93)	10 (10)	64 (100)	6 (13)
Occasional	0 (0)	6 (06)	0 (0)	16 (35)
Infrequent light	2 (2)	11 (11)	0 (0)	6 (13)
Frequent light	2 (2)	31 (30)	0 (0)	17 (37)
Moderate	1 (1)	21 (20)	0 (0)	1 (2)
Heavier	2 (2)	24 (23)	0 (0)	0 (0)
TOTAL	95	103	64	46

Table 12: Coronary heart disease risk factors by sex and ethnic category. Means (age-adjusted for all variables except height) ± standard errors

	Males		Females	
	Asian	Non-Asian	Asian	Non-Asian
Current smokers (%)	82%	45%	22%	39%
	p<0.001		NS	
Height (cm)	165 ±1	171 ±1	151 ±1	160 ±1
	p<0.001		p<0.001	
Body mass index (kg m^{-2})	23.9 ±0.4	26.6 ±0.4	23.7 ±1.0	26.1 ±0.7
	p<0.001		p=0.06	
Systolic blood pressure (mmHg)	119 ±2	129 ±2	113 ±3	123±3
	p<0.001		p<0.05	
Diastolic blood pressure (mmHg)	78 ±1	81 ±1	75 ±3	78 ±2
	NS		NS	
Plasma fibrinogen (g/l)	3.03 ±0.11	3.14 ±0.10	3.04 ±0.12	3.17 ±0.09
	NS		NS	
Plasma factor VIIc (% of reference value)	90 ±4	105 ±3	97 ±7	99 ±1
	p<0.01		NS	
Plasma total cholesterol (mmol/l)	5.53 ±0.15	6.02±0.13	5.37 ±0.25	6.09 ±0.18
	p<0.05		p<0.05	
Plasma HDL cholesterol (mmol/l)	1.13 ± 0.04	1.43±0.04	1.19 ±0.08	1.45 ±0.05
	p<0.001		p<0.05	
Percent total cholesterol as HDL	21.3 ±1.0	25.3±0.9	22.4 ±1.5	25.2 ±1.0
	p<0.01		NS	
Plasma triglycerides (mmol/l)	2.59 ±0.22	1.76 ±0.13	1.77 ±0.26	1.10 ±0.11
	p<0.001		p<0.01	
Serum insulin (mU/l)	65 ±8	32 ±4	57 ±13	27 ±4
	p<0.001		p<0.01	

Table 13 - Height (cm) by age, sex and ethnic category

Means ± standard errors

	Men		Women	
	Asian	Non-Asian	Asian	Non-Asian
35-44	166 ±1	171 ±2		
40-49			151 ±1	160 ±3
45-54	166 ±1	173 ±1		
50-59			150 ±2	160 ±1
55-	165 ±2	168 ±1		
ALL			151 ±1	160 ±1
ALL	165 ±1	171 ±1		

Table 14 - Weight (kg) by age, sex and ethnic category

Means ± standard errors

	Men		Women	
	Asian	Non-Asian	Asian	Non-Asian
35-44	67.0	74.5		
	±2.5	±2.1		
			40-49	58.6	67.3
45-54	66.7	80.8		±1.7	±5.3
	±1.9	±2.1		
			50-59	53.0	66.2
55-	63.9	77.3		±2.1	±3.6
	±2.0	±1.9		
			ALL	56.2	66.5
ALL	65.9	78.0		±1.4	±2.9
	±1.2	±1.2		

Table 15 - Body mass index (kg m^{-2}) by age, sex and ethnic category

Means ± standard errors

	Men		Women	
	Asian	Non-Asian	Asian	Non-Asian
35-44	24.2 ±0.9	25.4 ±0.6		
40-49			25.6 ±0.7	26.3 ±2.2
45-54	24.3 ±0.6	26.8 ±0.5		
50-59			23.5 ±0.8	25.8 ±1.2
55-	23.5 ±0.5	27.3 ±0.7		
ALL			24.7 ±0.5	26.0 ±1.1
ALL	24.0 ±0.4	26.7 ±0.4		

Table 16 - Systolic blood pressure (mmHg) by age, sex and ethnic category
Means ± standard errors

	Men		Women	
	Asian	Non-Asian	Asian	Non-Asian
35-44	116 ±4	119 ±3		
40-49			115 ±3	110 ±4
45-54	118 ±3	122 ±2		
50-59			109 ±4	126 ±4
55-	122 ±3	144 ±4		
ALL	112 ±2	122 ±3		
ALL	119 ±2	129 ±2		

Table 17 - Diastolic blood pressure (mmHg) by age, sex and ethnic category
Means ± standard errors

	Men		Women	
	Asian	Non-Asian	Asian	Non-Asian
35-44	79 ±3	78 ±3		
40-49			76 ±2	77 ±2
45-54	78 ±2	80 ±2		
50-59			73 ±2	79 ±2
55-	78 ±3	84 ±2		
ALL	78 ±1	81 ±1	75 ±2	79 ±2

Table 18 - Mean plasma fibrinogen (g/l) by age, sex and ethnic category
Means ± standard errors

	Men		Women	
	Asian	Non-Asian	Asian	Non-Asian
35-44	2.85 ±0.20	2.65 ±0.12		
40-49			3.08 ±0.12	2.94 ±0.16
45-54	3.12 ±0.18	3.41 ±0.21		
50-59			3.19 ±0.22	3.21 ±0.14
55-	3.23 ±0.14	3.32 ±0.13		
ALL	3.12 ±0.11	3.19 ±0.10	3.13 ±0.12	3.12 ±0.11

Table 19 - Factor VIIc as percent of reference value by age, sex and ethnic category. Means ± standard errors

	Men		Women	
	Asian	Non-Asian	Asian	Non-Asian
35-44	97 ±7	105 ±7		
40-49			101 ±8	96 ±12
45-54	85 ±5	104 ±6		
50-59			89 ±5	97 ±6
55-	89 ±6	106 ±6		
ALL	96 ±5	96 ±6		
ALL	89 ±3	105 ±4		

Table 20

Fatty acid composition of cholesterol esters by sex and ethnic category (Means ± standard errors)

	Male		Female	
	Asian (27)	Non-Asian (44)	Asian (37)	Non-Asian (38)
Saturated (%)	14.2 ±0.3	12.8 ±0.2	14.2 ±0.2	12.3 ±0.2
	p<0.001		p<0.001	
Polyunsaturated:				
w6 series (%)	56.6 ±1.4	58.3 ±1.1	55.3 ±0.9	60.1 ±0.9
	NS		p<0.01	
w3 series (%)	2.78 ±0.22	2.23 ±0.17	3.38 ±0.16	2.72 ±0.16
	p=0.05		p<0.01	
Ratio of polyunsaturated to saturated	4.28 ±0.18	4.81 ±0.14	4.21 ±0.14	5.21 ±0.14
	p<0.05		p<0.001	

Table 21: Prevalence of diabetes by age, sex and ethnic category

	Male		Female	
	Asian	Non-Asian	Asian	Non-Asian
35-44	2/17	1/22	1/2	0/12
45-54	10/32	4/34	9/36	0/11
55-64	4/22	3/28	0/3	3/18
All, age-adjusted	22%	10%	23%	4%

Mantel-Haenszel odds ratio Asian/non-Asian = 3.1 ($p<0.01$)

Table 22 - Insulin-glucose ratio (mU/mmol) by age, sex and ethnic category. Known diabetics excluded. Means ± standard errors

	Men		Women	
	Asian	Non-Asian	Asian	Non-Asian
35-44	14.7 ±1.6	6.9 ±0.8		
40-49			12.2 ±1.9	6.8 ±1.2
45-54	15.5 ±2.7	7.9 ±1.0		
50-59			11.8 ±1.8	6.9 ±1.1
55-	15.4 ±3.9	8.9 ±1.7		
ALL			12.0 ±1.3	6.8 ±0.8
ALL	15.2 ±1.6	8.0 ±0.7		

Table 23 - Insulin-glucose ratio (mU/mmol) by time of sampling, sex and ethnic category. Known diabetics excluded. Means ± standard errors

	Men			Women	
	Asian	Non-Asian		Asian	Non-Asian
<105 min	13.7 ±1.2	9.7 ±1.7	<105 min	11.4 ±1.9	10.5 ±2.5
105-134 min	18.7 ±3.6	7.4 ±0.7	105-134 min	13.9 ±2.2	6.6 ±0.9
>134 min	13.4 ±7.5	4.7 ±1.2	>134 min	10.9 ±2.7	3.3 ±0.4
ALL	15.2 ±1.6	8.0 ±0.7	ALL	12.0 ±1.3	6.8 ±0.8

Table 24 - Percent total cholesterol as HDL by age, sex and ethnic category
Means ± standard errors

	Men		Women	
	Asian	Non-Asian	Asian	Non-Asian
35-44	19.6 ±1.3	27.8 ±2.5		
40-49			20.6 ±1.1	28.5 ±3.1
45-54	21.9 ±1.5	24.8 ±1.6		
50-59			20.2 ±0.9	25.8 ±2.0
55-	21.5 ±1.4	23.8 ±1.4		
ALL			20.4 ±0.7	26.7 ±1.7
ALL	21.2 ±0.8	25.2 ±1.0		

Table 25 - Age- and ethnicity-adjusted correlations - men

	Total chol					
HDL chol	-0.149	HDL chol				
Tri-glyceride	0.472 **	-0.381 **	Tri-glyceride			
Insulin	0.064	-0.195 *	0.287 **	Insulin		
Systolic BP	0.192 *	0.050	0.084	0.213 *	Systolic BP	
Diastolic BP	0.103	0.069	0.098	0.181 *	0.686 **	Diastolic BP
Body mass index	0.328 **	-0.210 *	0.411 **	0.352 **	0.234 **	0.315 **

* p<0.05

**p<0.01

Table 26 - Age- and ethnicity-adjusted correlations - women

	Total chol					
HDL chol	0.223	HDL chol				
Tri-glyceride	0.319 **	-0.334 **	Tri-glyceride			
Insulin	-0.065	-0.304 *	0.120	Insulin		
Systolic BP	0.169	0.112	-0.068	0.129	Systolic BP	
Diastolic BP	0.228	0.019	0.012	-0.151	0.498 **	Diastolic BP
Body mass index	-0.118	-0.249 *	0.409 **	0.408 **	0.118	0.015

* p<0.05

**p<0.01

Table 27: Age distribution of participants by ethnic group

Age (years)	South Asian	European	Other
40-49	30	52	8
50-59	10	78	4
60-65	5	37	2
TOTAL	45	167	14

Table 28: Age-adjusted means for anthropometric variables by ethnic group

	South Asian	European	
Height (cm)	167.2	172.8	p<0.001
Weight (kg)	68.6	76.1	p<0.001
Body mass index (kg m^{-2})	24.3	25.3	NS
Biceps skinfold (mm)	5.5	5.4	NS
Triceps skinfold (mm)	11.8	12.1	NS
Subscapular skinfold (mm)	21.5	18.3	p<0.05
Supra-iliac skinfold (mm)	27.5	23.2	p<0.01
Anterior thigh skinfold (mm)	15.9	13.7	p<0.05
Waist/hip ratio	0.933	0.920	NS
Abdominal diameter/hip ratio	2.35	2.26	p<0.05
Systolic blood pressure (mmHg)	127	126	NS
Diastolic blood pressure (mmHg)	81	80	NS

Table 29: Age-adjusted means for metabolic measurements by ethnic group. Known diabetics are excluded.

	South Asian	European	
Fasting plasma cholesterol (mmol/l)	5.79	5.84	NS
2-hour plasma HDL cholesterol (mmol/l)	1.18	1.19	NS
Fasting plasma triglyceride (mmol/l)	1.22	1.12	NS
Change in triglyceride between fasting and 2 hours	+3%	-5%	p<0.01
Fasting serum insulin (mU/l)	9.4	7.7	p<0.05
2-hour serum insulin (mU/l): adjusted for age only	36.1	20.5	p<0.001
adjusted for age and height	32.3	21.2	p<0.01
Fasting plasma glucose (mmol/l)	5.3	5.2	NS
2-hour plasma glucose (mmol/l)	5.3	4.8	NS
Fasting plasma free fatty acids (µeq/l)	364	400	NS
2-hour plasma free fatty acids (µeq/l)	141	127	NS
Ratio of 2-hour to fasting free fatty acid level	0.41	0.34	p=0.06

Table 30

Anthropometric indices of obesity ranked by strength of association with fasting serum insulin (adjusted for age and ethnicity)

	Percent variance explained	Significance level
L3-4 waist / hip circumference ratio	16.1%	p<0.001
Smallest waist / hip circumference ratio	15.6%	p<0.001
Trunk skinfolds (supra-iliac + sub-scapular)	15.6%	p<0.001
Body mass index	14.5%	p<0.001
Abdominal diameter /hip circumference ratio	13.2%	p<0.001
Average waist / thigh circumference ratio	8.5%	p<0.001
Arm skinfolds (biceps + triceps)	6.0%	p<0.001

Table 31

Anthropometric indices of obesity ranked by strength of association with 2-hour serum insulin (adjusted for age and ethnicity)

	Percent variance explained	Significance level
Trunk skinfolds (supra-iliac + sub-scapular)	5.7%	$p<0.001$
Abdominal diameter / hip circumference ratio	4.3%	$p<0.01$
Smallest-waist / hip circumference ratio	4.1%	$p<0.01$
L3-4 waist / hip circumference ratio	3.1%	$p<0.01$
Body mass index	3.1%	$p<0.01$
Average waist / thigh circumference ratio	2.5%	$p<0.05$
Arm skinfolds (biceps + triceps)	2.2%	$p<0.05$

Table 32: correlations between anthropometric and laboratory measurements with all ethnic groups included. (Coefficients > 0.19 significant at $p<0.01$)

	Fasting FFA	2-hour FFA	Fasting insulin	2-hour insulin	Fasting glucose	2-hour glucose	Fasting TG	2-hour TG	Change in TG	HDL chol	Waist-hip ratio	Trunk skinfolds	BMI	Sys BP
2-hour free fatty acids	0.27													
Fasting insulin	0.07	0.20												
2-hour insulin	0.18	0.06	0.57											
Fasting glucose	0.35	0.31	0.36	0.16										
2-hour glucose	0.38	0.24	0.18	0.43	0.47									
Fasting TG	0.17	0.33	0.33	0.29	0.25	0.24								
2-hour TG	0.08	0.34	0.41	0.32	0.23	0.19	0.96							
Change in TG	-0.29	0.08	0.40	0.17	0.06	-0.23	0.07	0.33						
HDL cholesterol	0.07	-0.09	-0.33	-0.21	0.06	-0.07	-0.43	-0.46	-0.25					
Waist-hip ratio	0.05	0.16	0.40	0.23	0.20	0.10	0.37	0.42	0.41	-0.34				
Trunk skinfolds	0.01	0.22	0.41	0.30	0.16	0.21	0.32	0.37	0.34	-0.33	0.55			
Body mass index	0.01	0.13	0.35	0.16	0.09	0.07	0.26	0.29	0.30	-0.30	0.60	0.67		
Systolic BP	0.30	0.18	0.20	0.15	0.12	0.09	0.15	0.11	0.01	-0.01	0.24	0.17	0.25	
Diastolic BP	0.11	0.11	0.09	0.12	0.04	0.02	0.10	0.11	0.11	0.04	0.17	0.15	0.18	0.66

Table 33: correlations between anthropometric and laboratory measurements based on data for Europeans only. (Coefficients > 0.21 significant at p<0.01)

	Fasting FFA	2-hour FFA	Fasting insulin	2-hour insulin	Fasting glucose	2-hour glucose	Fasting TG	2-hour TG	Change in TG	HDL chol	Waist-hip ratio	Trunk skinfolds	BMI	Sys BP
2-hour free fatty acids	0.27													
Fasting insulin	0.08	0.18												
2-hour insulin	0.26	0.06	0.53											
Fasting glucose	0.31	0.30	0.36	0.20										
2-hour glucose	0.38	0.22	0.08	0.41	0.33									
Fasting TG	0.13	0.37	0.27	0.26	0.17	0.16								
2-hour TG	0.06	0.37	0.35	0.27	0.20	0.12	0.97							
Change in TG	-0.25	0.09	0.38	0.08	0.07	-0.22	0.08	0.33						
HDL cholesterol	0.08	-0.10	-0.37	-0.20	-0.04	-0.01	-0.38	-0.42	-0.30					
Waist-hip ratio	0.07	0.20	0.42	0.20	0.23	0.06	0.32	0.38	0.46	-0.34				
Trunk skinfolds	0.04	0.23	0.35	0.21	0.14	0.18	0.28	0.33	0.32	-0.34	0.56			
Body mass index	0.01	0.17	0.36	0.15	0.14	0.05	0.22	0.27	0.38	-0.28	0.63	0.73		
Systolic BP	0.31	0.23	0.22	0.22	0.16	0.15	0.21	0.17	0.11	-0.08	0.32	0.20	0.25	
Diastolic BP	0.05	0.11	0.08	0.17	0.02	0.08	0.16	0.17	0.11	0.00	0.23	0.15	0.18	0.59

Table 34: Principal component analysis of relationships between anthropometric measurements and metabolic measurements related to glucose tolerance

	Eigenvectors		
	1	2	3
Percent of standardized variance explained	30%	14%	10%
	Loadings on variables		
Fasting free fatty acids	0.08	0.51	-.03
2-hour free fatty acids	0.19	0.13	-.01
Fasting insulin	0.36	-.04	-.21
2-hour insulin	0.29	0.20	-.31
Fasting glucose	0.19	0.22	-.25
2-hour glucose	0.17	0.41	-.25
Fasting triglyceride (TG)	0.28	0.08	-.16
Change in TG from fasting to 2h	0.24	-.38	0.02
HDL cholesterol	-.27	0.18	0.26
Waist-hip ratio	0.37	-.21	0.09
Trunk skinfolds	0.36	-.17	0.12
Body mass index	0.33	-.24	0.20
Systolic blood pressure	0.22	0.34	0.48
Diastolic blood pressure	0.19	0.21	0.59

Table 35: Age distribution of participants by ethnic group

	European	South Asian	Afro-Caribbean	Other
Age (years)				
40-49	193	180	16	3
50-59	141	97	25	2
60-66	40	13	4	0
TOTAL				

Table 36: Age-adjusted means for anthropometric variables by ethnic group

	South Asian	European	
Body mass index (kg m^{-2})	25.6	25.9	NS
Triceps skinfold (mm)	10.6	10.5	NS
Subscapular skinfold (mm)	21.5	18.3	p<0.001
Supra-iliac skinfold (mm)	25.4	20.8	p<0.001
Anterior thigh skinfold (mm)	13.1	12.8	NS
Supra-patellar skinfold (mm)	9.3	10.2	p<0.01
Waist/hip ratio	0.971	0.931	p<0.001
Abdominal diameter/hip ratio	2.26	2.17	p<0.001
Systolic blood pressure (mmHg)	126	122	p<0.01
Diastolic blood pressure (mmHg)	81	77	p<0.001

Table 37: Measures of obesity by age and ethnic group

Means with standard deviations in parentheses

		South Asian	European
	AGEGROUP		
Body mass index ($kg\ m^{-2}$	40-49	25.6 (3.6)	25.8 (3.3)
	50-64	25.7 (2.6)	25.9 (3.3)
Total trunk skinfolds (mm)	40-49	50.5 (14.1)	40.5 (14.2)
	50-64	50.0 (14.5)	39.9 (13.8)
Waist-hip ratio	40-49	0.961 (0.054)	0.919 (0.055)
	50-64	0.977 (0.061)	0.937 (0.061)

Table 38: Age-adjusted means for metabolic measurements by ethnic group.
Known diabetics are excluded.

	South Asian	European	
Fasting plasma cholesterol (mmol/l)	5.91	6.16	p<0.01
2-hour plasma HDL cholesterol (mmol/l)	1.12	1.20	p<0.01
Fasting plasma triglyceride (mmol/l)	1.41	1.30	p=0.05
Change in triglyceride between fasting and 2 hours	+1.9%	-5.3%	p<0.001
Fasting serum insulin (mU/l)	9.6	7.7	p<0.001
2-hour serum insulin (mU/l)	30.9	19.9	p<0.001

Table 39; CHD risk factors by social class (manual versus non-manual) and ethnic group:

	European		South Asian	
	Manual (375)	Non-Manual (196)	Manual (248)	Non-Manual (41)
Systolic BP	124	121	125	125
Diastolic BP	77	77	80	83
log BMI	3.25	3.24	3.24	3.22
Total trunk skinfolds(mm)	39	41	50	48
Waist-hip ratio	0.93	0.92	0.97	0.95
Fasting cholesterol (mmol/l)	5.82	6.03 p=0.08	5.64	6.00 p=0.05
HDL chol (mmol/l)	1.16	1.21	1.12	1.03 p=0.05
Fasting TG(mmol/l)	1.49	1.42	1.55	2.03 p<0.01
2-hour TG(mmol/l)	1.40	1.35	1.59	2.09 p<0.01
Fasting insulin (mU/l)	7.5	7.9	9.7	9.7
2-hour insulin (mU/l)	17.0	21.3 p<0.01	29.4	37.2 p=0.09

Table 40: Prevalence of diabetes by age and ethnic group

	South Asian	European
40-49	12% (21/180)	3% (5/193)
50-59	14% (14/97)	7% (10/141)
60-64	23% (3/13)	5% (2/39)

Mantel-Haenszel odds ratio South Asian/European = 3.4
(95% confidence interval 1.9 - 6.1)

Table 41: Age-standardized prevalence of impaired glucose tolerance and diabetes by ethnic group

	South Asian	European
Normal	76.8%	91.1%
Impaired glucose tolerance	8.7%	4.1%
Diabetic	14.5%	4.7%

Table 42: Comparison of waist-hip ratio and body mass index for strength of associations with blood pressure and metabolic variables: percent within-group variance explained after controlling for age
(With this sample size any additional effect accounting for at least 3.2% of the variance in South Asians or 2.5% of the variance in Europeans is significant at $p<0.01$)

	South Asian		European	
	Waist-hip ratio %	Body mass index %	Waist-hip ratio %	Body mass index %
Systolic blood pressure	2.9	2.8	10.8	7.2
Diastolic blood pressure	5.2	7.1	5.5	8.0
HDL cholesterol	1.3	1.9	6.7	5.7
Fasting triglyceride	9.3	5.1	15.0	11.2
Fasting insulin	16.4	14.2	19.0	21.3
2-hour insulin	11.6	2.8	13.6	14.2

Table 43: Comparison of waist-hip ratio and body mass index for strength of associations with blood pressure and metabolic variables: additional percent within-group variance explained by each after controlling for the other.
(With this sample size any additional effect accounting for at least 3.2% of the variance in South Asians or 2.5% of the variance in Europeans is significant at $p<0.01$)

	South Asian		European	
	Waist-hip ratio %	Body mass index %	Waist-hip ratio %	Body mass index %
Systolic blood pressure	0.8	1.0	3.9	0.6
Diastolic blood pressure	1.7	3.1	0.4	1.9
HDL cholesterol	0.4	1.1	1.0	0.5
Fasting triglyceride	3.4	0.4	3.0	0.8
Fasting insulin	5.1	3.0	2.2	4.0
2-hour insulin	7.7	2.1	1.6	1.8

Table 44: Prevalence of glucose intolerance (defined as diabetes or IGT by WHO criteria) by tertile of body mass index and waist-hip ratio

		Europeans		South Asians	
FREQUENCY COL PCT		Normal	Diabetic or IGT	Normal	Diabetic or IGT
Tertile of age-adjusted body mass index	1	122 35.36	3 10.00	84 35.90	12 21.82
	2	114 33.04	11 36.67	79 33.76	18 32.73
	3	109 31.59	16 53.33	71 30.34	25 45.45
	TOTAL	345	30	234	55
Tertile of age-adjusted waist-hip ratio	1	124 35.94	1 3.33	87 37.18	9 16.36
	2	113 32.75	12 40.00	83 35.47	14 25.45
	3	108 31.30	17 56.67	64 27.35	32 58.18
	TOTAL	345	30	234	55

Table 45: Prediction of glucose intolerance by waist-hip ratio and body mass index, contrasting the top tertile for each variable with the lower two tertiles:-

	Europeans		South Asians	
	Sensitivity	Specificity	Sensitivity	Specificity
Body mass index:	53%	68%	45%	70%
Waist-hip ratio:	57%	69%	58%	73%

Mantel-Haenszel analysis contrasting highest tertiles of body mass index and waist-hip ratio with lowest two tertiles:-

	Europeans	South Asians
	Odds ratio (95% CI)	Odds ratio (95% CI)
Body mass index controlling for waist-hip ratio:	1.80 (0.70 - 4.65) NS	1.15 (0.57 - 2.31) NS
Waist-hip ratio controlling for body mass index:	2.46 (0.95 - 6.35) NS	3.62 (1.85 - 7.06) $p<0.001$

Table 46: Surveys comparing plasma triglyceride and HDL cholesterol levels in Blacks and Whites

Year	Survey	Age	Men		Women		Ref. no
			Black	White	Black	White	
			Triglyceride (mmol/l)				
1977	Northwick Park (UK)	18-64	0.82	1.28	1.00	0.98	254
1981	Cincinnati LRC	40-59	1.13	1.47	0.95	1.07	255
1980	LRC Prevalence Survey	25-44	1.15		0.93		256
1980	Evans County	-	1.26	1.49	1.19	1.42	257
1989	CARDYA Study	18-30	0.79	1.02	0.72	0.78	253
			HDL cholesterol (mmol/l)				
1981	Cincinnati LRC	40-59	1.27	1.09	1.37	1.34	255
1980	LRC Prevalence Survey	25-44	1.43	1.19	1.53	1.53	256
1989	NHANES II	20-74	1.34	1.21	1.43	1.45	258
1980	Evans County	-	1.46	1.18	1.53	1.44	257
1989	CARDYA Study	18-30	1.38	1.21	1.43	1.45	253

Table 47: Mortality of Pimas resident in the Gila River Indian Community during 1965-80[267], compared with US Whites in 1970

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Table 48: San Antonio Heart Study: anthropometric and metabolic findings in residents aged 25-64 by sex and ethnic group[268,270]

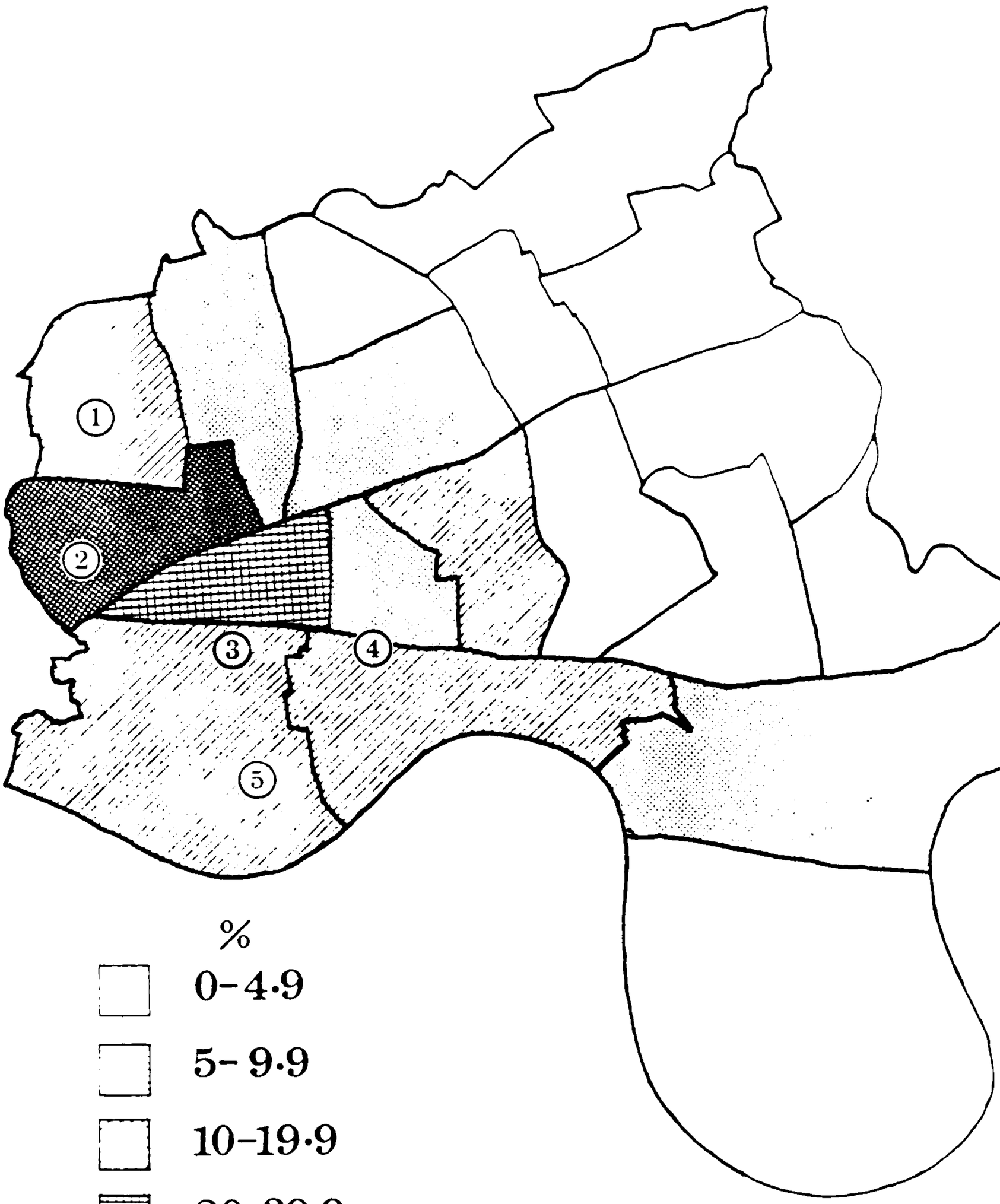
Table 49: Framingham Study: comparison between men and women for strength of association between risk factors and CHD[282].

Table 50: Mean plasma cholesterol in surveys of South Asians in the UK, compared with the native British population

Group studied	Age range	Sex	Mean plasma cholesterol (mmol/l) South Asian	Native British	Ref. no.
mainly Gujarati Hindus	35-54	M	5.4	-	18
		F	4.6	-	
mainly Gujarati Hindus	45-64	M	5.4	6.1	60
Bangladeshis	35-69	M	5.5	6.0	29
		F	5.4	6.1	
Punjabi Sikhs	40-64	M	5.9	6.2	(this thesis)

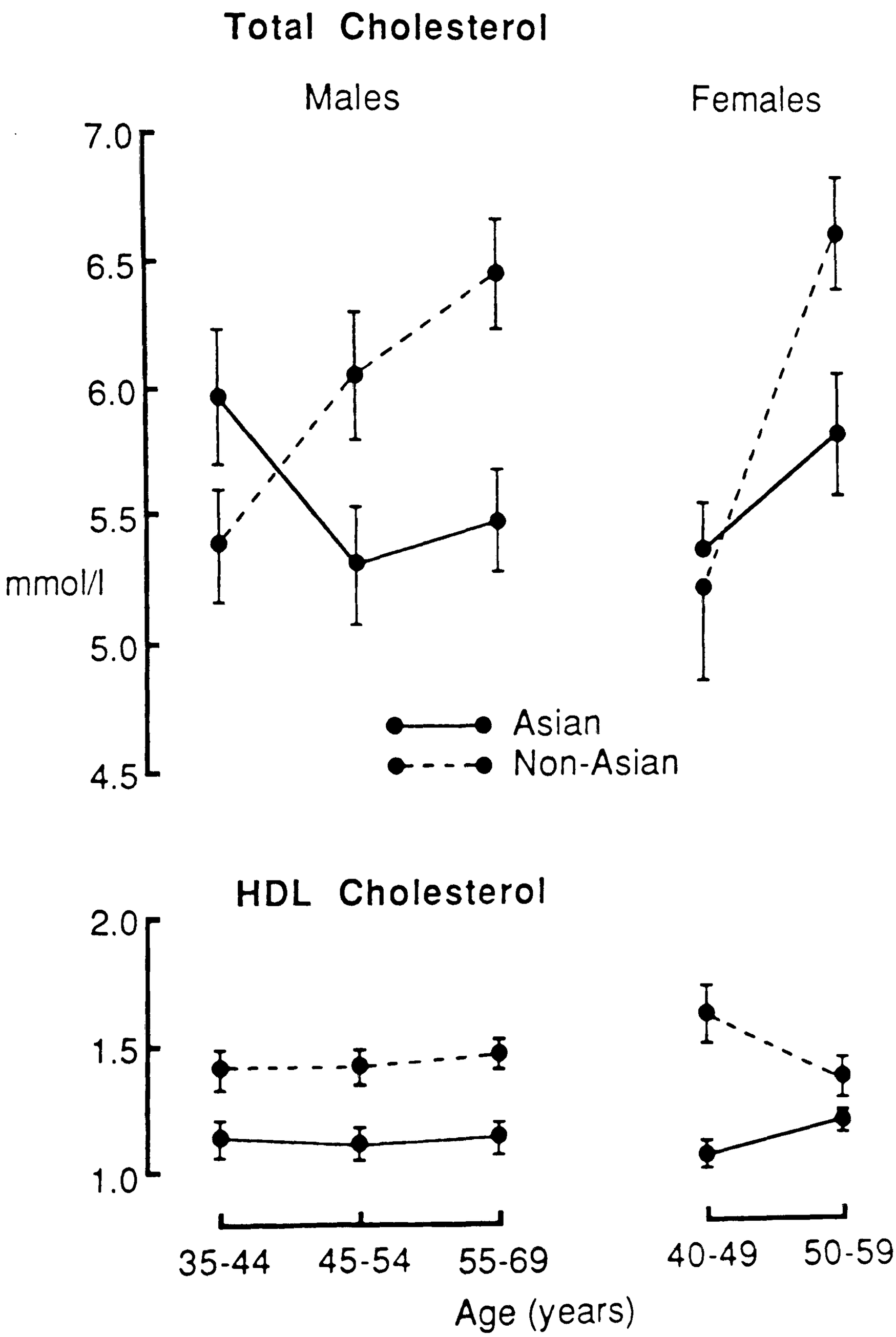
Appendix B

Figure 1: Electoral wards of Tower Hamlets showing ethnic composition and general practices (numbered 1 to 5) included in the survey



Percent of electorate of Bangladeshi origin, 1987

Figure 2: Plasma total and HDL cholesterol in East London Study



Appendix B

Figure 3: Plasma triglyceride and serum insulin in East London Study

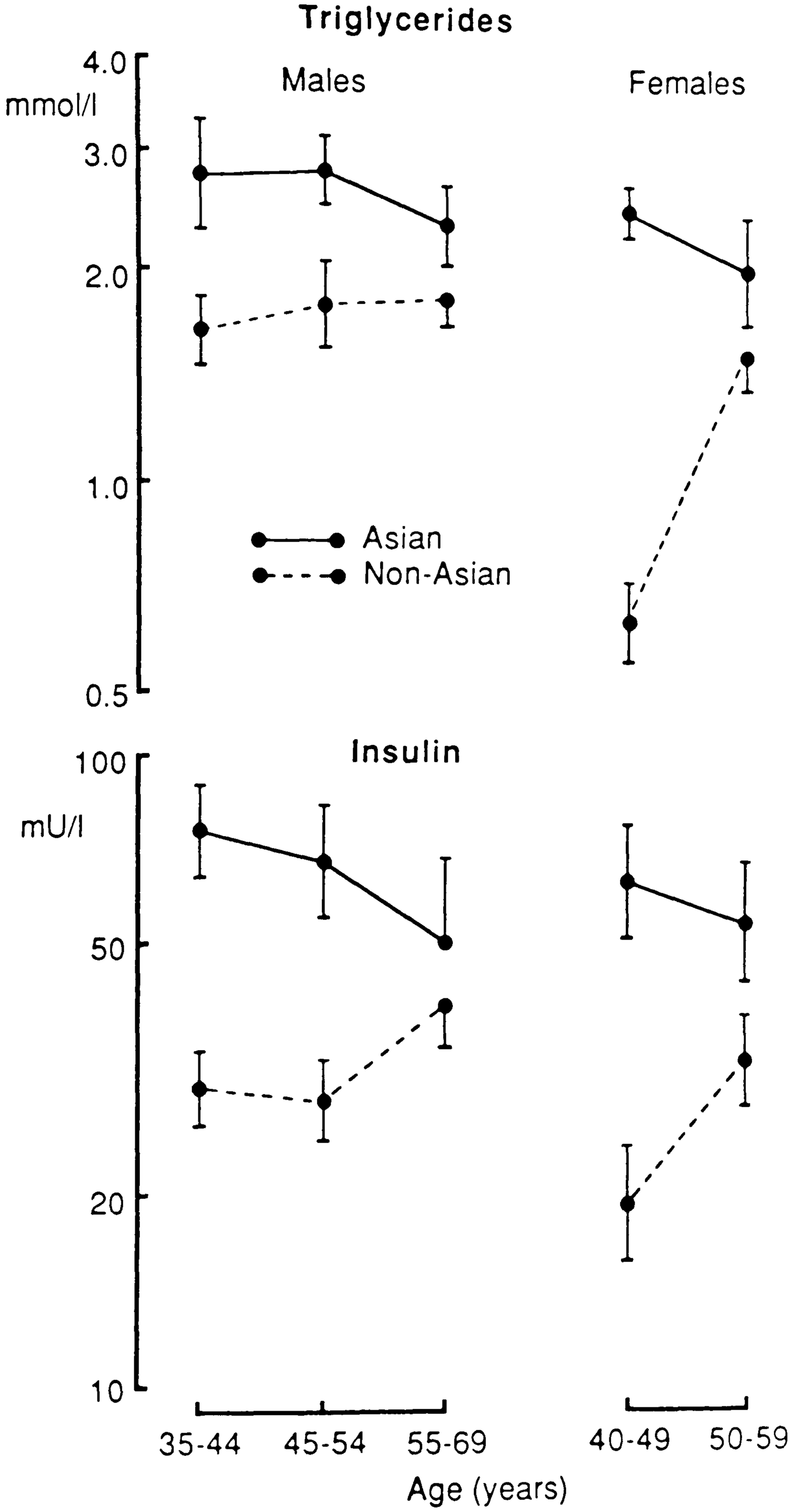


Figure 4: Frequency distributions of waist-hip ratio in the Diabetes and Coronary Risk Study

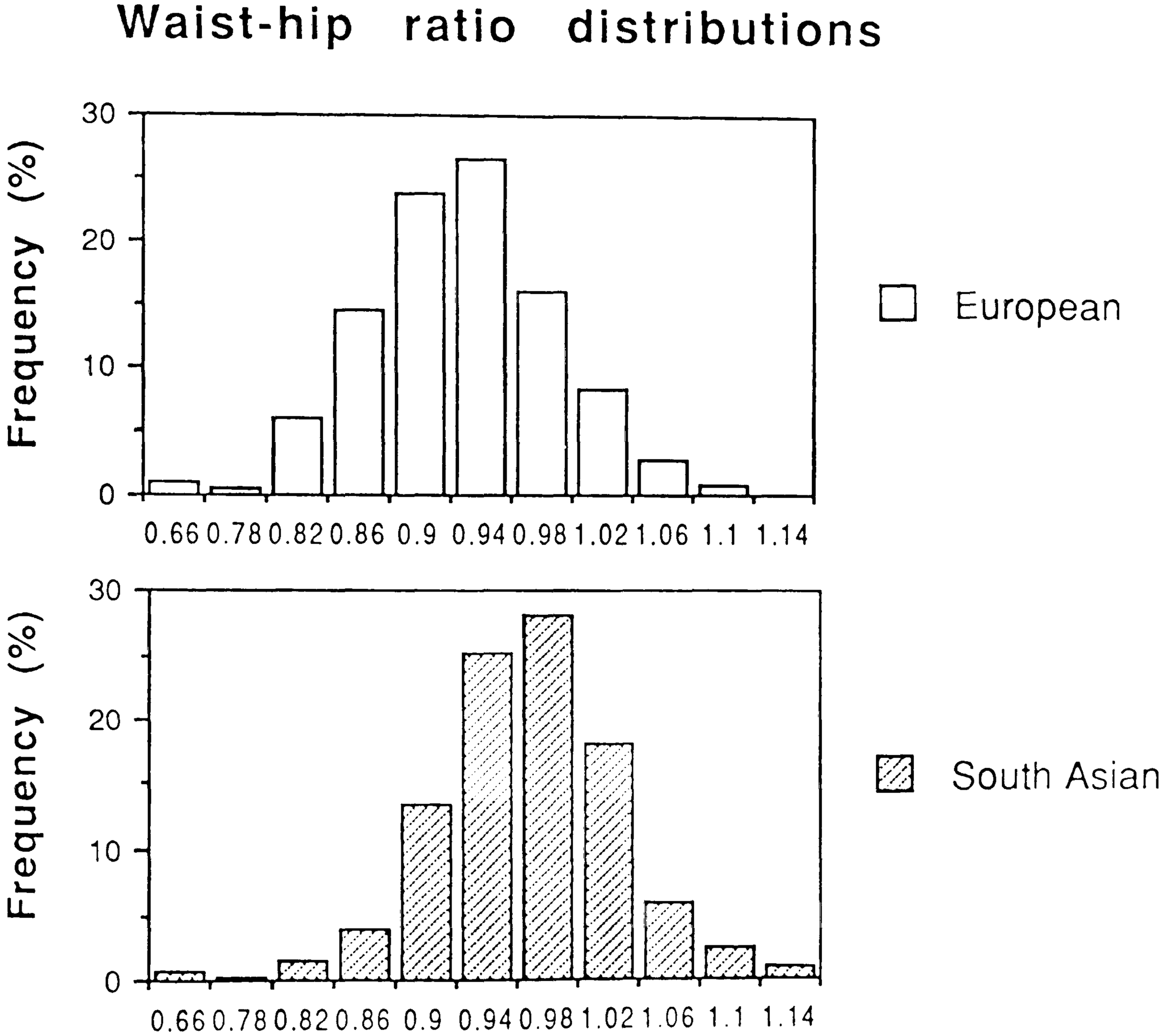
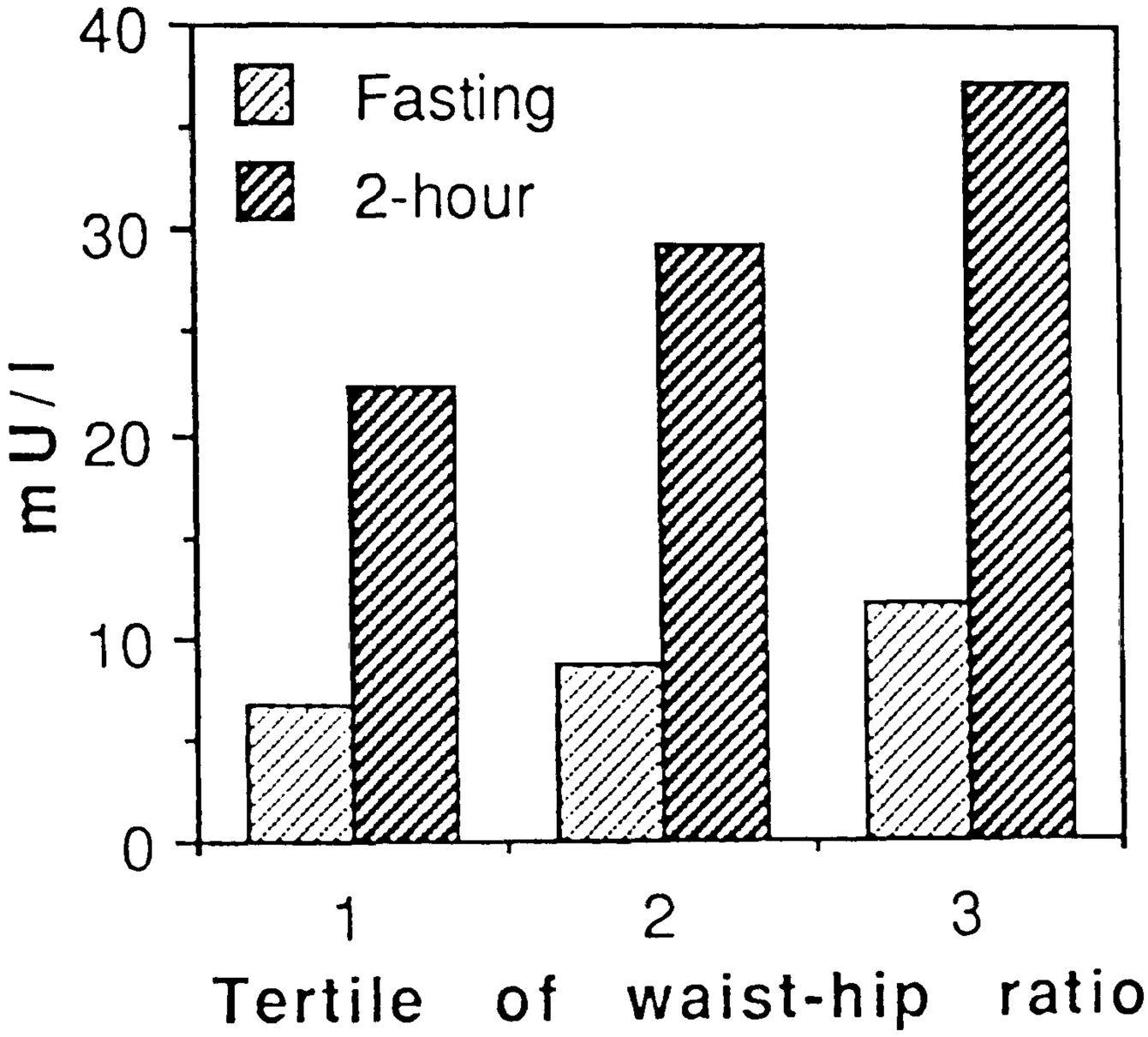


Figure 5: Mean serum fasting and 2-hour insulin levels by tertiles of waist-hip ratio within each ethnic group in the Diabetes and Coronary Risk Study



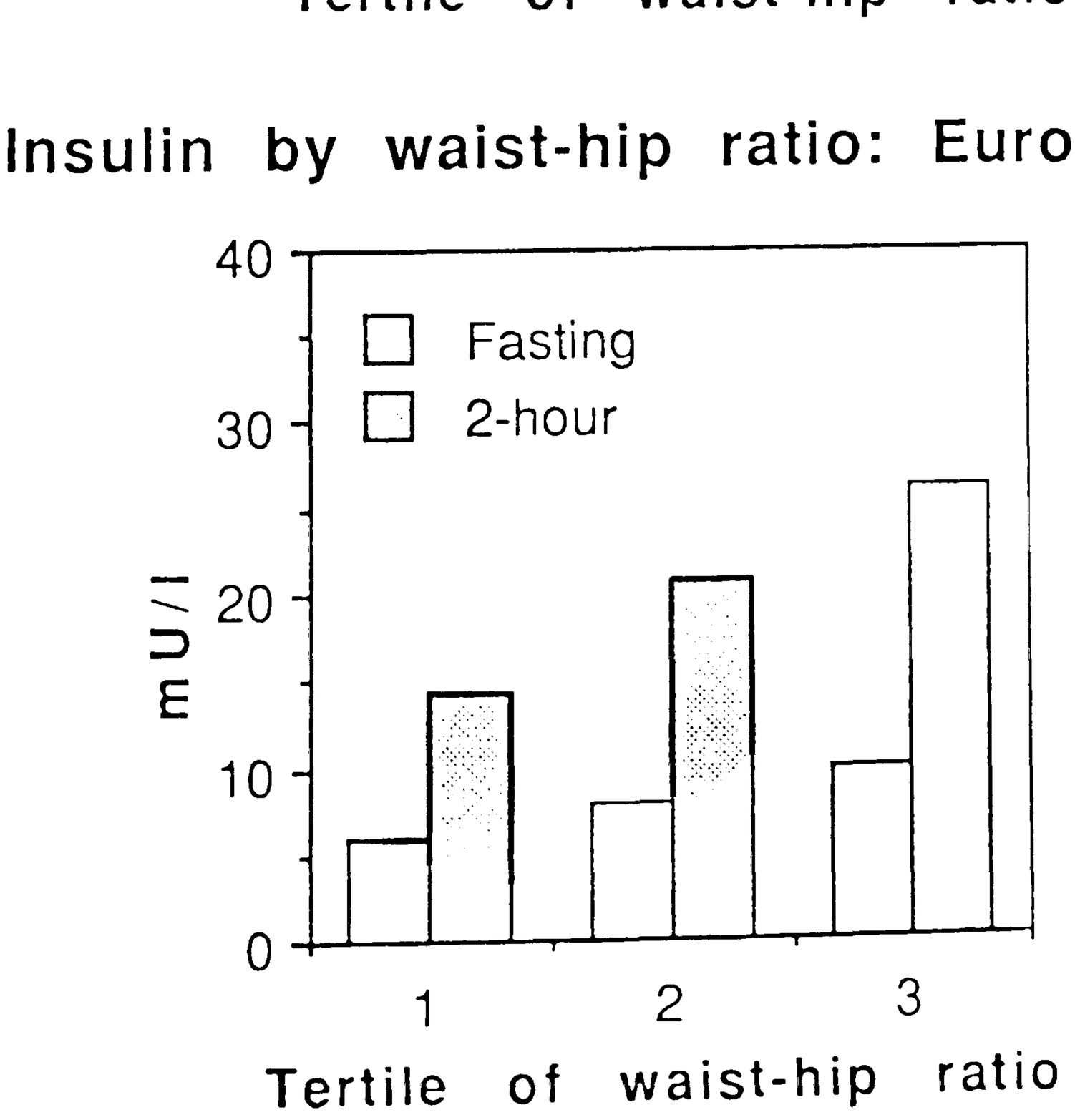
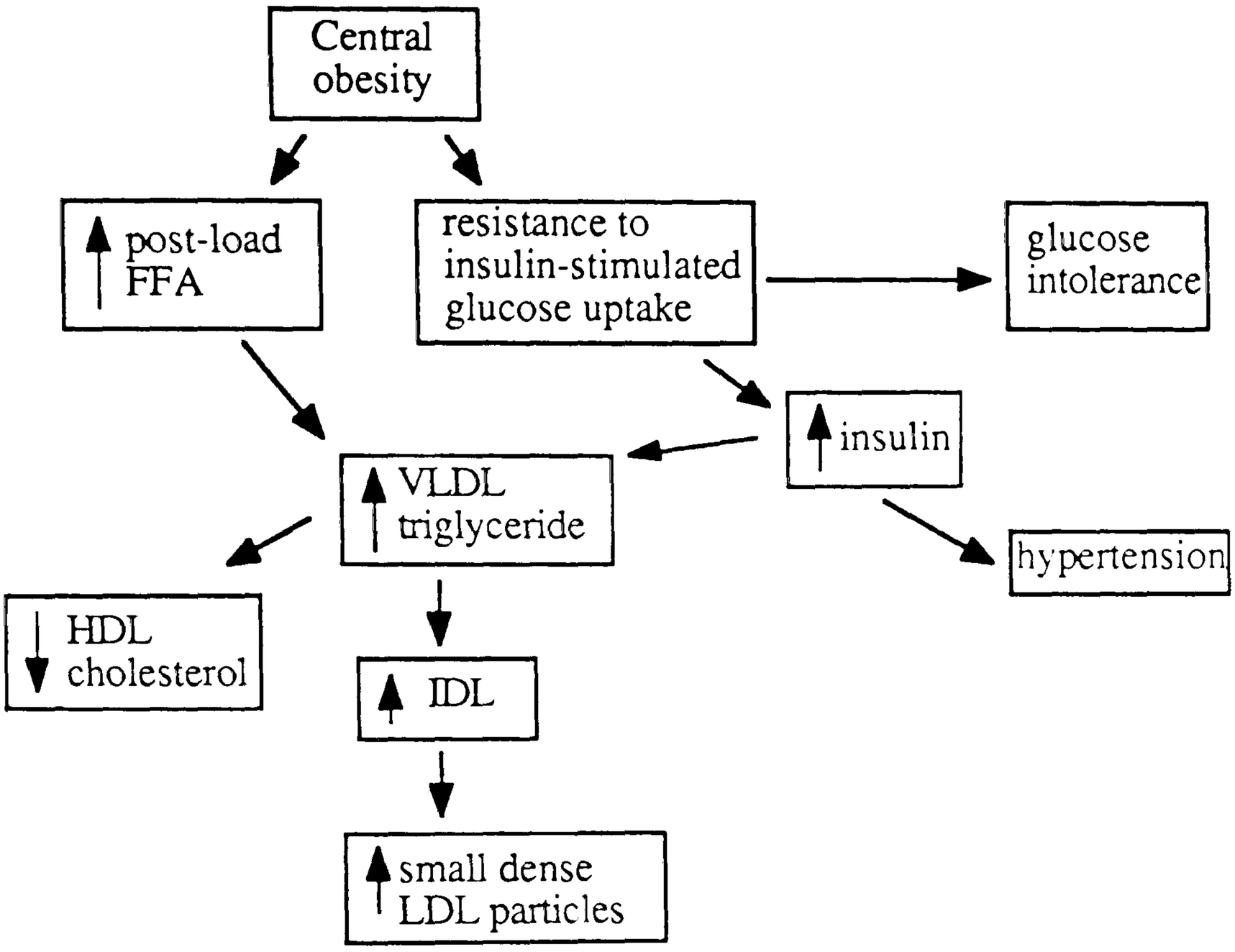


Figure 6: The insulin resistance syndrome: interrelationships



Appendix B

Sample size calculation for Diabetes and Coronary Risk study

Let P_C = the prevalence in the control group

$Q_C = 1-P_C$

P_e = the prevalence in the experimental group

$Q_e = 1-P_C$

N = the number in each group

$Z_{\alpha/2}$ = 1.96 (centile 97.5 of a standard normal distribution)

Z_{β} = 1.28 (the 90th centile of a standard normal distribution)

then we have[194]

$$| P_e - P_C | = Z_{\alpha/2} \sqrt{\frac{2P_C Q_C}{N}} + Z_{\beta} \sqrt{\frac{2P_C Q_C + 2P_e Q_e}{N}}$$

The equation is solved for P_e iteratively, using the standard calculus method.

Putting N = 1500

P_C = 0.05

we obtain P_e = 0.0769775

Relative risk = P_e / P_C =1.53955

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