EFFECTS OF EXERCISE ON CARDIOVASCULAR DISEASE RISK MARKERS IN SOUTH ASIAN VERSUS WHITE EUROPEAN MEN

by

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Abstract

Globally, cardiovascular disease (CVD) is a major cause for morbidity and mortality. Exaggerated postprandial lipaemia has been implicated in the development of atherosclerosis, and by lowering postprandial triacylglycerol (TAG) concentrations, atherogenic progression may be delayed. Many studies have revealed that exercise, in particular acute exercise, can attenuate postprandial TAG concentration. Most of this evidence relates to studies conducted in Western participants. South Asians are a population predisposed to CVD, and their adverse lipid profiles and physical inactivity may be among the underlying reasons. Hence, the studies described in this thesis examined the potential of acute bouts of exercise to favourably modify postprandial lipaemia and other CVD risk markers in young, healthy, South Asian men.

The first experimental study described in this thesis compared the effect of 60 minutes of brisk walking on postprandial TAG concentration in 15 South Asian and 14 White European men. Trials were conducted over two days with exercise (or rest) taking place on day 1 and postprandial testing on day 2. A key finding from this study was that postprandial TAG, glucose and interleuklin-6 (IL-6) concentrations were elevated in South Asian compared with White European participants after consumption of high fat meals. This study also revealed a non-significant trend for brisk walking to reduce postprandial TAG concentrations in response to high fat meals in both groups.

The second experimental study reported here examined the effect of 60 minutes of treadmill running at 70% of $\dot{V}O_2$ max on postprandial lipaemia and other CVD risk makers on the next day in 10 South Asian and 10 White European men. A significant main effect of trial was shown for postprandial TAG, IL-6 and soluble intercellular adhesion molecule-1 (sICAM-1), showing that TAG and IL-6 concentrations were lower on the exercise trial while sICAM-1 concentrations were higher on the exercise trial. In addition, ethnic group differences were observed for postprandial TAG, glucose and insulin concentrations indicating higher values in South Asians than White Europeans. A significant trial by group interaction effect was also observed for TAG, indicating a greater decrease after exercise in the South Asian men than the European men.

In the third experimental study in this thesis the effect of 30 minutes of treadmill running on one day was compared with running for 30 minutes on three consecutive days in 11 South Asian men with regards to postprandial lipaemia. Neither a single bout of running nor three consecutive days of running influenced postprandial TAG in response to high fat meals when compared with the response on a control trial. It is not clear why exercise was ineffective in reducing postprandial lipaemia in this study but possibly the energy expenditure of exercise was insufficient to elicit change.

The final experimental chapter described in this thesis combined the data from the first three studies. The objective of this chapter was to enhance the sample size in an effort to clarify the effects of acute exercise and to clarify the effects of ethnic group with respect to several fasting and postprandial CVD risk markers. The key findings were: 1) fasting and postprandial TAG and postprandial glucose concentrations were significantly reduced by exercise; 2) There were significant main effects of ethnic group for fasting high density lipoprotein cholesterol (HDL-C), total cholesterol/ HDL-C, IL-6 and systolic blood pressure (SBP), indicating lower values of HDL-C and SBP and higher values of total cholesterol/HDL-C and IL-6 in South Asian participants. Additionally, there were significant main effects of ethnic group for postprandial TAG and IL-6 indicating higher values in South Asian participants.

Taken together, these data indicate that South Asians have an adverse CVD risk factor profile in comparison with White Europeans and this may explain, at least in part, their elevated risk of CVD. Importantly, the data produced within this thesis show for the first time that acute bouts of exercise can be effective for lowering postprandial plasma TAG concentrations in South Asians, at least transiently. Thus, exercise has the potential to serve as a ‘non-pharmacological’ medicine in South Asians.

Key words: cardiovascular disease, exercise, postprandial lipemia, inflammation, physical activity, triacylglycerol, South Asians, White Europeans

I prefer to be a dreamer among the humblest,
with visions to be realized, than
lord among those without dreams and desires.

Khalil Gibran

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Preface

An overview of the publications and communications of the research presented in this thesis is given below.

Under Review

S.P. Arjunan, N.C. Bishop, A.Reischak-Oliveira & D.J. Stensel. (In Press) The effect of prior exercise on postprandial plasma triglyceride concentrations in men of South Asian versus European descent. *Medicine and Science in Sports and Exercrise*. Accepted on 23 December 2012.

Conference communications

Chapter five:
The effect of prior exercise on postprandial plasma triglyceride concentrations in men of South Asian versus European descent.
BASES 2011 annual conference - University of Essex (oral presentation)

Chapter five:
The effect of exercise on postprandial plasma triglyceride concentrations in men of South Asian versus European descent
Postgraduate Research Student Conference 2011 - Loughborough University
(poster presentation)

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Abbreviations

The expressions above will be written in full when mentioned first and then abbreviated for the rest of the thesis.

ANOVA	Analysis of variance
AUC	Area under the concentration versus time curve
BMI	Body mass index
CHD	Coronary heart disease
CRP	C-reactive protein
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
EPC	Endothelial progenitor cell
HDL-C	High density lipoprotein cholesterol
IHD	Ischaemic heart disease
IL-6	Interleukin-6
LDL-C	Low density lipoprotein cholesterol
MAP	Mean arterial pressure
RPE	Rating of perceived exertion
SBP	Systolic blood pressure
SD	Standard deviation
SEM	Standard error of the mean
sICAM-1	Soluble intercellular adhesion molecule-1
sVCAM-1	Soluble vascular cellular adhesion molecule-1
TAG	Triacylglycerol
TC	Total cholesterol
TNF-α	Tumor necrosis factor α
$\dot{V}O_2max$	Maximal oxygen uptake
WHO	World health organisation

1 Introduction

Cardiovascular disease (CVD) encompasses a range of diseases that include coronary heart disease (CHD) and stroke and it is the major cause of morbidity and mortality globally (WHO, 2011). CVD accounted for 17.3 million deaths in 2008, representing 30% of all global deaths. Of these deaths, an estimated 7.3 million were due to CHD and 6.2 million were due to stroke (WHO, 2011). By 2030, it is predicted that around 24 million people will die each year from CVD, mainly from CHD and stroke. These are projected to remain the leading causes of death (WHO, 2011).

In congruence, CVD is also responsible for more deaths in the United Kingdom (UK) than any other single cause according to the British Heart Foundation (BHF, 2009). The ethnic group most affected by CVD are South Asians (BHF, 2009) who come from the Indian sub-continent. Geographically, the Indian subcontinent is a region critically affected by CVD and it makes up one quarter of the world's population (Ramaraj & Chellappa, 2008). Those who have their origin from the Indian sub-continent are collectively known as South Asians and this includes people from India, Pakistan, Bangladesh, Nepal, Sri Lanka and Bhutan (Joshi et al, 2007). South Asians comprise the largest ethnic minority group (4.1%) living in the UK (Wild & McKeigue, 1997) and they have a higher risk of CVD than Europeans (Wild et al, 2007; BHF, 2009) although the reasons for this are uncertain.

Among people living in the UK, the earlier onset of CHD among South Asian migrants and the higher incidence of CHD is most marked in those younger than 40 years of age (about a 3 fold difference), whereas it is less marked in those older than 60 years of age (about a 1.5 fold difference) based on the analysis of UK mortality data (Balarajan, 1991). The increased risk of CVD is further evident from a recent cardiovascular risk assessment study conducted in the UK which identified that 92% of male and female South Asians had at least one modifiable CVD risk factor (Rao et al, 2012). Of these, 52% were hypertensive, 40% were obese, 75% had central obesity and 10% had a total cholesterol/high density lipoprotein cholesterol (HDL-C) ratio greater than six (Rao et al, 2012).

Since the 1950s, there has been an increased awareness that people with ancestral origins in the Indian subcontinent are highly susceptible to CHD (Patel and Bhopal, 2004). Danaraj and colleagues (1959) were possibly the first to highlight this issue. They observed a seven fold higher prevalence of CHD among Indians than Chinese living in Singapore. Another study in Singapore revealed that Indians are more prone than Malays and Chinese to developing central obesity with insulin resistance, hyperinsulinaemia and glucose intolerance (Hughes et al, 1997). In 1963, Adelstein identified this phenomenon in South Africa where mortality rates for CVD/CHD in mainly Indian men and women were much higher than in white men and women (Adelstein, 1963). These findings have since been confirmed in the USA (Palaniappan et al, 2004) and Canada (Sheth et al, 1999).

It is important to recognise that the term "South Asian" refers to a heterogeneous population with important differences in diet, culture, religion and lifestyle among different South Asian populations. Studies have identified a three to five fold increase in the risk of myocardial infarction and cardiovascular death in South Asians as compared with other ethnic groups (McKeigue et al, 1989; Eapen et al, 2009). With respect to the prevalence of vascular risk factors, Bangladeshis fare the worst, followed by Pakistanis and then Indians (Bhopal et al, 1999). Data from the 2001 Census of England and Wales showed that people born in Bangladesh had the highest rates of death due to CVD, followed by those born in Pakistan (Wild et al, 2007). However, a review paper reported that among South Asians blood pressure is highest in Indians, slightly lower in Pakistanis and much lower in Bangladeshis (Agyemang and Bhopal, 2002).

Various factors are associated with the lifestyle of populations across the world that has changed dramatically in the 20th century. These epidemiological transitions have been brought about by many developments in science and technology that now affect every facet of human existence (Prabhakaran and Yusuf, 2010). Most human societies have moved from agrarian diets and active lives to fast foods and sedentary behaviour. These changes have fuelled the epidemic of obesity, diabetes, hypertension and dyslipidaemia which are risk factors for CVD/CHD (Prabhakaran and Yusuf, 2010). The prevalence of traditional risk factors has been on the rise in South Asians and may contribute to their high CHD prevalence. The INTERHEART study identified nine traditional risk factors that contribute to the high CHD burden in the South Asian population. These factors are obesity, alcohol

consumption, physical inactivity, diabetes, hypertension, diet, psychosocial factors, dyslipidaemia and smoking (Joshi et al, 2007). The INTERHEART study also reported that South Asians have their first acute myocardial infarction five years earlier than those from other countries (Joshi et al, 2007). In patients with acute myocardial infarction, the high prevalence of conventional risk factors among South Asians largely explained their younger age at presentation compared with Europeans (Joshi et al, 2007). Other emerging risk factors (e.g.: interleukin-6 (IL-6) and soluble intercellular adhesion molecule-1 (sICAM-1)) may also contribute, predisposing South Asians to heart disease along with conventional cardiac, metabolic and environmental factors (Kolluri et al, 2009). Environmental changes that come from adopting the habits of other cultures can further increase these risks. Thus, the prevalence of CHD in South Asians globally is significantly higher than any other ethnic group in the past forty years. (Kolluri et al, 2009).

South Asians have higher plasma triacylglycerol (TAG), lower HDL-C concentrations, higher low density lipoprotein cholesterol (LDL-C) concentrations, and a higher prevalence of hypertension, type 2 diabetes, impaired glucose tolerance, increased fasting glucose, insulin resistance and the metabolic syndrome than other populations (Tziomalos et al, 2008). This may be due to genetic factors predisposing to high levels of metabolic CVD risk factors. Alternatively/additionally, environmental influences may contribute to the adverse CVD risk profiles in South Asians (Reddy & Yusuf, 1998).

One environmental factor which may contribute to the excessive CVD risk in South Asians is physical inactivity. In their review of physical activity levels among South Asians living in the UK Fischbacher and colleagues (2004) identified 12 studies in adults and five in children all of which reported lower levels of physical activity among UK South Asians than the general population. These findings have since been confirmed by data from a diabetes screening programme in Leicester, UK (Yates et al, 2010). This study was the first to comprehensively investigate ethnic-specific differences in both levels of physical activity and associations between physical activity and markers of metabolic and vascular health (Yates et al, 2010). According to the Health Survey for England regardless of sex, age and type of physical activity, South Asians are 60% less active than White Europeans (Williams et al, 2011). Many studies have confirmed this (Kamath et al, 1999; Owen et al, 2009; Misra et al, 2012). The INTERHEART study also found that South Asian patients

with myocardial infarction and healthy South Asian controls were both less physically active than other ethnic groups and that the population attributable risk for physical inactivity in South Asian people is comparable to that for other major CHD risk factors (Joshi et al, 2007).

It can be postulated that there are possible barriers to physical activity among South Asians. Physical activity is a foreign concept to the cultural identity of South Asian communities (Caperchione et al, 2009). Lifestyle factors, such as physical activity are therefore perceived as irrelevant to the disease process (Lawton et al, 2006). Moreover, the physiological response to physical activity may even be viewed as unhealthy and likely to exacerbate illness (Caperchione et al, 2009; Lawton et al, 2006). Cultural taboos against South Asian females and the view of physical activity beyond daily work as selfish may also be determinants of physical inactivity (Caperchione et al, 2009). Language barriers, being unfamiliar with the wider community, fear of racism, crime and social deprivation have all been cited as barriers to physical activity among South Asians (Caperchione et al, 2009).

Although, such barriers exist, it is critical to understand that physical inactivity is a well-established risk factor for CVD/CHD (Wannamethee & Shaper, 2001; Yusuf et al, 2004; Rastogi et al, 2004; Mohan et al, 2005; Rao et al, 2012). Regular physical activity acts through numerous pathways to reduce the risk of CVD. These mechanisms include reduced adiposity, improved lipid and glucose profiles, reduced blood pressure and improved endothelial and immune function (Warburton et al, 2006). Regular moderate intensity physical activity is associated with a 30% to 50% reduction in the risk of CHD, obesity, diabetes and stroke (Wannamethee et al, 2000; Batty, 2002). Despite higher rates of earlier CHD in South Asians and a tendency for low levels of physical activity, no studies have addressed the acute effects of exercise in this population although observational evidence suggests a cardio-protective role of physical activity in South Asians (Rastogi et al, 2004; Mohan et al, 2005; Rao et al, 2012).

One particular CVD risk factor which is positively influenced by exercise is postprandial lipaemia. Zilversmit (1979) presented evidence that the postprandial period may aggravate the atherosclerotic process. Thereafter, many investigations have suggested that exercise

attenuates postprandial lipaemia by reducing hepatic very low density lipoprotein-TAG secretion and by increasing TAG uptake within skeletal muscle (Tsetsonis et al, 1996; 1997; Hardman, 1998; Petit and Cureton, 2003, Katsanos, 2006; Malkova and Gill, 2006; Miyashita et al, 2006; 2008; MacEneaney et al, 2009, Hurren et al, 2011). Postprandial lipaemia is more predictive of future CVD than fasting TAG alone (Bansal et al, 2007; Nordestgaard et al, 2007) and exercise has a tendency to decrease the risk of developing CVD/CHD in part through a reduction in atherosclerotic plaque formation (Gill and Malkova, 2006; Warburton et al, 2006).

Though acute bouts of aerobic exercise performed the day prior to meal ingestion have been found to attenuate postprandial lipaemia these studies have been conducted predominantly in Western populations (Miyashita et al, 2008; MacEneaney et al, 2009; Hurren et al, 2011). To date, there are no data on the effect of prior exercise on postprandial lipaemia and other CVD risk markers in South Asians. This represents an important void in understanding the extent to which exercise may ameliorate CVD risk in South Asians.

Despite the high prevalence of CHD and low levels of physical activity among South Asians few studies have examined the effects of exercise/physical activity on CVD/CHD or on risk factors for CVD/CHD in this population. Whether exercise/physical activity has any cardio-protective effects in South Asians remains to be determined. Thus, the primary purpose of the studies contained within this thesis was to investigate the influence of acute bouts of exercise on postprandial lipaemia and other CVD risk markers in South Asians compared with White Europeans.

The first study in this thesis (Chapter four) examined the effect of prior walking on postprandial lipaemia and resting blood pressure in South Asian versus White European men. Study two (Chapter five) investigated the effects of an acute bout of running on postprandial lipaemia and on several other CVD risk markers including insulin, glucose, IL-6 and sICAM-1 in South Asian and White European men. Study three (Chapter six) examined the effects of a single bout of running versus three consecutive days of running on postprandial lipaemia in men of South Asian descent. The final study in this thesis (Chapter seven) involved a cross-sectional comparison of several fasting and postprandial

CVD risk markers in South Asians and White Europeans. Collectively, the studies presented in this thesis begin to address the very limited attention to date on the potential of exercise to modify CVD risk markers in South Asians.

2 Literature review

2.1 Introduction

This review will begin by briefly defining heart disease and discussing its aetiology. Recent heart disease statistics will then be presented for the UK, for other countries and then specifically for South Asians. After this there is a review of traditional and emerging risk factors for heart disease before these risk factors are specifically discussed in South Asians. Following this there is a discussion of some of the key literature examining the relationship between physical activity/exercise and heart disease/all-cause mortality risk and then a review of some key studies examining physical fitness and heart disease/all-cause mortality risk. Very few of these studies involve South Asian participants. Towards the end of the review there is a discussion of the acute and then the chronic effects of exercise on heart disease risk factors. The final section of the review focuses specifically on studies which have examined physical activity/physical fitness levels and their relationship with CVD risk in South Asians.

2.2 Heart disease definition and aetiology

Heart disease is a term used for a variety of disorders that affect the heart or make it less efficient by reducing its supply of oxygen or by reducing its ability to pump effectively (World Health Organization - WHO 2009). The term heart disease is used interchangeably with cardiovascular disease (CVD) which refers to anything that is related to the heart (cardio) and blood vessels (vascular). Congenital heart disease, angina (chest pain), arrhythmia (defects in the rhythm of the heart), arteriosclerosis, coronary artery disease, pulmonary heart disease, and myocarditis (inflammation of the heart muscle) all come under the ‘umbrella’ of heart disease.

The main components of CVD are coronary heart disease (CHD), stroke and hypertension which are leading causes of death in both developed and developing nations (WHO, 2009). In CHD the artery progressively narrows due to the build-up of plaque, a condition called atherosclerosis. Atherosclerosis is a process that is the principal contributor to the

pathogenesis of myocardial infarction, cerebral infarction, gangrene and loss of function in the extremities (Ross, 1993). In normal circumstances a protective response to insults to the endothelium and smooth muscle cells of the wall of the artery, consists of the formation of fibrofatty and fibrous lesions preceded and accompanied by inflammation. The advanced lesions of atherosclerosis, which may occlude the artery concerned, result from an excessive inflammatory fibro proliferative response to numerous different forms of insult (Ross, 1993).

This results in insufficient blood flow, called ischaemia, to the heart and eventually leads to a heart attack. Stroke, is a brain ischaemia due to a thrombosis (formation of a blood clot) or a haemorrhage (profuse bleeding from a ruptured blood vessel) of a blood vessel within the brain. These conditions hamper the functionality of the brain. Hypertension or high blood pressure is where the pressure of the blood being pumped out from the heart strains the artery walls. The Joint National Committee on Prevention, Detection, Evaluation and Treatment defined hypertension as an elevated systolic blood pressure of 140 mm Hg and above and/or a diastolic blood pressure of 90 mm Hg and above which then becomes a contributor to all major heart diseases (Chobanian et al, 2003). If blood pressure levels are consistently elevated this increases the risk of stroke, CHD and kidney failure.

In Greek, athero refers to gruel or paste and sclerosis to hardness. Atherosclerosis entails deposits of waste products like fatty substances, cholesterol and cellular waste products in the lining of the artery (Mallika et al, 2007). This results in the formation of plaque which comprises of low density lipoprotein cholesterol (LDL-C), smooth muscle cells, fibrous tissue and calcium. The artery is segmented into three layers, intima, media and adventitia. The intima is the inner most layer where it is most intimate with the blood and this layer is also known as the endothelium. It is believed that atherosclerosis is initiated by damage to the endothelium. Plaque formation within the endothelium creates rough areas which stimulate blood clots and impair blood flow and hence oxygen transport to organs such as the heart, kidney and intestines (Mallika et al, 2007). This may result in the death of the organ cells or severe damage (American Heart Association - AHA, 2009). Atherosclerotic lesions start to develop early in life independently of race, sex or geographical origin. The rate of fatty streak development is higher between 15 and 25 years of age, while raised lesions begin developing slowly during the second decade of life, progressing steadily

during the third and more rapidly during the fourth (Sternby et al, 1999). Thus, cardiovascular disease is a slow and progressive disease that begins in childhood hence preventive measures must begin early (McGill et al, 2000).

2.3 Heart disease statistics

According to the World Health Organisation (WHO, 2011) CVD causes 17.3 million deaths in the world each year and by 2030 almost 24 million people will die from CVD. Some forms of CVD are more common among certain racial and ethnic groups. For example, African Americans are more likely to suffer from hypertension and are at a greater risk of heart disease than whites (AHA, 2012). Risk factors for CVD in other minority groups have also been studied as in the case of the South Asians. Related studies generally have used the white population as a comparison.

2.3.1 United Kingdom

Cardiovascular disease is responsible for more deaths in the UK than any other single cause according to the British Heart Foundation (BHF 2009). Cardiovascular disease caused 190,000 deaths in 2007 and it was also a major catalyst for premature death before the age of 75 (29% of men and 21% of women) in the UK (BHF 2009). 2.6 million people in the UK are living with CHD. Half of all CVD cases are due to CHD and one-third are due to stroke. Coronary heart disease was responsible for 91,000 deaths in 2007 accounting for 19% of deaths in men and 13% of deaths in women (BHF 2009). Coronary heart disease is also the most common cause of premature death in the UK (18% in men and 10% in women). Nearly all deaths from CHD are from a heart attack. Approximately 1.4 million people over the age of 35 years have had a heart attack and 2 million have suffered from angina (BHF 2009). In 2007 alone, heart attack affected 141, 000 people and 720, 000 people had a definite heart failure. The mortality rate from CHD has been decreasing since the 1970s, but CHD incidence has been on the rise from the 1980s, particularly in men aged 75 and older.

2.3.2 Other countries

In comparison with Western Europe, Australia and Japan, levels of CHD in the UK are moderately high (BHF 2009). The main cause of mortality in almost all European Union countries in 2008 (OECD, 2010) was related to ischaemic heart disease (IHD) and stroke. Together, they comprised 60% of all cardiovascular deaths in European Union countries for that year. The highest mortality rates were reported in central and eastern European countries for both males and females (OECD, 2010).

According to AHA (2012), cardiovascular disease is the leading cause of death in the United States killing on average 2200 people per day, an average of one person every 39 seconds. One or more types of CVD affect an estimated 82.6 million American adults and out of these an estimated 40 400 000 are ≥60 years of age. The breakdown of CVD by type is as follows, hypertension (74.5 million), CHD (16.3 million), myocardial infarction (7.9 million), angina pectoris (9 million), heart failure (5.7 million), stroke (7 million) and congenital cardiovascular defects (650 000 to 1.3 million) (AHA, 2012). Cardiovascular disease is responsible for half of all deaths in the United States. Cancer, the second largest killer, accounts for only half as many deaths. The AHA 2012 estimates that 68% of patients with diabetes die of some form of CVD.

Cardiovascular disease is on the rise in India affecting Indians prematurely or 5 to 6 years earlier than their western counterparts (Xavier et al, 2008). The presence of CHD in the urban population is estimated to be from 7% to 13% and in the rural population from 2% to 7% (Prabhakaran & Yusuf, 2010). Increasing rates of urbanisation and major economic changes (such as improved transportation) have led to changes in lifestyle patterns for a large proportion of individuals in India resulting in decreased physical activity levels for many Indians. Availability of energy saving devices have been responsible for increasing weight in the urban population leading to diabetes, hypertension and dyslipidaemia (Reddy, 1999). A reversal of socio-economic gradients for CHD risk factors has emerged in the Indian population (Reddy et al, 2007; Ajay et al, 2008). These culminating with lack of support mechanisms for evidence based treatments and follow-up for acute myocardial infarction, mean that there is almost 50% higher mortality among the poor compared with the rich in India (Xavier et al, 2008).

Thirty-two per cent of all mortality resulted from this chronic disease according to a study administered in 45 villages in a southern state of India (Joshi et al, 2006). In India, the prevalence of diabetes (a major risk factor for CVD and CHD) is projected to increase from 32 million in 2000 to 69.8 million in 2025. Similarly, the prevalence of hypertension is projected to increase from 118 million in 2000 to 214 million in 2025 (Kearney et al, 2005). These projections suggest that more people will suffer from CHD in India in the future. The productive years of life lost in those aged 35 to 64 years is also on the rise. In 2000, it was 9.2 million and this is expected to increase to 17.9 million by 2030 (Leeder et al, 2005). Once thought to be a disease of the 'rich', CVD is now fast affecting the poor in rural and urban settings. Lack of awareness of the risk factors for CVD contributes to the morbidity and mortality of South Asians within and outside of India (Rastogi et al, 2004).

According to a Canadian study, South Asians were represented as a strong and independent determinant for CVD in Canada (Anand et al, 2000). Interestingly, South Asians had less atherosclerosis than Europeans, yet they had higher cardiovascular disease rates suggesting a paradox. This prevalence of CVD was highest in South Asians followed by Europeans and then Chinese. Anand and colleagues (2000) also found a higher prevalence of plasma lipid and glucose abnormalities in South Asians than in other ethnic groups (Anand et al, 2000). Another, study also identified that Canadians of South Asian origin have an increased prevalence of CVD compared with Canadians of European and Chinese origin (Sheth et al, 1999). Major causes of CVD were IHD and cerebral vascular disease. Canadian men of South Asian origin had a higher mortality rate for IHD than the men of European origin while men of Chinese origin had the lowest mortality rate among these men (Sheth et al, 1999).

Furthermore, similar findings have been identified in Singapore by Danaraj and colleagues in 1959. Postmortem autopsies of 9,568 bodies revealed that Indians had a high rate of severe premature heart disease (Danaraj et al, 1959). It also revealed a rate of coronary atherosclerosis seven times higher in Indians than in Chinese (Danaraj et al, 1959). Hence, this was the first study to conclusively report the predicament of CVD in South Asians. Following this, Hughes and colleagues (1990) reported that diabetes was more common in South Asians (Indians) which may account for their higher risk of IHD than the Malays and Chinese in Singapore. One other study also reiterated this in Singapore showing South

Asians to have more than a three times higher risk of developing CHD than Chinese and Malays (Lee et al 2001). This phenomenon was also seen in South Africa where a higher mortality rate from CVD/CHD was found in Indian men and women than in white men and women (Adelstein, 1963).

2.3.3 South Asians living in the UK

The South Asian population who are born or have their origins from the Indian subcontinent (comprising of India, Pakistan, Bangladesh, Nepal, and Sri Lanka) are highly susceptible to CVD (Ramaraj & Chellappa, 2008). Since the 1950s and 1960s gradual awareness took place of this susceptibility (Patel & Bhopal, 2004). Censuses have shown a greater excess in mortality rates in Indian subcontinent born South Asians than the general population of England and Wales. This has been evident from the studies of Balarajan (1991) and Wild and McKeigue (1997).

South Asians make up 4.1 % of the UK population and they are the largest ethnic minority group (Wild and Mckeigue, 1997). South Asians living in the UK are more likely to suffer from CVD than the general population (BHF 2009). They also experience a higher prevalence of non-insulin dependent diabetes mellitus, lower plasma high density lipoprotein cholesterol (HDL-C) concentrations and higher plasma triglyceride concentrations (Hughes et al, 1989; Knight et al, 1992; McKeigue et al, 1991). The incidence rate of myocardial infarction has been reported to be higher in South Asians compared with other ethnic groups. (Wild et al, 2007). Asian survivors of first myocardial infarction have also been identified to have a higher prevalence of hyperinsulinaemia and they tend to be generally younger than whites (Hughes et al, 1989). The description South Asians give of their symptoms is often atypical and this makes it difficult for medical staff in the initial diagnosis and interpretation to take immediate action. Hence, the process of treatment in South Asians is delayed (Barakat et al, 2003; Teoh et al, 2007). In addition, impaired glucose tolerance, and central obesity exacerbate coronary artery disease in South Asians. On the whole, mortality ratios of CVD, CHD and stroke are also higher in South Asians in UK than the local population (Wild et al, 2007). This is further evident from a recent cardiovascular risk assessment study conducted in the UK which screened almost equal numbers of male and female South Asians. It identified that 92% of them had at least

one modifiable CVD risk factor placing them in a high CVD risk population (Rao et al, 2012). With respect to the most prevalent CVD risk factors 52% were hypertensive, 40% were obese, 75% had central obesity and 10% had total cholesterol/HDL-C ratio values greater than six (Rao et al, 2012). Estimates suggest a three to five fold increased risk of myocardial infarction and cardiovascular death among migrant South Asians than other ethnic groups (Eapen et al, 2009).

South Asians, innately have been known to have higher plasma triacylglycerol (TAG), lower HDL-C and higher low density lipoprotein cholesterol (LDL-C) concentrations than other groups. South Asians also appear to be more susceptible to hypertension, type 2 diabetes, impaired glucose tolerance, increased fasting glucose concentration, insulin resistance and the metabolic syndrome than other ethnic groups (Tziomalos et al, 2008). This may be due to genetic factors predisposing them to high levels of metabolic cardiovascular risk factors. Alternatively, environmental influences may be responsible (Reddy & Yusuf, 1998).

Although South Asians in general suffer from a higher risk of CHD than other groups in the UK there is also a variation in risk of CHD within the South Asian population. Pakistani and Bangladeshi men born in the sub-continent of India but living in the UK now are more than two times more likely to die from CHD than the national average. Pakistani women are two and half times more prone to CHD than the national average (BHF 2009). In terms of prevalence among them, Bangladeshis are worst affected followed by Pakistanis and then Indians (Bhopal et al 1999). This is the same for CVD (Wild et al, 2007). However, for blood pressure, Indians have a higher prevalence of hypertension followed by Pakistanis and lastly Bangladeshis (Agyemang et al, 2002). South Asians resemble more of a heterogeneous than a homogeneous group. There is conflicting evidence over whether hypertension is more common in South Asian groups. One study found diastolic blood pressure among South Asian (mainly Punjabi) men in Glasgow was higher than in the general population but this was not so for South Asian women or for systolic blood pressure (Williams et al, 1994). South Asian groups in Newcastle, particularly Bangladeshis, were found to have lower blood pressure than Europeans (Bhopal et al, 1999).

2.4 Risk factors for heart disease

Risk factors are conditions that elevate the danger of contracting heart disease. They can be categorised into modifiable and non-modifiable risk factors. Examples of modifiable risk factors are smoking, physical inactivity, obesity, high blood pressure and high blood cholesterol. Age, sex, hereditary and ethnicity are examples of non-modifiable risk factors. These may be categorised as traditional risk markers. In addition are the emerging risk markers. The following are a few examples: C-reactive protein (CRP), interleukin-6 (IL-6), soluble intercellular adhesion molecules (sICAM-1), soluble vascular cellular adhesion molecule-1 (sVCAM-1).

2.4.1 Traditional risk factors

2.4.1.1 Modifiable risk factors

Hypertension or high blood pressure may be related to a variety of factors including age, ethnicity, family history, overweight, low physical activity, high sodium intake, excessive alcohol consumption and psychosocial stress (AHA, 2012). Hypertension substantially contributes to high death rates from IHD, cerebrovascular disease and renal failure (Joshi et al, 2006). There is a change with age in the relative importance of SBP and DBP as risk indicators. Below 50 years of age, DBP is the major predictor of IHD risk, whereas above 60 years of age, SBP is more critical (Franklin et al, 2001). Each 20 mm Hg increase in SBP or 10 mm Hg increase in DBP doubles the risk of a fatal coronary event (Lewington et al, 2002). In the Chicago Heart Association Detection Project in Industry, men 18 to 39 years of age at baseline with a blood pressure of 130 to 139/85 to 89 mm Hg or with stage 1 hypertension (140 to 159/90 to 99 mm Hg) accounted for nearly 60% of all excess IHD, overall CVD, or all-cause mortality (Miura et al, 2001). In addition, resting heart rate and blood pressure, even within the normal ranges, proportionately raise the risk for developing diabetes mellitus in middle-aged men and women. The adverse effects of heart rate and blood pressure are independent of each other as well as the influences of age, body mass index, smoking, drinking, exercise and education. Resting heart rate and blood pressure may affect glucose tolerance and lead to the development of diabetes mellitus (Nagaya et al, 2010).

Moreover, there is a strong correlation between time of the day and cardiovascular events which often coincide with the early morning surge in blood pressure (Kario et al, 2003). The risk as a result of the morning surge has also been noted after rising from afternoon siesta (Bursztyn et al, 1999). The sudden activation of the sympathetic nervous system may be the main mediator of the morning surge (Panza et al, 1991). Arousal from sleep is associated with increases in both epinephrine and norepinephrine which could be the mechanism responsible (Dodt et al, 1997). It is estimated that over seven million people worldwide die each year as a result of raised blood pressure (WHO, 2005).

Hypercholesterolaemia is another risk factor for heart disease. Cholesterol is a fat-like substance produced by the liver that travels in the blood. It is found in all body cells and is the raw material for the manufacture of steroid hormones and bile acids. Its insolubility in water, a property that makes it useful in cell membranes also makes it hazardous. Accumulation of this errant cholesterol in the artery wall can lead to plaque formation, eventually leading to atherosclerosis and CHD. Low density lipoprotein is the carrier for the most cholesterol in human plasma (Brown and Goldstein, 1986). The idea that cholesterol plays a causal role in atherogenesis is supported by a large body of experimental, epidemiological and clinical evidence (Lind, 2002; Stamler et al. 1986). Accordingly, hypercholesterolemia has been implicated in atherosclerosis appearance and progression by starting a cascade of cellular and molecular events leading to endothelial dysfunction, plaque instability and cardiovascular events (Ross, 1993). It is estimated that approximately 4.4 million people worldwide die each year as a result of raised total cholesterol levels (WHO, 2005).

Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces (WHO, 2011). It is categorised into type 1 which is the inability to produce insulin and type 2 or adult onset which is also known as non-insulin dependent diabetes (i.e. the pancreas produces insulin but the tissues are unresponsive to it). Apart from these there is gestational diabetes which relates to elevated blood glucose concentrations induced during pregnancy. This can actually pave the way to the development of type 2 diabetes. Of the two main forms of diabetes type 2 is the most prevalent (WHO, 2011). Certain ethnic groups have a greater risk of developing diabetes. It is evident that people suffering from diabetes have a high

risk of developing CVD. Diabetes can also lead to complications such as blindness, amputation and kidney failure. Oxidative stress mediated by reactive oxygen species is also promoted by the diabetic state (Baynes et al, 1999). Diabetes affected over 220 million people around the world in 2005 and 1.1 million people died of diabetes in 2005 (WHO, 2009a). Atherosclerosis, the main cause of CHD, occurs with higher than normal frequency in patients with diabetes and pre-diabetes and is the major cause of morbidity and mortality in diabetic patients (Nathan et al, 1997; Meigs et al, 1997). However, the mechanism responsible for the increased risk for atherosclerosis in diabetes is still controversial (Kuusisto et al, 1994). The response to injury hypothesis of atherosclerosis states that the injurious response initially occurs to the endothelium of the artery, leading to endothelial dysfunction (Ross, 1993). Indeed, endothelial dysfunction has been shown to occur in patients with diabetes (Ross, 1993; Calver et al, 1992) and chronic hyperglycaemia is implicated as a cause for endothelial dysfunction (Kuusisto et al, 1994; Ting et al, 1996). However, Type 2 diabetes and impaired glucose tolerance (IGT) are often associated with other risk factors such as hypertension, dyslipidaemia and obesity, each of which may cause endothelial dysfunction (Nathan et al, 1997; Meigs et al, 1997; Kuusisto et al, 1994).

Obesity and overweight arise as people expend fewer calories than they consume so that energy intake exceeds energy expenditure. This can lead to elevations in cholesterol concentrations, blood pressure and several other disease risk factors increasing the risk of coronary artery disease and diabetes and a variety of other diseases/conditions (Poirier et al, 2006). Being overweight is defined as having a body mass index (BMI) over 25 $kg \cdot m^2$ (weight in kilogrammes divided by height in metres squared) and those with a BMI above 30 $kg \cdot m^2$ are considered obese in accordance with the National Heart, Lung, and Blood Institute (NHLBI, 2010). Obesity increases the risk of insulin resistance and diabetes in particular and these in turn are related to atherogenic dyslipidaemia (Yudkin et al, 1999). Obesity may affect the heart through its influence on risk factors such as dyslipidaemia, hypertension, glucose intolerance, inflammatory markers, sleep apnoea/hypoventilation and the prothrombotic state (Poirier et al, 2006). Overweight and obesity predispose to or are associated with numerous cardiac complications such as CHD, heart failure and sudden death because of their impact on the cardiovascular system (Poirier et al, 2006). It is estimated that approximately 2.6 million people die each year as a result of being overweight or obese according to the WHO (2005).

As discussed below, a sedentary lifestyle is another major risk factor for CHD which is well established and is associated with a 2-fold increase in risk for CHD (Wannamethee & Shaper, 2001). According to the WHO, an estimated 1.9 million deaths are caused globally by chronic diseases resulting from inadequate physical activity. The American College of Sports Medicine and the American Heart Association recommend that adults perform at least 30 minutes of moderate intensity physical activity on most days of the week or alternatively, vigorous intensity physical activity for at least 20 minutes on three days of the week or a combination of both (Haskell et al, 2007). The Global Recommendations on Physical Activity for Health suggest 150 minutes of moderate intensity aerobic physical activity throughout the week or at least 75 minutes of vigorous intensity aerobic physical activity throughout the week or an equivalent combination of moderate and vigorous intensity activity (WHO, 2010). Physical activity helps to decrease the risk of morbidity and mortality that may arise through CVD, stroke, type 2 diabetes, colon cancer and breast cancer. In addition, physical activity also helps to burn calories, control cholesterol, manage bodyweight, lower blood pressure, strengthen heart muscle, manage osteoporosis and manage musculoskeletal conditions (WHO, 2009b). As a result, a lower heart rate is achieved, stroke volume increases and this leads to an increased cardiac output. These enable the heart to function more effectively and efficiently. Furthermore, physical activity helps to raise the level of HDL-C and possibly lowers LDL-C (Hardman, 2007). Physical inactivity or sedentary activity may be related to obesity and the risk for chronic disease through an increase in energy intake and not just because of a lower energy expenditure (Rastogi et al, 2004). Physical inactivity may also give rise to biological setbacks such as increases in blood pressure, low HDL-C, decreased insulin sensitivity, poor endothelial function and increased atherogenic cytokine production (Pate et al, 1995; DHHS, 1996). Physical inactivity also leads to lower energy expenditure and reductions in lean body mass (Rastogi et al, 2004).

Smoking has a widespread effect on heart disease. The nicotine, tar and carbon monoxide components cause fatty plaque to build up in the arteries eventually causing insufficient blood supply to the heart. Smoking raises blood cholesterol and it also impairs fibrinolysis raising the risk of a blood clot and hence a heart attack. Many are well informed that smoking causes lung cancer but many are unaware of its adverse effects on the heart. Smoking increases the heart rate, tightens the arteries and creates irregularities in the

heartbeat. Cigarette smoking triples the risk of dying of CHD. On average, adults who smoke cigarettes die 13 to 14 years earlier than non-smokers (AHA, 2009). Smoking results in impaired endothelial function, increased intima media thickness, decreased nitric oxide bioavailability and increased atherosclerotic plaque formation (Antoniades et al, 2008). Children exposed to passive smoking have been found to have increased oxidative stress. This suggests that the generation of free radicals in the vascular wall has been stimulated by the inhaled smoke. This implies that passive smoking affects the non-smoker in the same way as a smoker (Kosecik et al, 2005). In 2001, tobacco-related mortality was 4.9 million globally and this figure is estimated to reach 10 million by 2020 if appropriate action is not taken (WHO, 2002).

Excessive alcohol consumption is another element that impairs the function of the heart which brings about high blood pressure, stroke, irregular heartbeats, and cardiomyopathy (disease of the heart muscle) (BHF 2010). Drinking alcohol also increases caloric intake facilitating weight gain and hence overweight. In addition, binge drinking results in adverse effects such as hypercoagulability or tissue damage (U.S.DHHS, 2005). Evidence from observational studies has shown that moderate alcohol consumption (one to two drinks per day) is associated with a lower risk of cardiovascular disease. Moderate alcohol consumption also is associated with reduced risk of all-cause mortality among middle-aged and older adults and may help to keep cognitive function intact with age (U.S.DHHS, 2005).

In addition, psychosocial factors including stress may also elevate the risk of CVD. This possibly relates to different personalities differently in terms of their mental and emotional state. According to Williams and colleagues (2009), psychosocial factors may contribute to CHD in both males and females. Psychosocial factors have been shown to influence CHD risk (Rozanski et al, 2005). Factors such as depression and chronic work stress are independently associated with increased risk of heart disease whereas social networks and support appear to be protective (Nicholson et al, 2006; Bosma & Marmot, 1997; Rosengren et al, 2004). A recent study examined the stress hormone - cortisol. Cortisol is produced in order to help the body recover from stress and regain its physiological stability. High levels of cortisol are associated with death from CVD. In a six year study, Vogelzangs and colleagues (2010) investigated 861 participants aged over 65 years measuring their urinary

cortisol concentration and its association with all-cause and cardiovascular mortality. This study found that those with the highest levels of urinary cortisol had a five-fold higher risk of death form CVD (Vogelzangs et al, 2010). However, no relation was found between high urinary cortisol and other causes of death.

2.4.1.2 Non-modifiable risk factors

Generally, men have a higher tendency to suffer a heart attack than women. Women have an innate protection against CVD due to the hormone oestrogen (Stork et al, 2004). As a regulator of inflammation, oestrogen exerts several anti-inflammatory effects. Oestrogen plays a critical anti-inflammatory role through endothelial generation of nitric oxide (NO). Nitric oxide is an important vasoprotector. Oestrogen helps to attenuate oxidative stress and inflammation through its antioxidant properties (Chakrabarti et al, 2008). With menopause the concentration of this hormone decreases placing postmenopausal women at a higher risk of CVD (Stork et al, 2008). By the age of 65 the chances of heart attack are similar between men and women.

The risk of developing CVD increases with age. This may be due to the thickening of the heart's walls together with stiffening and hardening of the arteries. This in turn affects the stroke volume, cardiac output and heart rate. Higher levels of inflammation have been observed in older adults (Najib et al, 2012). In addition, calcification and plaque necrosis are more common in plaque from older adults which reflects the chronic level of the disease (Najib et al, 2012).

The risk of having heart disease is also linked to hereditary. This is a case when a parent has a heart condition and this can be passed down the family tree. Congenital cardiovascular defects or congenital heart defects may arise from abnormal formation of the heart or major blood vessels (AHA, 2009).

2.4.2 Emerging risk factors

In addition to traditional risk factors are the emerging risk factors which are significant predictors of atherosclerosis and its complications. These are numerous, but we will examine, C-reactive protein (CRP), interleukin 6 (IL-6), tumour necrosis factor alpha

(TNF-α), soluble vascular adhesion molecules (sVCAM-1), soluble intercellular adhesion molecules (sICAM-1), homocysteine, fibrinogen and progenitor cells.

C-reactive protein is a circulating acute phase reactant that is highly augmented all through the inflammatory reaction to tissue injury or infection (Hackam and Anand, 2003). The liver helps to synthesise CRP and IL-6 and other proinflammatory cytokines are responsible for stimulating its release (Pearson et al, 2003). C-reactive protein strongly predicts future CHD and type 2 diabetes mellitus in adults (Misra, 2004). Elevated CRP concentrations are associated with overweight, obesity and insulin resistance which may influence the development of atherosclerosis and type 2 diabetes mellitus in adulthood. C-reactive protein concentrations are also positively associated with endothelial dysfunction and other CVD risk factors in children (Misra, 2004). C-reactive protein has limited clinical value in CVD risk stratification or predicting response to statin therapy in elderly people (Sattar et al, 2009). C-reactive protein concentrations are increased in heart failure and higher concentrations of CRP gravely affect the haemodynamic and neurohormonal profiles which have been related to more serious heart failure and poor quality of life. C-reactive protein is also associated with mortality and morbidity in relation to CVD (Anand et al, 2004).

Interleukin-6 is a major pro-inflammatory cytokine produced in a variety of tissues, including activated leukocytes, adipocytes, and endothelial cells (Pradhan et al, 2001). It acts on the liver to stimulate the production of several acute-phase proteins (Cardellini et al. 2007). Contracting skeletal muscle has been found to be the main source of IL-6 in the circulation in response to exercise (Pederson, 2009). Circulating IL-6 levels have been reported to be elevated in subjects with IGT or type 2 diabetes (Muller et al, 2002) and have been shown to predict development of type 2 diabetes (Pradhan et al, 2001). Higher circulating IL-6 levels have been reported in severe congestive heart failure (Torre-Amione et al, 1996). They are prognostic indicators in multiple myeloma (Pelliniemi et al, 1995). Higher IL-6 levels may also reflect cellular damage, such as oxidative stress (Baeuerle et al, 1996). Lastly, IL-6 may counter regulate levels of tumour necrosis factor- α and interleukin-1β (Tilg et al, 1997, Xing et al, 1998) so that higher IL-6 levels may reflect damage from other cytokines. Interleukin-6 has been shown to predict all-cause mortality as well as cardiovascular mortality (Harris et al, 1997; Volpato et al, 2001). It is suggested

that IL-6 is more closely related to risk of fatal myocardial infarction and stroke (fatal CVD) than to nonfatal vascular events in the elderly at risk (Sattar et al, 2009).

Tumour necrosis factor alpha (TNF-α) is a multifunctional cytokine that exerts a series of biological actions in different cells, tissues, organs and species. It has also been demonstrated to regulate and interfere with energy metabolism, especially lipid homeostasis (Chen et al, 2009). Thus, it plays an important role in both acute and chronic inflammation. Tumour necrosis factor alpha could have an effect on lipid metabolism as it suppresses free fatty acid (FFA) uptake and promotes lipogenesis. Furthermore, it induces lipolysis, inhibits lipid metabolism related enzyme activity, regulates cholesterol metabolism, and regulates other adipocyte derived adipokines. (Chen et al, 2009). The critical role of TNF-α in adipocytes, chronic inflammation and adipocytes biology has been found recently (Langin et al, 2006; Popa et al, 2007). Increased plasma TNF-α levels have been found in patients with hypercholesterolaemia. A positive correlation between TNF-α and very low density lipoprotein cholesterol (VLDL-C), triacylglycerol (TAG) and total cholesterol concentrations has been observed in hyperlipidaemic patients (Jovinge et al, 1998). High concentrations of TNF-α induce the production of reactive oxygen species (ROS) which are chemically reactive molecules containing oxygen and this results in endothelial dysfunction in type 2 diabetes (Zhang et al, 2009). Endothelial dysfunction related with TNF-α in pathophysiological conditions is related to excess production of ROS and a decrease in nitric oxide bioavailability. The bioavailability of nitric oxide seems to be decreased by TNF-α because of the reduction in nitric oxide production and the augmented removal of nitric oxide (Goodwin et al, 2007; Picchi et al, 2006; Greenberg et al, 1993).

Soluble vascular adhesion molecules and sICAM-1 play an important role in the adhesion of leukocytes to the vascular endothelium. Their involvement facilitates movement of circulating leukocytes across the endothelium into the vessel wall. This serves as a primary cause of atherogenesis. In inflammatory, neoplastic and CVD concentrations of sICAM-1 and sVCAM-1 are elevated. Though this establishment serves to help in predicting clinical outcome, the mechanism and significance of the elevated concentrations are frequently ambiguous (Blann and Yip, 2000). Higher levels of sICAM-1 and sVCAM-1 are found in people with hypertriglyceridaemia (Ceriello et al, 2004). Ethnic differences in serum lipid levels may affect cellular adhesion pathways and present a possible mechanism for the

ethnic difference in CHD risk (Lupattelli et al, 2000; Abe et al, 1998). Adhesion molecule concentrations are positively related to serum cholesterol and TAG concentrations but negatively related to HDL-C concentration (Rohde et al, 1999). It is interesting to note that HDL-C is inversely related to CHD risk and it may assist in reducing cytokine-stimulated expression of endothelial cell adhesion molecules (Cockerill et al, 1995; Abe et al, 1998; Rohde et al, 1999). Increased levels of sICAM-1 have been associated with an increased risk of ischaemic stroke in patients with CHD (Tanne et al, 2002). In particular, sVCAM-1 and CRP have been shown to be the most important predictors of the risk of future CVD death (Blankenberg et al, 2001). Interestingly, smoking is a great contributor to the concentrations of sICAM-1. Abstaining from smoking has a significant effect in reducing circulating sICAM-1 concentrations (Scott et al, 2000).

Regulation of vascular tone, platelet aggregation, leukocyte adhesion, inflammation, thrombosis, fibrinolysis, and angiogenesis are numerous functions controlled by the vascular endothelium (Libby et al, 2002; Vogel, 1997). A shift to a proatherogenic phenotype, assisting the adhesion and trans-endothelial migration of circulating leukocytes is represented by the expression of adhesion molecules on activated endothelium cells. Levels of soluble adhesion molecules in the circulation reveal an augmented expression on the endothelium (Leeuwenberg et al 1992). Hence, soluble adhesion molecules are used as biomarkers of endothelial dysfunction.

Homocysteine, is a highly reactive sulphur containing amino acid. It is formed as a consequence of the metabolism of the essential amino acid methionine (Mangoni and Jackson, 2002). Homocysteine is re-metabolised by cells in numerous probable pathways involving various enzymes. Folate, cobalamin (vitamin B_{12}) and pyridoxine (vitamin B_6) are B vitamins used as substrates by these enzymes (De Bree et al, 2002). Elevation in oxidative stress, endothelial dysfunction, platelet activation, hypercoagulability, vascular smooth muscle cell proliferation and endoplasmic reticulum stress can bring about vascular damage. Homocysteine may be responsible for inducing this damage (Mangoni and Jackson, 2002; De Bree et al, 2002; Werstuck et al, 2001). B vitamins are an effective therapy for reducing homocysteine concentrations (Chambers et al, 2000).

Fibrinogen is an acute phase reactant and a circulating glycoprotein. It acts at the last stage in the coagulation response to vascular and tissue injury (Herrick et al, 1999). Soluble fibrin fragments are the most abundant component of blood clots and they are produced by the cleavage of thrombin (Herrick et al, 1999). Determination of blood viscosity, stimulation of platelet aggregation, vasoconstriction at sites of vessel wall injury and regulation of cell adhesion, chemotaxis and proliferation are many of the possible roles it plays in vascular disease (Di Minno et al, 1990; Danesh et al, 1998; Fuster et al, 1992). Fibrinogen is associated with IHD and peripheral vascular disease (Fowkes, 1995). Patients with diabetes, hypertension, obesity and physically inactive lifestyles have been found to have high concentrations of fibrinogen (Maresca et al, 1999).

Endothelial progenitor cells (EPCs) obtained from the bone marrow play a role in endothelial repair. Impaired mobilisation or depletion of endothelial progenitor cells contribute to endothelial dysfunction and progression of CVD (Hill et al, 2003). Hence, EPCs may have implications for endothelial health and homeostasis. Endothelial progenitor cells circulate in the blood and contribute to neovascularisation. Predisposition to CVD due to, for example, diabetes is associated with reduced circulating EPC numbers which may be indicative of chronic vascular injury (Loomans et al, 2004; Tepper et al, 2002). In addition, a study by Werner and colleagues (2005) found a significantly higher incidence of death from cardiovascular causes during a 12 month period in patients with low baseline levels of EPCs. They also established that patients with high numbers of EPCs had a reduced risk of revascularization. Moreover, circulating EPCs in patients with CVD can be used to identify patients at high risk for major adverse cardiac events (Werner et al, 2005). Furthermore, during a myocardial infarction a strong chemokine signal mobilises progenitors from the bone marrow into the circulation (Shintani et al, 2001). Hence elevated EPCs may be indicative of a myocardial infarction.

2.4.3 Heart disease risk factors in South Asians

South Asians are a population susceptible to CVD. Many risk factors give rise to this disease and thus we will examine some of the most prominent ones. South Asians appear to have more atherogenic lipid profiles than White Europeans as they have higher plasma TAG and lower HDL-C concentrations predisposing them to atherogenesis and this may

also reflect underlying insulin resistance (Chowdhury & Lasker, 2002; Anand et al, 2000; McKeigue et al, 1991; Chambers et al, 2001). A large HDL-C size is associated with cardioprotection (Bhalodkar et al, 2004). In the Framingham Offspring Study 211 South Asian and 1684 European men were examined and although concentrations of HDL-C were similar in both populations concentrations of large, more protective HDL particles were found to be lower and concentrations of small HDL particles were found to be higher in South Asian than in European men (Bhalodkar et al, 2004). In addition, LDL particle size in South Asians is smaller though total LDL concentrations are comparable with other populations. This is critical because small LDL particles are more susceptible to oxidation and thus are more atherogenic (Kulkarni et al, 1999).

Hypertension (a major CVD risk factor) is highly prevalent in South Asians (McKeigue et al, 1991; Agyemang & Bhopal, 2002). Several studies have reported lower mean systolic but higher diastolic blood pressure in South Asian men and women than in European men and women (Agyemang & Bhopal, 2002). The prevalence of hypertension is higher in South Asian men than in European men (Agyemang & Bhopal, 2002). Inconclusive results were found regarding the prevalence rates of hypertension in women of South Asian and European origin (Agyemang & Bhopal, 2002). Mean blood pressure and the prevalence of hypertension also differed within the South Asian population (Bhopal et al, 1999). The Newcastle Heart Project study and the 1999 Health Survey of England identified lower mean systolic and diastolic blood pressures in Bangladeshi males and females than in their Pakistani and Indian counterparts (Bhopal et al, 1999). The prevalence of hypertension was also lower among Bangladeshi males and females than among Pakistani and Indian men and women. It was also found that Indians had higher blood pressure levels than Pakistanis (Bhopal et al, 1999). Thus due to their lower HDL-C and higher blood pressure South Asians are highly vulnerable to CHD risk (Chowdhury and Lasker, 2002).

The prevalence of type 2 diabetes mellitus is substantially higher in South Asians residing abroad than in White Europeans (Anand et al, 2000; McKeigue et al, 1991; Chambers et al, 2001). One study revealed that about 20% of South Asians (whether in the UK or indigenous to Asia) over the age of 50 years are affected by diabetes (Mather & Keen, 1985; Ramachandran et al, 1997). In South Asians, this disease seems to present itself at a younger age compared with Europeans (Mather & Keen, 1985; Ramachandran et al, 1997).

At diagnosis, South Asians have been shown to have greater complications with early-onset type 2 diabetes including established macrovascular disease, retinopathy and nephropathy (Chowdhury and Lasker, 2002). Compared with White Europeans, South Asians tend to have a higher risk of diabetic complications, especially renal disease and CHD (Mather & Keen, 1985; Ramachandran et al, 1997). South Asians also have a higher prevalence and faster progression of nephropathy than White Europeans. Poorer glycaemic, blood pressure and lipid control have been identified in South Asians with type 2 diabetes (Chowdhury et al, 2006). India's diabetes patient population was estimated to be 50.8 million in 2010 and it is predicted to reach 79.4 million in 2030 (Misra & Khurana, 2011).

In addition, South Asians also have a higher prevalence of IGT and increased fasting glucose levels than White Europeans (Anand et al, 2000; Chambers et al, 2001). Insulin resistance is also higher in South Asians compared with White Europeans (McKeigue et al, 1991; Chambers et al, 2001). South Asians are also affected by acute coronary syndromes and the patients are younger, more likely to be diabetic and tend to report a higher intensity of pain over a greater area of the body (including over the backs) than White Europeans. In South Asians both in England and Wales, CHD is the primary cause of death and this risk is brought about by hyperinsulinaemia and central obesity which is common among this group (Mckeigue et al, 1993, Balarajan et al, 1991).

Nearly 13% of Asian Indian children and young adults in India have subclinical inflammation, and almost 20% have insulin resistance, indicating a high risk for CHD in adulthood (Misra, 2004). Notably, higher CRP concentrations have been found in Asian Indian adults in comparison with Europeans (Misra, 2004). In addition to CHD; metabolic syndrome, carotid artery atherosclerosis, stroke, peripheral vascular disease and future development of type 2 diabetes can be correlated to CRP (Chambers et al, 2001; Tamakoshi et al, 2003; Cao et al, 2003; Han et al, 2002).

It has been suggested that South Asians have a greater impairment of endothelial function than White Europeans and this is not accounted for by established CVD risk factors (Murphy et al, 2007). South Asians have lower levels of progenitor cells which are involved in endothelial repair and regeneration. The reduced EPCs in South Asians could be a defect responsible for CVD. It was also found that EPC count was independently

predicted by ethnicity (Murphy et al, 2007). In patients with established CVD an impaired functional capacity of EPCs is a known occurrence (Vasa et al, 2001, Heeschen et al, 2004). The primary reason for lower circulating EPC numbers in South Asians may be due to a reduced systemic nitric oxide bioavailability. In both progenitor cell mobilisation and function, nitric oxide plays a critical role and this has been evident from several studies (Murphy et al, 2007). Insulin resistance is likely an initiator in this process (Loomans et al, 2004; Tepper et al, 2002).

Some studies report higher homocysteine concentrations in South Asians than White Europeans. It has been suggested that raised homocysteine concentrations may account for twice as many CHD deaths in South Asians than White Europeans and this may contribute to their increased CHD risk (Anand et al, 2000; Chambers et al, 2000). Raised homocysteine concentrations in South Asians may also be related to their reduced vitamin B_{12}, B_6 and folate levels implying that the increased CHD risk in this group may be reduced by dietary vitamin supplementation (Chambers et al, 2000).

The Wandsworth Heart and Stroke Study examined 664 males and females who were made up of 261 European White, 188 African Origin and 215 South Asians. All of these participants were free from diseases and treatments of any kind. This study investigated ethnic differences in circulating soluble adhesion molecules among the ethnic groups who were living in England (Miller et al, 2003). Those of Caribbean or West African descent were found to have lower levels of sICAM-1 and sVCAM-1 than White Europeans and South Asians. This finding may explain why there is a high risk of CHD in South Asians (Miller et al, 2003). On the contrary, though the morbidity and mortality rates from CHD in British South Asians are high, they did not have higher adhesion molecule values than White Europeans. Studies have identified that soluble adhesion molecules are associated with CHD (Miller et al, 2003) but it may be that adhesion molecules are not as critical in the development of CHD in South Asians and there may be some fundamental genetic vulnerability affecting them (Miller et al, 2003).

Data suggest that the proposed cut-offs for defining overweight and obesity are not appropriate for South Asians and that they are at risk of developing obesity related comorbidities at lower levels of BMI and waist circumference (Deurenberg et al, 2001;

Vikram et al, 2003). A recent consensus statement for South Asians proposed BMI cut off points of 23 to 24.9 kg·m^2 for overweight and ≥25 kg·m^2 for obesity. These are lower than the internationally prescribed guidelines for overweight, (25 to 29.9·kg m^2) and obesity (≥30 kg m^2). (Misra et al, 2009). Similarly, due to high morbidities seen at lower waist circumferences in South Asians cut off points of ≥90 cm and ≥80 cm (for males and females respectively) have been proposed for South Asians in contrast to the international guidelines of ≥102 cm and ≥88 cm (for males and females respectively) (Misra et al, 2009).

Sedentary lifestyles or physical inactivity have been associated with a 1.5 to 2.4 fold elevation in CHD risk (Pate et al, 1995). One study has demonstrated a strong and dose-dependent inverse relationship between leisure-time exercise and non-fatal CHD among South Asians. This study also observed a positive association between sedentary activity and CHD risk (Rastogi et al, 2004). Physical inactivity is also associated with the various components of the metabolic syndrome (Mohan et al, 2005). Regular physical activity reduces the risk of obesity, blood lipid abnormalities, hypertension and non-insulin dependent diabetes mellitus and has been shown to substantially reduce the risk of CHD (Pate et al 1995; DHHS, 1996). In consideration of the severe CVD burden among South Asians, a recent consensus statement for physical activity guidelines has been outlined specifically for this ethnic group (Misra et al, 2012). According to these recommendations South Asians should perform 60 minutes of physical activity daily comprising of 30 minutes of aerobic activity, 15 minutes of resistance activity and 15 minutes of work related activity (Misra et al 2012).

2.5 Exercise and heart disease

Exercise is a planned, structured and repetitive form of activity and it is a subset of physical activity. It has a final or an intermediate objective, the improvement or maintenance of physical fitness (Caspersen et al, 1985). Advancement of automation in today's modern world has strongly affected the energy gradients between occupations. Automated machines have transformed several of the high energy occupations to almost a sedentary level. With this evolvement the protective benefits gained through physical activity are absent (Davies, 1997). Hence, energy expenditure during leisure time has to be increased to produce a beneficial effect.

In addressing the following section the terms exercise and physical activity will be used interchangeably. As exercise is a subset of physical activity, they will be subsumed as one to explain the studies conducted and the effects of physical activity/exercise on the risk of heart disease.

2.5.1 Physical activity, heart disease and mortality

Numerous studies have examined physical activity and illustrated its non-pharmacological benefits. In the following sections, a few selected studies and how their findings have served to emphasise the importance and relationship of physical activity and CVD will be elaborated.

Any bodily movement produced by skeletal muscles is termed physical activity and its energy expenditure can be measured in kilojoules (kJ) or kilocalories (kcal). Occupational activity, sports activity, conditioning, household or other activities in daily life all involve physical activity (Caspersen et al, 1985). According to the American College of Sports Medicine (ACSM) (Haskell et al, 2007) and AHA (Haskell et al, 2007), adults are recommended to perform 30 minutes of moderate intensity physical activity 5 days a week or 20 minutes of vigorous intensity physical activity on 3 days a week or a combination of moderate and vigorous activity. This should equate to between 450 and 750 metabolic equivalent (MET) minutes a week. This value serves as the least required to achieve significant health benefits in addition to the routine activities of daily living (Haskell et al, 2007).

Many studies have investigated the relationship between physical activity and heart disease. Of these, possibly the most notable was a study on London transport workers published in 1953 which demonstrated a striking association between lower levels of exercise and heart disease (Morris et al 1953). It examined the bus, tram and trolleybus conductors who climbed an average of 500 to 750 steps per working day and the drivers who sat for most of their working time. Bus drivers were found to have a higher prevalence of heart disease than bus conductors and it was proposed that this was due to the difference in physical activity levels between these two occupations. In the same study, Morris and colleagues also investigated postal workers and civil servants. This disclosed that the

physically active postmen were less likely to have CHD which struck less active civil servants (telephonists, clerks, executives) at an earlier age. Though the active group was not immune from diseases, they were affected by less severe disease in the case of angina pectoris which was more prevalent but less severe in the active individuals. Essentially, physical activity at work appeared to have a beneficial effect in terms of CHD risk in middle aged men.

The San Francisco Longshoremen and Harvard College Alumni studies also identified an association between heart disease and physical inactivity. Paffenbarger and colleagues (1970) found that active cargo handlers (who expended more than 1000 kcal/day) had distinctly lower CHD rates than their sedentary colleagues. In 1975, Paffenbarger and Hale published a study which observed the outcome of repeated bursts of work activity in 6351 longshoremen during an 8 hour shift. They found a defensive element innate in this high energy work in relation to CHD mortality. In a further investigation, 3975 longshoremen with a high energy work activity of 29.3 kJ per min were compared with the lowest energy work activity group of 4.19 kJ per min. The high energy group had half the rate of myocardial infarction (Brand et al, 1979). It was found that regardless of smoking or high systolic blood pressure cargo handling longshoremen experienced lower death rates than their sedentary counterparts. Physical activity and its energy expenditure provided protective measures (Paffenbarger et al, 1970).

Being physically active when young and stopping its continuity in adulthood does not appear to protect against heart disease. In order to gain optimal protection it appears that one has to pursue physical activity throughout adult life. In a study of Harvard college alumni, activities were categorised according to their energy expenditures and a weekly physical activity index was calculated for each study participant. Low energy expenditure was classified as anything less than 8372 kJ/week and high energy expenditure was classified as anything above 8372 kJ/week. It was found that the high energy expenditure group had lower rates of heart attack and angina pectoris and were affected by cardiac death at an older age (Paffenbarger et al, 1978). In another study which examined physical activity, all-cause mortality and longevity of college alumni, Paffenbarger and colleagues (1986) noted positive effects until the age of 80 years in those men expending more than 8374 kJ /week. In addition, Sesso and colleagues (2000) followed 12,516 middle aged and

older men with an age range from 39 to 88 years. They found a 20% lower CHD risk in men who expended more than 4200 kJ/week in total physical activity. This relationship between physical activity and CHD also extended to men with multiple coronary risk factors. Furthermore, Hardman (2001) identified that critical to cardioprotection against CVD is intensity relative to one's capacity. This is important because what could be warm-up intensity for one person could be almost maximal load for someone else. Besides, VO_2 max also declines with age in middle age and beyond thus a given MET value may indicate a greater relative intensity for older people.

Moreover, physical activity is associated with a lower risk of fatal heart attacks by 40% and non-fatal heart attacks by 50%. This was found in individuals who were involved in vigorous exercise (involving peaks in energy expenditure of $\geq$ 31.5 kJ/min/ $\geq$ 7.5 kcal/min) in comparison with their colleagues who failed to report vigorous leisure time activity. Morris and colleagues (1980) suggested that vigorous exercise provided a protective shield on the ageing heart against ischaemia and its effects. Family history of CVD increases the chances of cardiovascular mortality. Even with this situation as long as individuals were involved in vigorous exercise, they were able to halve their risk of mortality compared with those who did not take part in vigorous exercise (Morris et al, 1980).

These studies have highlighted the importance of physical activity for optimal cardiovascular and general health. Likewise, studies comparing physically active women with inactive women have demonstrated that mortality can be delayed and this was revealed in a review paper assessing 38 studies conducted in the United States and Europe. There was a 20% difference on average in death rates between the most and least active women (Oguma et al, 2002). Even lower levels of energy expenditure may reduce mortality risk in women (Andersen et al, 2000; Lissner et al, 1996). The Iowa Women's study observed an inverse relationship between moderate intensity physical activity and mortality (Kushi et al, 1997). Congruent with this, the Canadian Fitness Survey showed that men who expended more than 0.5 kilocalories per kilogram body weight per day had a 20% lower mortality risk than those who did not. Similarly, women experienced a 30% decrease in mortality risk when they expended more than 3.0 kilocalories per kilogram body weight per day. This study also found that modest participation in low intensity activities helps in the reduction in mortality risk (Villeneuve et al, 1998). Furthermore, the Nurses' Health

study and the Women's Health study observed associations between moderate intensity physical activity and lower risk of CHD (Manson et al, 1999; Lee et al, 2001). In addition higher levels of physical activity are also associated with fewer years of disability before death, helping women to live more fruitful lives (Ferrucci et al, 1999). These studies and many others over the past 10 to 20 years have shown that premature mortality in women can be averted by physical activity. Moderate intensity physical activity of 30 minutes per day on most days of the week can postpone mortality in women as well as men (Oguma et al, 2002).

Sedentary lifestyle or physical inactivity has also been associated with an increased CHD risk (Pate et al, 1995). Rastogi and colleagues (2004) conducted a hospital based case-control study and collected data from 350 cases of acute myocardial infarction and 700 controls matched by age, gender and hospital in New Delhi and Bangalore. They demonstrated that an equivalent of 3.6 hours per day of sedentary activities such as television viewing was associated with nearly a 90% increased risk of CHD. Long hours of standing while at work seem to also increase the risk. While low levels of physical activity lead to low energy expenditure and lower lean body mass, physical inactivity or sedentary activities may be associated with obesity and risk for chronic disease through not only increased energy intake but also lower energy expenditure. Therefore, these findings emphasise the association between increased sedentary activity and CHD (Rastogi et al, 2004). As a result, this study was the first of its nature to demonstrate the harmful effects of physical inactivity on health and the significance of leisure time exercise in the prevention of CHD risk among Indians (Rastogi et al, 2004).

The Nurses' Health Study compared walking with vigorous exercise in the prevention of CHD in women. The findings from this study indicate that both walking and vigorous exercise are substantially associated with reductions in the incidence of CHD (Manson et al, 1999). In both of these activities, the magnitude of reduction was similar when total energy expenditure was similar (Manson et al, 1999). This suggests that 3 hours or more of brisk walking each week could elicit a 30% to 40% decrease in the risk of coronary events in women. A combination of increased walking time and vigorous exercise would enhance the risk reductions (Manson et al, 1999). The Iowa Women's Health Study found that moderate and vigorous activity were inversely related to overall mortality and mortality

due to CVD. Even infrequent moderate intensity activity as little as once per week was associated with decreased death compared with a sedentary lifestyle (Kushi et al, 1997). Walking at least 4 hours per week was related with substantial reductions in cardiovascular risk among elderly women and men (LaCroix et al, 1996). The Honolulu Heart Program findings showed that walking was associated with a lower overall mortality rate in older physically capable men. The twelve-year cumulative mortality rate was significantly lower in men who walked more than a mile each day than in those who walked shorter distances (Hakim et al, 1998).

Twenty-one year old follow-up of the Israeli Ischaemic Heart Study investigated self-reported physical activity with long-term CHD and all-cause mortalities. Excluding those with known CVD, they examined 8463 male government employees aged 40 years or older representing six areas of birth (looking at various occupations such as clerks, teachers, drivers, cleaning personnel, longshoremen, postmen, jail workers, judges and physicians) in either 1963 or 1965 from an original base of 10,059 (Eaton et al, 1995). This study found that among middle-aged men baseline self-reported leisure-time exercise and not work related activity was related to a significantly lower risk of CHD and all-cause mortality. Moreover, low levels of physical activity, such as walking on a less than daily basis, were nearly as valuable as more moderate to vigorous forms of self-reported leisure time physical activity in predicting decreased rates of CHD and all-cause mortality. In addition, this inverse relationship of leisure-time physical activity and CHD death also appeared to be independent of age, blood pressure, cigarette smoking, HDL-C and total cholesterol levels, body mass and other potential confounders (Eaton et al, 1995).

2.5.2 Physical fitness and heart disease

Physical fitness is a set of characteristics one has or achieves. This could be categorised into health and skill components which can be measured with specific tests (Caspersen et al, 1985). The health components of fitness comprise of cardiovascular endurance, muscular strength, muscular endurance, flexibility and body composition. Skill based components comprise of agility, balance, coordination, speed, power, reaction time and are related to athletic performance.

The most commonly studied component of physical fitness in relation to health is aerobic power. This attribute is also called maximal oxygen uptake, cardiovascular fitness, cardiorespiratory fitness, or endurance fitness. Physical fitness, especially cardiorespiratory fitness is an essential element to assess health risks. According to Whaley and Kaminsky (1995), this provides greater accuracy than clinical or physical activity questionnaires in investigating health risks in individuals. On the contrary, they believe that non-exercise test prediction in large epidemiological studies estimating cardiorespiratory fitness is not sufficiently accurate to assess the value of fitness for health.

Health equates to not only freedom of diseases but also the functional ability to participate and enjoy the variety of activities that life offers (Blair et al, 1992). Exercise improves an individual's physical fitness and a higher level of fitness is seen in exercise trained individuals (Blair et al, 1992). During an eight and a half year follow up study, the heart rate attained at stage 2 of a submaximal treadmill test was used as an index of fitness to investigate the association between fitness and CHD mortality (Ekelund et al, 1988). In addition, middle aged executives were tested on a treadmill to evaluate their physical fitness (Blair et al, 1992). The results from these studies showed that the least fit individuals were significantly more likely to be affected by CHD compared with the fittest individuals. Furthermore, a seven year study by Lie and colleagues (1985) examined CHD incidence among 122 middle aged Norwegian cross country skiers and among 2014 healthy men who were tested on a bicycle ergometer to elicit a VO_2 peak. These studies noted a strong, graded and inverse association between physical fitness and a number of coronary risk factors and an inverse relationship between high physical fitness and the risk of dying from CHD (Lie et al, 1985).

The Coronary Artery Risk Development in Young Adults (CARDIA) fitness study examined 3989 black and white men and women over 20 years. Baseline fitness was inversely associated with diabetes incidence in all race and sex groups (Carnethon et al, 2009). Hence, low fitness was significantly associated with diabetes incidence. In addition, Carnethon and colleagues (2005) suggested that fitness decreases the risk for diabetes through the regulation of body mass. Fitness may also protect against diabetes development through improved muscle insulin sensitivity, improved endothelial function and autonomic function and a reduced inflammation and oxidative stress (LaMonte et al, 2005; Carnethon

& Craft, 2008). These studies are relevant here because diabetes is a major risk factor for CVD.

Others have investigated relationships between physical fitness and hypertension incidence. It was reported that persons with low physical fitness had a relative risk of 1.5 times for the development of hypertension when compared with highly fit persons. This was after controlling for age, sex, body mass index, and blood pressure (Blair et al, 1984). In another study, the relative risk of hypertension in Japanese men, after adjusting for age, initial blood pressure, body fat, and other confounders, was 1.9 times higher in the least fit compared with the fittest group (Sawada et al, 1993). In addition, lower systolic blood pressure (127 versus 144 mm Hg) and lower diastolic blood pressure (79 versus 87 mm Hg) was found in men with high physical fitness compared with men with low physical fitness (Holtermann et al, 2010).

In a study by Lee and colleagues (2010), it was found that men with higher cardiorespiratory fitness had a larger risk reduction in mortality than men who met the recommended physical activity level (≥500 MET - minutes/week). Furthermore, women who had a high cardiorespiratory fitness showed a 41% lower risk than women who met the recommended(≥500 MET - minutes/week) physical activity level and the latter group did not reveal a significantly lower risk (Lee et al, 2010). The inverse association between cardiorespiratory fitness and mortality was approximately 40% to 70% stronger (lower mortality risk) than that of self-reported physical activity which indicated approximately a 20% to 50% lower risk of mortality in the most active people (Lakka et al, 1994; Kampert et al, 1996; Park et al, 2009). In addition to these findings, an inverse association between cardiorespiratory fitness and mortality among sedentary but not active men were identified (Hein et al, 1992). On the contrary, cardiorespiratory fitness was significantly inversely associated with mortality in the group classed as active but not in the sedentary group in another study (Park et al, 2009). Thus, whether the effects of cardiorespiratory fitness on the reduction in risk of mortality vary between physical activity levels is an area that needs further research (Lee et al, 2010).

The Copenhagen Male Study investigated physical demands at work, physical fitness and 30 year IHD and all-cause mortality risk. They found increased risk of IHD mortality was

associated with increasing work demands among men of low and medium levels of physical fitness (Holtermann et al, 2010). However, this was not found in the highly fit men. Similar results were observed for all-cause mortality. Moreover, among men with high physical fitness there was a 45 % lower risk of IHD mortality and a 38 % lower risk for all-cause mortality compared with those who had low physical fitness. In this study, men reporting high levels of leisure time activity had a higher physical fitness than men classifying themselves as sedentary during leisure time (VO_2 max: 36.9 ml/kg/min versus 31.1ml/kg/min). High work demands generally have a minor influence on physical fitness thus this study emphasises the importance of physical activity during leisure time for improving aerobic capacity. These findings support the importance of physical fitness and its positive role against CVD and all-cause mortality (Holtermann et al, 2010).

The Women's Health Initiative Observational Study examined 73,743 postmenopausal women 50 to 79 years of age estimating total physical-activity, walking, vigorous exercise, and hours spent sitting as predictors of the incidence of coronary events and total cardiovascular events (Manson et al, 2002). Physical-activity scores displayed a strong, graded, inverse association with the risk of both coronary events and total cardiovascular events. There were similar findings among white women and black women. Both walking and vigorous exercise were associated with substantial reductions in the incidence of cardiovascular events among postmenopausal women, irrespective of race or ethnic group, age, and body-mass index. In contrast, prolonged sitting predicted increased cardiovascular risk (Manson et al, 2002).

2.6 Exercise and heart disease risk factors

Cardiovascular disease has been reviewed thus far from the clinical perspective. Now, we will assess it in the context of epidemiology in relation of exercise and heart disease risk factors. Exercise and its prevention of CHD has been evident in many studies (Morris et al, 1953; Paffenbarger et al, 1970; Morris et al, 1980; Blair et al, 1992; Gill et al, 2003; McAuley et al, 2009; Williams et al, 2010). Exercise produces both acute (short-term) effects and chronic (long-term training adaptations) effects which will influence metabolism. Hence the next section will examine the acute effects of exercise and the section after will examine the chronic effects of exercise.

2.6.1 Acute effects of exercise

This section will discuss the acute effects of exercise and its influence on selected CVD risk factors including lipid/lipoprotein metabolism, blood pressure, insulin sensitivity and platelet aggregation. Importantly, single bouts of exercise elicit acute, transient cardiovascular and metabolic responses.

Prior exercise reduces the triglyceride response to a subsequent meal and this is known as the postprandial effect (Hardman, 2007). Postprandial lipaemia is associated with impaired endothelial function and inflammation (MacEneaney et al, 2009). Hence, the exercise effect is an important feature because an exaggerated postprandial triglyceride response is a risk factor for atherosclerosis (Hardman, 2007). A study compared African American women and white women to determine whether ethnicity influenced postprandial lipaemia after an acute bout of exercise. A walk test at 60% of maximal oxygen uptake was performed for 90 minutes, 12 hours before an oral fat tolerance test. African American women had a great reduction in postprandial lipaemia than white women (Shannon et al, 2008). In another study, a 90 minute bout of exercise at 60% of maximal oxygen uptake was conducted in endurance trained and untrained women of similar age and body mass index (Tsetsonis et al, 1997). The aim was to compare the lipaemic response to a high fat meal in these two groups of women. Exercise caused a 30% reduction in postprandial lipaemia in trained women the next morning. In untrained women, exercise also reduced lipaemia but levels were 40 to 50 % higher in the untrained women than in the trained women. Furthermore, there was a reduction in plasma insulin concentrations in the trained women after exercise and fat oxidation was elevated after exercise in both groups (Tsetsonis et al, 1997).

In a study by Ho and colleagues (2011) a single bout of 30 minutes of treadmill walking significantly decreased postprandial triglycerides in overweight and obese participants. They also demonstrated that 30 minutes of resistance exercise (leg press, leg curl, leg extension, bench press and rear deltoid row) was more effective in increasing insulin sensitivity when compared with aerobic exercise in these participants. Thus, Ho and colleagues (2011) suggest that overweight and obese individuals can reduce CVD risk factors through 30 minutes of aerobic exercise which helps to decrease the circulating

levels of triglycerides or 30 minutes of resistance exercise which helps to increase insulin sensitivity. These outcomes may help to reduce the risk of developing type 2 diabetes and CVD.

Furthermore, physical inactivity reduces insulin sensitivity hence increasing insulin resistance. This reduced insulin sensitivity plays a detrimental role, increasing the risk of type 2 diabetes which in turn increases the risk of CVD. Regular exercise enhances insulin sensitivity and reduces the risk for diabetes and CVD (Knowler et al, 2002). In relation to CVD, studies have suggested that the augmented insulin sensitivity and reduced insulin secretion observed in people who exercise regularly are largely a consequence of the acute effects of the last bout of exercise rather than of long-term training adaptations. A study demonstrated that the insulin sensitising effects of exercise lasted for 3 days in middle aged people with normal glucose tolerance (King et al, 1995). Likewise, another study found a single bout of moderate intensity exercise lowered hepatic glucose production the next day in type 2 diabetic patients (Devlin and Horton, 1985). These outcomes could be associated with an increase in insulin sensitivity within skeletal muscle and an increased ability of muscle to synthesise glycogen (Perseghin et al, 1996). These in turn may be related to an increase in the number and activity of GLUT 4 glucose transporters in muscle (Houmard et al, 1993; 1995) and the content and activity of hexokinase which catalyses the phosphorylation of glucose. Its activity in increased by physical training (Koval et al, 1998). This highlights the importance of maintaining the frequency of exercise to benefit insulin sensitivity.

Exercise is also effective in reducing blood pressure in hypertensive participants. In hypertensive participants post-exercise blood pressure was lower for 12.7 hours and on exercise days the mean arterial pressure (MAP) was lower by 6 mm Hg than on non-exercise days (Pescatello et al, 1991). Due to the recognised acute and chronic blood pressure lowering benefits of exercise, the American College of Sports Medicine recommends people with high blood pressure perform a minimum of 30 minutes of moderate intensity (40% - <60% peak oxygen consumption (VO_2peak)) aerobic exercise on most days of the week (Pescatello et al, 2004).

Finally, platelets play an important role in the pathogenesis of CVD. Strenuous exercise activates platelets acutely while training at moderate intensity suppresses platelet aggregation in overweight middle-aged men, young healthy men and young women (Rauramaa et al, 1986; Wang et al, 1995; Wang et al, 1997). Physical activity increases the release of nitric oxide which is a potent mediator of anti-platelet effects that helps in platelet reactivity (Wang et al, 1995). However, the resting and exercise induced reductions in platelet aggregation reverses back to the pre-training value after de-training (Wang et al, 1995; 1997). Hence, engaging in regular physical activity is essential. This was also evident in a study by Wang and colleagues (1994) involving strenuous and moderate intensity acute exercise on a bicycle ergometer. This revealed that platelet adhesiveness and aggregation may be increased by strenuous exercise in both healthy participants and patients with stable angina. On the other hand, platelet function can be significantly suppressed by moderate intensity exercise in the healthy and it tends to be depressed in patients with stable angina. The effects of acute exercise tend to be more pronounced in sedentary than in active people (Wang et al, 1994). Another study by Hurlen and colleagues (2000) found a fall in coagulation markers with a significant reduction in fibrinogen after an acute bout of exercise. This suggests that there was no generation of thrombin and fibrin during exercise.

2.6.2 Chronic effects of exercise

It is believed that long-term training induces non-transient adaptations which may assist in preventing CVD (Thompson et al, 2001). Here, discussion will be based on insulin sensitivity, platelet aggregation, vascular inflammation, blood pressure and lipid/lipoprotein metabolism.

Exercise impacts lipoprotein metabolism and increases HDL-C. Exercise in the form of walking or jogging resulting in an expenditure of 5024 to 9211 kJ/week helped to increase HDL-C by 2 to 3 mg/dl and reduced triglycerides by 8 to 20 mg/dl (Durstine et al, 2001). A greater energy expenditure was found to increase HDL-C by 2 to 8 mg/dl and reduce TAG by 5 to 38 mg/dl. Training volume exerts a positive influence on blood lipids (Durstine et al, 2001). This is evident from many studies (Tsetsonis and Hardman 1996; Gill et al, 2002). According to the US Runners' Health Study the mileage and not speed (intensity)

covered by a runner is critical for predicting HDL-C concentration (Williams, 1998). In addition, intervention studies have reported that a period of endurance training can reduce postprandial concentrations of TAG and TAG rich lipoproteins and in some instances increase TAG clearance (Weintraub et al, 1989; Thompson et al, 1988). In addition, Cohen and colleagues (1989) found enhanced TAG clearance in well-trained individuals compared with untrained individuals and they suggested that chronic exercise training decreases postprandial lipaemia more effectively than acute exercise. In a study by Thompson and colleagues (1988), 8-11 months of exercise training in previously sedentary men enhanced fat tolerance and increased HDL-C concentrations.

There is a general belief that increased levels of physical activity will result in an improvement in both insulin sensitivity and glucose metabolism. In a 16 month study, Potteiger and colleagues (2003) investigated 66 healthy overweight young males and females (age range 17 to 35 years) for glucose and insulin responses. Both sexes performed the exercise at the same relative intensity and duration predominantly walking on a motorised treadmill. They were also allowed to exercise on stationary bikes and stationery elliptical trainers for 1 out of 5 days in a week. Improvements in insulin sensitivity were observed in males when cardiorespiratory fitness improved and there was a reduction in body mass and body fat. In females, improvements in $\dot{V}O_2$ max without weight loss did not lead to improvement in insulin sensitivity (Potteiger et al, 2003). These findings may suggest the importance of both improvements in cardiovascular fitness and changes in body weight and body fat for improving insulin sensitivity. In another study, one week of daily intense exercise helped to reduce insulin resistance and improve glucose tolerance in men with type 2 diabetes mellitus. This result provided justification for the assertion that regularly performed vigorous exercise can be useful as a natural ‘medication’ for people with type 2 diabetes (Rogers et al, 1988). The increased insulin sensitivity and reduced insulin secretion associated with exercise have usually been observed when participants are studied 12-16 h after exercise (Heath et al, 1983; King et al, 1988a; King et al, 1988b; King et al, 1987; LeBlanc et al, 1981). This has important implications for exercise prescription and the prevention of conditions such as impaired glucose tolerance or insulin resistance.

Many studies have examined the chronic effects of exercise on coagulation and fibrinolysis. One example of a well-controlled study is that of Rauramma and colleagues

(1986). In this study, moderate intensity regular exercise in middle aged, overweight and mildly hypertensive men in east Finland was conducted to examine platelet aggregation. The exercise intervention was effective in reducing platelet aggregation. Hence, regular exercise may have a long term inhibitory effect on platelet aggregation. This might also assist in protecting against atherosclerosis and IHD (Rauramma et al, 1986). Greater changes in fibrinolytic activity and venous occlusion were observed in active men involved in maximal exercise when compared with inactive men. This would improve the body's ability to dissolve thrombi if they form. Individuals with CVD have been found to exhibit impaired fibrinolytic activity. Thus, regular physical activity may enhance fibrinolytic activity and this may serve as an additional exercise induced cardio protective mechanism (Szymanski et al, 1994).

Besides these risk factors, inflammation has a pivotal role in the continual progression of atherosclerosis. Exercise, however, may alleviate this situation. A few studies have shown that chronic exercise training decreases the concentration of inflammatory markers (e.g., IL-6, TNF-α, CRP) elicited after an acute bout of exercise in untrained patients with CHD (Smith et al, 1999; Gielen et al, 2003; Kasapis & Thompson, 2005; Gleeson, 2007). A recent study also found this in untrained CHD patients where acute exercise caused a marked increase in CRP and sVCAM-1. With four months of training there was a significant decrease in the CRP response but no significant change was seen in sVCAM-1 after acute exercise (Fernandes et al, 2011). This could have been the case as most studies have examined trained athletes while addressing the acute effects of exercise and hence this contradiction in inflammatory activity (Kasapis & Thompson, 2005). However, this study suggested that chronic exercise training may moderately reverse the inflammatory response caused by acute exercise in patients with CHD (Fernandes et al, 2011).

Moreover, regular participation in physical activity reduces the risk of developing hypertension. Habitual physical activity is also associated with other health benefits that favourably modulate hypertension (Cornelissen & Fagard, 2005). Furthermore, the effect of exercise in 8 acute and 14 exercise training studies were conducted on European White men. They were overweight and sedentary with an average age of 44 years. The training studies suggested that exercise training produces greater blood pressure reductions than acute exercise and this was more evident in those who had the highest blood pressure

values initially. These findings may be related to the higher pre-exercise blood pressures in the exercise training participants (Thompson et al, 2001).

The associations between different types of physical activity and the incidence of hypertension have been assessed in several different populations. A study of male university alumni reported that vigorous exercise in the post-college years protected against future hypertension (Paffenbarger et al, 1983; 1991). In middle-aged Finnish men the total amounts and intensities of baseline physical activity were inversely associated with the risk of future hypertension (Haapanen et al, 1997). In Japanese men, the duration of walk to work and leisure-time physical activity was significantly associated with a lower risk for hypertension (Hayashi et al, 1999). In the Atherosclerosis Risk in Communities Study, the incidence of hypertension was lower in white men in the highest quartile of leisure-time physical activity than in men in the least active quartile (Pereira et al, 1999).

2.7 Exercise studies in South Asian populations

In recent years there has been increasing interest in the exercise/physical activity levels of South Asians and the extent to which these may explain the increased CVD risk in South Asians. Fiscbacher and colleagues (2004) reviewed 12 studies in adults and 5 studies in children and young people which had compared physical activity levels between South Asians and Europeans. Data pertaining to activities in adults were collected mainly through questionnaires. One study utilised pedometers (over 7 days) in addition to questionnaires. Mean daily walking distance by pedometer was 1.8 km per day for the Indian origin group and 2.4 km per day for the Northern European group (Shaukat et al, 1995). Two of the five studies in children assessed physical fitness using bicycle ergometer tests, the other three used physical activity questionnaires. Hardy and Eston (1985) compared the level of fitness of ‘Anglo-Saxon’ and first generation expatriate Indian students none of whom were regularly active in sport. In the other fitness study, the cardiorespiratory fitness of ethnic minorities in Britain was examined due to the lack of information in this area (Bettiol et al, 1999). In both studies, maximal oxygen uptake was estimated by a submaximal test and this only gave a predictive value. These studies revealed a considerable disparity in maximum oxygen uptake (Hardy and Eston, 1985) and poorer physical fitness and lack of cycling skills (Bettiol et al, 1999) in the South Asian children. Apart from these findings, a

12 week progressive resistance training programme in Asian Indians with type 2 diabetes was also conducted to evaluate its effectiveness. The training study assessed several exercises which included biceps flexion, shoulder flexion, hip flexion, finger grip, knee extension and heel rise at 10 repetitions of two sets (Misra et al, 2008). After three months of training, significant improvements were found in insulin sensitivity, blood glucose, lipids and truncal and peripheral subcutaneous adipose tissue.

In addition, a study comparing premenopausal Indian and Pakistani women with American women of European descent revealed the South Asian women to be at greater risk of CVD than their American counterparts. However, the South Asian women in increasing their physical activity levels are likely to decrease overall and regional adiposity, thereby improving their lipid profiles (Kamath et al, 1999). This was ascertained using the Five-City Project physical activity recall questionnaire (Sallis et al, 1985).

A study by Davey and colleagues (2000) demonstrated a 12% increase in $\dot{V}O_2$ max with twelve weeks of supervised exercise. Ninety-two sedentary South Asian and European men and women aged 35-49 years participated in this study. Maximal oxygen uptake was measured using a graded exercise treadmill test based on a modified Bruce protocol and it was higher among Europeans than South Asians with significance persisting after adjustment for sex and age. Participants were given individually tailored exercise programs requiring them to perform three 30 minute sessions of interval walking/jogging later progressing to jogging/running. Participants had to work at 65-70% of $\dot{V}O_2$ max. Exercise also improved mean insulin sensitivity by 40% within 24 hours of the final exercise session but not five days after it.

A validated physical activity questionnaire was used in a hospital based case-control study investigating physical activity and CHD in India. Data from 350 cases of acute myocardial infarction and 700 controls matched by age, gender and hospital in New Delhi and Bangalore were collected. Brisk walking as much as 35-40 minutes per day appeared to protect from CHD. This study is the first of its nature to demonstrate the harmful effects of physical inactivity on health and the significance of leisure time exercise in the prevention

of CHD risk among Indians (Rastogi et al, 2004). This study also indicated the low physical activity levels among Indians in urban cities.

The Chennai Urban Population Study was the first study conducted in South Asians in India that demonstrated physical inactivity's association with components of the metabolic syndrome and CHD in this population. Using a validated questionnaire, the study emphasised the need for increased physical activity in preventing the metabolic syndrome and CHD in India. Strikingly, it also showed that only 6.2% of this urban population exercised regularly (Mohan et al, 2005). The INTERHEART study has also echoed the substantially lower prevalence of leisure time physical activity in South Asians (6.1%) compared with the rest of the world (21.6 %).

Furthermore, an interview based study focusing on promoting physical activity among South Asian women with CHD and diabetes also documented low physical activity that was related to a lack of motivation, poverty, transport, time and competing respsonsibilities (Srikantharajah and Kai, 2007). Another study investigated ethnic differences among South Asian, Black African-Caribbean and White European origin children in physical activity levels assessed using the Actigraph activity monitor (Owen et al, 2009). The findings revealed that British South Asian children have lower physical activity levels than White European and black African-Caribbean children (Owen et al, 2009).

Among these studies, it was also reported that South Asians have reduced cardiorespiratory fitness (assessed using a treadmill test) and a reduced capacity for fat oxidation during submaximal exercise compared with matched Europeans. These factors were associated with their lower insulin sensitivity, independent of adiposity both at the whole body level and at the skeletal muscle level (Hall et al, 2010), This study involved 20 participants from each ethnic group who were matched for age.

There have been very few thorough accounts illustrating South Asian physical activity levels. Thus information from the Health Survey for England (1999 to 2004) were utilised to compare leisure time physical activity levels among 5421 South Asians and 8974 White Europeans aged 18 to 55 years. The results conveyed very low physical activity levels in UK South Asians. This evidence of physical inactivity exposes the vulnerability of South

Asians to CVD (Williams et al, 2011). In addition, Yates and colleagues (2010) examined physical activity levels (using the International Physical Activity Questionnaire) among 1164 South Asians and 4310 White Europeans (males and females were almost equally represented) and relationships between physical activity and markers of diabetes and CVD. This study, which took place in Leicester, UK, showed that in White Europeans physical activity was inversely associated, with BMI, waist-circumference (men and women), 2-h glucose (women), and TAG (men) and positively associated with HDL-C (men). In South Asians physical activity was significantly inversely associated with waist-circumference (women) and positively associated with HDL-C (men). Importantly, the study also disclosed considerably lower levels of physical activity among South Asians than White Europeans (Yates et al, 2010).

One final point worth mentioning before closing this section is that physical activity questionnaires have often been the only feasible choice in large epidemiological studies, but they have limitations and can result in large measurement error (Shephard, 2003). These limitations are likely to become more pronounced in minority ethnic populations (Fischbacher et al, 2004) leading to further potential for inaccuracy. Thus, a potential area for future research is the development of physical activity questionnaires specifically for the South Asian population.

2.8 Summary and conclusions

Thus far this review has outlined clinical and epidemiological evidence in substantiating physical activity as a “pharmacological” tool. South Asians’ physical inactivity is likely to contribute to their high risk of CHD. Increasing physical activity in all South Asians should be a health priority for health professionals. Critically, there has not been any acute exercise study investigating postprandial lipaemia and other CVD risk factors in the South Asian population. Thus, the studies reported in this thesis are an attempt to explore and examine the acute effects of exercise on CVD risk factors in South Asian men.

3 General methods

This chapter describes the experimental methods used in the studies presented within this thesis as certain aspects of the methodology are common between studies. Loughborough University's Ethical Advisory Committee approved each of the studies described in this thesis and written informed consent was gained from study participants before participating in these research investigations. The information presented here describes the methods used in studies one (Chapter 4), two (Chapter 5), three (Chapter 6) and four (Chapter 7).

3.1 Participants

For the studies reported in this thesis participants were recruited from Loughborough University by e-mail advertisement, through friends, word of mouth and direct approach. Volunteers were given a participant information sheet (Appendix A) describing the demands of the study and the associated risks and discomforts. Volunteers provided written informed consent (Appendix B) and completed a health screen questionnaire (Appendix C) before any experimental procedures began. Participants also completed questionnaires assessing physical activity (Appendix D – studies one and two & Appendix E – study three) and verification forms (for South Asians only) to verify their country of birth, their mother tongue language, their religion and race, the country of their parents' birth and their family history of migration if there was any (Appendix F). All of the white European participants were UK citizens. All the participants were students completing their studies at Loughborough University and were reasonably physically active. Prior training was not a pre-requisite for participation in these studies but the physical demands of the test protocols ensured that all of the participants were reasonably fit.

Inclusion criteria for the recruitment of participants were as follows:

- male
- aged 18 to 40 years
- no personal history of cardiovascular disease, metabolic disease or dyslipidaemia
- not dieting or undertaking any extreme dietary habits

- not taking drugs known to affect digestion or metabolism – medical or illegal (for example anabolic steroids, marijuana, amphetamines, thyroid prescription drugs)
- weight stable within the last three months i.e. < 2.3 kg change in body weight (St Jeor et al, 1997)
- sufficient ability to complete the demands of the exercise protocols
- Body mass index (BMI) < 30 $kg \cdot m^{-2}$

3.2 Anthropometry

A digital weighing scale (Seca Ltd, Germany) was used to measure body weight to the nearest 0.1 kg and a portable stadiometer (Avery Industrial Ltd, Leicester, UK) was used to measure height to the nearest 0.1 cm. For both of these measurements participants wore light clothing and bare feet. Body mass index was calculated as weight (in kilograms) divided by height (in metres squared). Waist circumference was determined as the narrowest part of the torso above the umbilicus and below the xiphoid process (Stewart et al, 2011) using an inelastic polyfibre measuring tape (Hokanson, Washington, USA).

Subcutaneous fat measurements were taken to estimate body fatness. Skinfold measurement was taken using skinfold calipers (Harpenden, Burgess Hill, UK) at four anatomical sites (biceps, triceps, subscapular and suprailiac). These measurements were made in triplicate on the right hand side of the body with participants in a standing position. Measurements were made by rotating through the anatomical sites to allow the skin time to regain normal texture and thickness. Body density was calculated using Durnin and Womersley's (1974) predictive equations. Percentage body fat was determined using the Siri equation (Siri, 1956).

3.3 Heart rate measurement

During preliminary exercise tests and main trials heart rate was measured using a short-range telemetry (Sports tester PE_{3000}; Polar T31; Polar Electro, Kempele, Finland).

3.4 Rating of perceived exertion

Rating of perceived exertion (RPE) was assessed periodically using the Borg scale during preliminary exercise tests and main trials to determine participants' subjective exercise intensity (Borg, 1973). This scale ranges from six (no exertion) to 20 (maximal exertion).

3.5 Arterial blood pressure measurement

A digital blood pressure monitor (Omron M5-1, Matsusaka Co., Ltd, Japan) was used to measure blood pressure during preliminary screening and main trials. Measurements were taken in duplicate after a 5 minute rest in a semi-supine position and the mean of these measurements was used as the value.

3.6 Exercise tests

After familiarization with motorized treadmill walking/running (RUNRACE, Techno gym, Gambettola, Italy) participants completed two preliminary exercise tests: a submaximal, incremental treadmill running test (to determine the relationship between walking/running speed and oxygen uptake) and a maximum oxygen uptake ($\dot{V}O_2$ max) test.

3.6.1 Submaximal treadmill test

In studies one, two and three (Chapters 4, 5 and 6), a continuous submaximal test was performed on a level treadmill. This test involved four, four-minute stages of increasing intensity. Participants exercised at various speeds ranging from light/moderate to vigorous but not maximum. Initial running speed was between 5.5 and 9 $km \cdot h^{-1}$ (Chapters 5 and 6) and walking speed was between 4 and 5 $km \cdot h^{-1}$ (Chapter 4). The speed was increased by 0.5 or 1 $km \cdot h^{-1}$ at the end of each 4 minute stage depending on each participant's level of fitness. A one minute sample of expired air was collected into Douglas bags (Plysu Protection Systems, Milton Keynes, UK) in the final minute of each stage of the tests for the determination of oxygen consumption and carbon dioxide production. Short range telemetry (Sports tester PE_{3000}; Polar T31; Polar Electro, Finland) was used to evaluate

heart rate throughout the tests. Ratings of perceived exertion were assessed periodically during the tests using the Borg scale. Oxygen consumption was plotted against exercise speed at each stage to identify the relationship between submaximal running speed and oxygen consumption.

3.6.2 Maximal oxygen uptake test

After the submaximal test, participants were given 30 minutes to recover before the $\dot{V}O_2$ max test. This test involved an incremental uphill protocol at a constant speed until participants reached volitional exhaustion (Taylor, Buskirk and Henschel, 1955). The speed was ascertained from each participant's submaximal test performance. The initial treadmill gradient was set at 3.5% and the gradient was increased by 2.5% every 3 minutes. Expired air samples were collected for one minute between minutes 1:45 and 2:45 of each stage. Maximal oxygen consumption was determined from an expired air sample collected during the final minute of the test when participants signaled that they could only continue for one additional minute. Heart rate and RPE were monitored throughout the test. Participants were strongly motivated with verbal encouragement so as to enable them to complete the final collection.

3.7 Expired air analysis

Oxygen consumption and carbon dioxide production were determined from expired air samples using a paramagnetic oxygen analyser and an infrared carbon dioxide analyser, respectively (Series 1440; Servomex, Crowborough, Sussex, UK). These analysers were calibrated using gases of known concentration prior to testing. Expired air volumes were measured using a dry gas meter (Harvard Apparatus, Edenbridge, UK) and corrected to standard temperature and pressure dry. The temperature of the expired air was determined using a thermometer (Edale, type 2984, Model C, Cambridge, UK) during evacuation of Douglas Bags. Barometric pressure was measured using a Fortin barometer (F.D. and Company, Watford, UK).

3.8 Calculation of energy expenditure

Oxygen consumption and carbon dioxide production values were used to determine energy expenditure and substrate oxidation using the equations described by Frayn (1983).

Carbohydrate oxidation rate ($g \cdot min^{-1}$) = (VO_2 $L \cdot min^{-1}$ - (1.989*fat oxidized in grams))/0.828

Fat oxidation rate ($g \cdot min^{-1}$) = (VO_2 $L \cdot min^{-1}$ – VCO_2 $L \cdot min^{-1}$)/0.57

Energy expenditure (kJ) = (fat oxidized (grams)*39) + (CHO oxidized (grams)*17)

3.9 Physical activity and dietary control

The day before each main trial and on the first day of each main trial, participants recorded their food intake using a weighed food diary. The same food intake was consumed prior to the next main trial. Participants were also told not to consume coffee, tea or alcohol before the main trials. In addition, no strenuous physical activity was permitted during the day preceding the main trials and between day 1 and day 2 of the main trials. For study three, participants were asked to refrain from strenuous physical activity for four full days on each of the main trials (other than the activity performed as part of the experiment).

Participants fasted overnight (no food or drink except water) for 10 hours prior to the main experimental trials for each study. During this time water was permitted *ad libitum* and this was encouraged to avoid dehydration.

3.10 Test meals

The test meals were the same for all three studies. They consisted of white bread, butter, cheese, mayonnaise, crisps, chocolate milk shake powder and high fat milk. The amount of food consumed was adjusted for each participant based on their body weight and was kept constant throughout the trials. The macronutrient content of the test meal was 57% fat, 32%

carbohydrate and 11% protein and each meal provided 60 kJ (14.3 kcal) per kg body mass for a 70 kg participant. Participants consumed each meal within 15 minutes (Chapters 4 and 5) and 20 minutes (Chapter 6). Water was available *ad libitum* throughout the main trials.

The meal itself was designed at the laboratory by previous researchers (Miyashita et al, 2006). The meal provided enough fat to exaggerate postprandial lipaemia and it was palatable. Carbohydrate was included to invoke a realistic insulin response as people do not eat macronutrients in isolation. There is no standardized version of an oral fat tolerance test (OFTT), either clinically or experimentally, but this meal has been used in many studies from this laboratory. In addition, the food was halal/vegetarian which made it edible for South Asian Muslim/vegetarian participants. No one has tested the meal for repeatability which is one weakness.

3.11 Blood sample collection

On the morning of main trials participants arrived at the laboratory between 7.45 and 8.00 am for the first two studies (Chapters 4 and 5) and by 8.30 am for the third study (Chapter 6). On arrival at the laboratory, participants sat on a bed in a semi-supine position for 5 minutes while a cannula (BD Ven-flon, Becton-Dickinson, Helsingborg, Sweden) was inserted into an antecubital vein and a baseline blood sample was collected.

In all studies blood samples were drawn into pre-cooled 9 mL EDTA monovette tubes (Starstedt, Leicester, United Kingdom). The samples were immediately centrifuged at 1500 x g (3000 revs/min) for 10 minutes in a refrigerated centrifuge (Labofuge 400R, Thermo Scientific, Langenselbold, Germany) at 4ºC. The plasma supernatant was dispensed into eppendorf tubes and stored at -80ºC / -20ºC (depending on freezer availability) before analysis. After each blood sample collection 10 mL of non-heparinised saline solution (0.9% (v/w) sodium chloride, Baxter Healthcare Ltd, Norfolk, United Kingdom) was flushed through the cannula to maintain cannula patency. Participants adopted the semi supine position 5 minutes before blood was drawn. Two mL of blood was drawn into a syringe and discarded at the start of each blood collection to prevent sample contamination from saline. Prior to centrifugation of the blood samples collected at baseline and at the end of each trial, two 20 µL blood samples were collected from monovettes into micropippettes

for the measurement of haemoglobin and three 20 µL blood samples were collected from monovettes into microhaematocrit tubes for the measurement of haematocrit. Haemoglobin and haematocrit values were used to estimate changes in plasma volume across the main trial days (Dill and Costill, 1974).

3.12 Blood biochemistry

3.12.1 Haemoglobin and haemotocrit

Haemoglobin was determined using the cyanmethaemoglobin method with the aid of an ultra-violet spectrophotometer (CECIL CE 1011, Cecil Instruments Ltd., Cambridge, UK). Haematocrit was determined using a microliter-haematocrit centrifuge (MIKRO, 20, Andreas Hettich GmbH and Co. KG, Tuttlingen, Germany).

3.12.2 Lipids, lipoproteins and glucose

Plasma total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triacylglycerol and glucose concentrations were determined by enzymatic colorimetric methods using an automated bench top analyser (Pentra 400, HORIBA ABX Diagnostics, Montpellier, France). To ensure precision of analysis internal quality controls exhibiting normal and pathological values were run prior to sample analysis.

3.12.3 Insulin

Plasma insulin concentrations were determined using a commercially available enzyme-linked immuno sorbent assay (Mercodia, Sylveniusgatan, Uppsala, Sweden) with the aid of a plate reader (Expert Plus, ASYS, Eugendorf, Austria) to measure absorbance. To ensure precision of analysis internal quality controls (Mercodia diabetic antigen control) exhibiting low and high levels were assayed.

3.12.4 Interleukin 6 and soluble intercellular adhesion molecules

Plasma interleukin-6 (IL-6) concentrations were determined using commercially available enzyme-linked immuno sorbent assay kits (high sensitivity kit; R&D Systems, Abingdon, UK for IL-6 in study one, high sensitivity kit; Diaclone, Besançon, France for study two). For soluble intercellular adhesion molecule-1 (sICAM-1) a commercially available kit was also used (Diaclone, Besançon, France). For these assays a plate reader was used to measure absorbance (Expert Plus, ASYS, Eugendorf, Austria). To ensure precision of analysis internal quality controls exhibiting normal and pathological values were run during sample analysis.

3.12.5 Precision of analysis

To eliminate inter assay variation, samples from each participant were analysed in the same run. For TAG, glucose and insulin the within batch coefficient of variation for each assay was calculated by repeated measurements of a single plasma sample 10 times. Whereas, for IL-6 and sICAM-1 the within standard and quality control coefficient of variation was determined by the variation between each duplicate pair. Coefficient of variation values for each assay are displayed within the methods section of each experimental chapter.

3.13 Statistical analysis

Data were analysed using Predictive Analytics Software version 18.0 for Windows (SPSS, Inc., Somers, NY, USA). Data are presented as mean ± standard deviation (SD) in the text and tables and as mean ± the standard error of the mean (SEM) in figures. Area under the plasma concentration versus time curve (AUC) values have also been calculated using the trapezoidal method. The following statistical tests have been used in the experimental chapters within this thesis:

- Independent samples t tests
- Paired samples t tests
- Pearson Product Moment correlation
- One way analysis of variance (ANOVA)
- Two way ANOVA

- Three way ANOVA
- Bonferroni post-hoc tests (after ANOVA)

Statistical significance is accepted at the 5% level throughout this thesis. Further details about the statistical analysis are provided within each experimental chapter.

4 The effect of prior walking on postprandial lipaemia and resting blood pressure in South Asian versus European men

4.1 Introduction

Coronary heart disease (CHD) has emerged as the major cause of morbidity and mortality globally (World Health Organisation, 2012) and among South Asians in the recent past (Goswami et al, 2012). This is evident among South Asians in UK (Wild et al, 2007), the USA (Palaniappan et al, 2004) and Canada (Sheth et al, 1999). Since the 1950s, there has been an increased awareness that people with ancestral origins in the Indian subcontinent (India, Pakistan, Bangladesh, Sri Lanka and Nepal) known as South Asians are highly susceptible to CHD (Patel and Bhopal, 2004). Danaraj and colleagues (1959) made a definitive finding that the prevalence of CHD was seven fold higher in Indians than in Chinese in Singapore. In 1963, Adelstein identified this phenomenon in South Africa where mortality rates from cardiovascular disease (CVD)/CHD in mainly Indian men and women were much higher than in White men and women. Estimates suggest a three to five fold increased risk of myocardial infarction and cardiovascular death among migrant South Asians compared with other ethnic groups (Eapen et al, 2009).

South Asians, who are a heterogeneous group, comprise the largest ethnic minority (4.1%) in the United Kingdom (UK) (Wild & McKeigue et al, 1997). The incidence rate of myocardial infarction has been reported to be higher in South Asians compared with other ethnic groups. Mortality ratios of CVD, CHD and stroke are also higher in South Asians in the UK than the local population (Wild et al, 2007). This is further evident from a recent cardiovascular risk assessment study conducted in the UK which screened almost equal numbers of male and female South Asians. It identified that 92% of them had at least one modifiable CVD risk factor which places them in a high CVD risk population (Rao et al, 2012).

South Asians have higher plasma triacylglycerol (TAG), lower high density lipoprotein cholesterol (HDL-C) and higher low density lipoprotein cholesterol (LDL-C) concentrations than other groups. South Asians also appear to be more susceptible to hypertension, type 2 diabetes, impaired glucose tolerance, increased fasting glucose concentration, insulin resistance and the metabolic syndrome than other ethnic groups (Tziomalos et al, 2008). Despite documenting the higher rates of earlier CHD in South Asians, few studies have shed light on the reasons for this.

Several reasons have proposed to explain the elevated CVD/CHD risk experienced by South Asians (Reddy & Yusuf, 1998). Firstly, the increased risk may be due to genetic factors predisposing to high levels of metabolic cardiovascular risk factors associated with insulin resistance e.g. central adiposity, glucose intolerance, hyperinsulinaemia, and dyslipidaemia (metabolic syndrome). Secondly, the increased risk may be due to environmental influences which lead to weight gain as well as rises in blood cholesterol and blood pressure (Reddy & Yusuf, 1998). One possible environmental risk factor might be the prevalence of physical inactivity and numerous studies have identified that South Asians have low levels of physical activity (Kamath et al, 1999; Fischbacher et al, 2004; Owen et al, 2009; Williams et al, 2011; Yates et al, 2010; Misra et al, 2012). Furthermore, it has been estimated that physical inactivity explains > 20% of the excess CHD mortality experienced by UK South Asians even after adjsutment for potential confounders including socioeconomic status, smoking, diabetes and existing CVD (Williams et al, 2011).

Physical inactivity is a well-established risk factor for CHD (Wannamethee & Shaper, 2001; Rastogi et al, 2004; Mohan et al, 2005; Rao et al, 2012). Despite documenting higher rates of earlier CHD in South Asians and a tendency for low levels of physical activity no studies have addressed the acute effects of exercise in this population. Observational evidence suggests the cardio-protective role of physical activity on CHD and CHD risk markers in South Asians (Rastogi et al, 2004; Mohan et al, 2005; Rao et al, 2012). Furthermore, regular moderate intensity physical activity such as brisk walking is associated with a 30% to 50% reduction in the risk of CHD, obesity, diabetes and stroke in Western populations (Wannamethee et al, 2000; Batty, 2002). Whether the cardiovascular effects of physical activity have any cardio-protective elements in South Asians remains to be determined.

Thus, this study sought to evaluate the influence of an acute bout of brisk walking on postprandial triacylglycerol concentrations, a risk marker for CVD (Nordestgaard et al, 2007; Bansal et al, 2007) in South Asian and White European men. Walking was chosen because it is a popular and accessible activity that can be incorporated into daily activity routines with little risk (Morris and Hardman, 1997). Numerous studies have shown that an acute bout of exercise helps to lower postprandial TAG concentration but most of these studies have been conducted in Western populations (Miyashita et al, 2008; Hurren et al, 2011). In addition to postprandial lipaemia, this study examined other CVD risk markers including glucose, interleukin-6 and resting blood pressure.

4.2 Methods

4.2.1 Participants

With the approval of Loughborough University's Ethics Advisory Committee 15 South Asian and 14 White European men were recruited and they gave their written informed consent to participate in this study. The study sample size was calculated using G Power (version 3.1.3, Franz Faul, Universitat Kiel, Germany) which indicated that for TAG (the primary outcome variable) 10 participants per group would be sufficient to detect a difference in TAG with a power of 0.75 and a 5% level of significance. When calculating power using G-power, postprandial AUC TAG values were used in preference to fasting TAG values. This was done due to the strong correlation between postprandial TAG levels and elevated risk of developing cardiovascular disease. Participants were healthy and recreationally active and ranged in age from 21 to 30 years. Participants were non-smokers, with no personal history of CVD or metabolic disease, and none of them reported taking medication. They had a BMI < 30 $kg \cdot m^{-2}$. Participants were not dieting and did not have any extreme dietary habits. To verify ethnicity each South Asian participant completed a form providing details of their place and country of birth, their mother tongue language, their religion and race, the country of their parents' birth and their family history of migration. This revealed that seven of the participants were Indian nationals, five were UK Indians, one was a UK Pakistani and two were Sri Lankans from Sri Lanka.

4.2.2 Anthropometry

Prior to the main trials participants attended the laboratory for a screening and familiarization visit lasting approximately two hours. During this visit they completed a participant information form and questionnaires assessing health status, usual physical activity and ethnicity (South Asians only). Subsequently, weight was measured to the nearest 0.01 kg using a digital scale (Seca Ltd, Germany) and height was measured to the nearest to 0.1 cm using a stadiometer (Avery Industrial Ltd, Leicester, UK). Skinfold thickness was measured with calipers (Harpenden, Burgess Hill, U.K.) on the right hand side of the body at the biceps, triceps, subscapular and suprailliac. The sum of these four skinfold measurements was used to determine body density (Durnin & Wormersley, 1974) and body fat percentage (Siri, 1956). In addition, waist circumference was determined as

the narrowest part of the torso above the umbilicus and below the xiphoid process using a measuring tape (Hokanson, Washington, USA). Lastly, blood pressure was measured using a digital monitor (Omron M5-1, Matsusaka Co., Ltd, Japan).

4.2.3 Preliminary exercise tests

After familiarization with motorized treadmill walking (RUNRACE, Techno gym, Gambettola, Italy) participants completed two preliminary exercise tests: a submaximal, incremental treadmill walking test (to determine the relationship between walking speed and oxygen uptake) and a maximal oxygen uptake ($\dot{V}O_2$ max) test. The submaximal test was performed on a level treadmill and involved four, four-minute stages of increasing intensity. Initial walking speed was set between 4 and 5 km·h^{-1} and the speed was increased by 0.5 or 1 km·h^{-1} (depending on each participant's level of fitness) at the end of each stage. After a 30 minute recovery, $\dot{V}O_2$ max was determined with the use of an incremental uphill protocol at a constant speed until participants reached volitional exhaustion (Taylor, Buskirk and Henschel, 1955). The initial treadmill gradient was set at 3.5% for this test and the gradient was increased by 2.5% every 3 minutes. Short range telemetry (Polar T31; Polar Electro, Kempele, Finland) was used to evaluate heart rate throughout both tests. Ratings of perceived exertion (RPE) were assessed periodically during these tests using the Borg scale (Borg, 1973).

Expired air samples were collected into Douglas bags (Plysu Protection Systems, Milton Keynes, United Kingdom) during both of the preliminary exercise tests. An O_2/CO_2 analyser (Servomex 1440, Crowborough, Sussex, United Kingdom) was used to measure the oxygen and carbon dioxide percentages within the expired air samples. The analysers were calibrated using gases of known concentration prior to testing. A dry gas meter (Harvard Apparatus, Edenbridge, United Kingdom) was used to measure expired air volumes which were corrected to standard temperature and pressure dry. Data from the two preliminary exercise tests were used to determine the relative exercise intensity adopted by each participant at their self-selected brisk walking pace.

4.2.4 Main trials

Participants completed two, 2 - day trials (exercise and control) in a random order separated by an interval of at least one week. Trials were undertaken in block random order (block size of two) using software available at http://www.randomization.com/. On day one of the exercise trial, participants arrived at the laboratory between 8.00 am and 9.00 am and rested (reading, working at a computer, watching television, listening to music or playing video games) throughout the day until 5.00 pm. Participants consumed a standardized lunch at approximately 12.00 pm. At 3.30 pm, participants performed a 60 minute brisk walk at a pace which they were able to sustain i.e. participants were asked to walk as fast as was comfortably possible. The objective was to simulate a natural setting/daily activity hence intensity was not fixed. One minute samples of expired air were collected at 15 minute intervals during the walk to monitor the intensity of the walk i.e. minutes 14-15, 29-30, 44-45 and 59-60 during the walk. If necessary adjustments were made to the treadmill speed to ensure participants were walking as briskly as they could. Heart rate and RPE were also monitored during the walk. During day one of the control trial procedures were exactly the same as on day one of the exercise trial except that no walking was performed and four, five-minute resting expired air samples were collected at the time when walking was performed on day 1 of the exercise trial i.e. between 3.30 pm and 4.30 pm equivalent to minutes 10-15, 25-30, 40-45 and 55-60 during the walk. Oxygen consumption and carbon dioxide production were calculated from expired air samples as described previously. Energy expenditure was estimated from oxygen consumption and carbon dioxide production values using the equations of Frayn (1983).

On day two of the main trials participants arrived at the laboratory between 7.45 and 8.00 am having fasted overnight (no food or drink except water) for 10 hours. On arrival at the laboratory, participants sat on a bed in a semi-supine position for 5 minutes while a cannula (BD Ven-flon, Becton-Dickinson, Helsingborg, Sweden) was inserted into an antecubital vein and a baseline blood sample was collected. After this blood sample, baseline resting blood pressure was measured. Participants then consumed a prescribed test meal (see below) for breakfast. A clock was started the moment they commenced their meal and this was identified as 0 hour. The trial continued on for nine hours during which a total of 14 (including the fasting sample), 9 mL venous blood samples were collected and 10

(including the baseline measurement) blood pressure readings were taken. At 4 hours, a second test meal, identical to the first, was served as lunch to participants. Participants rested throughout day two of both the control and exercise trials and hence day two of these trials was identical. A schematic representation of the main trial protocol is displayed in Figure 4.1.

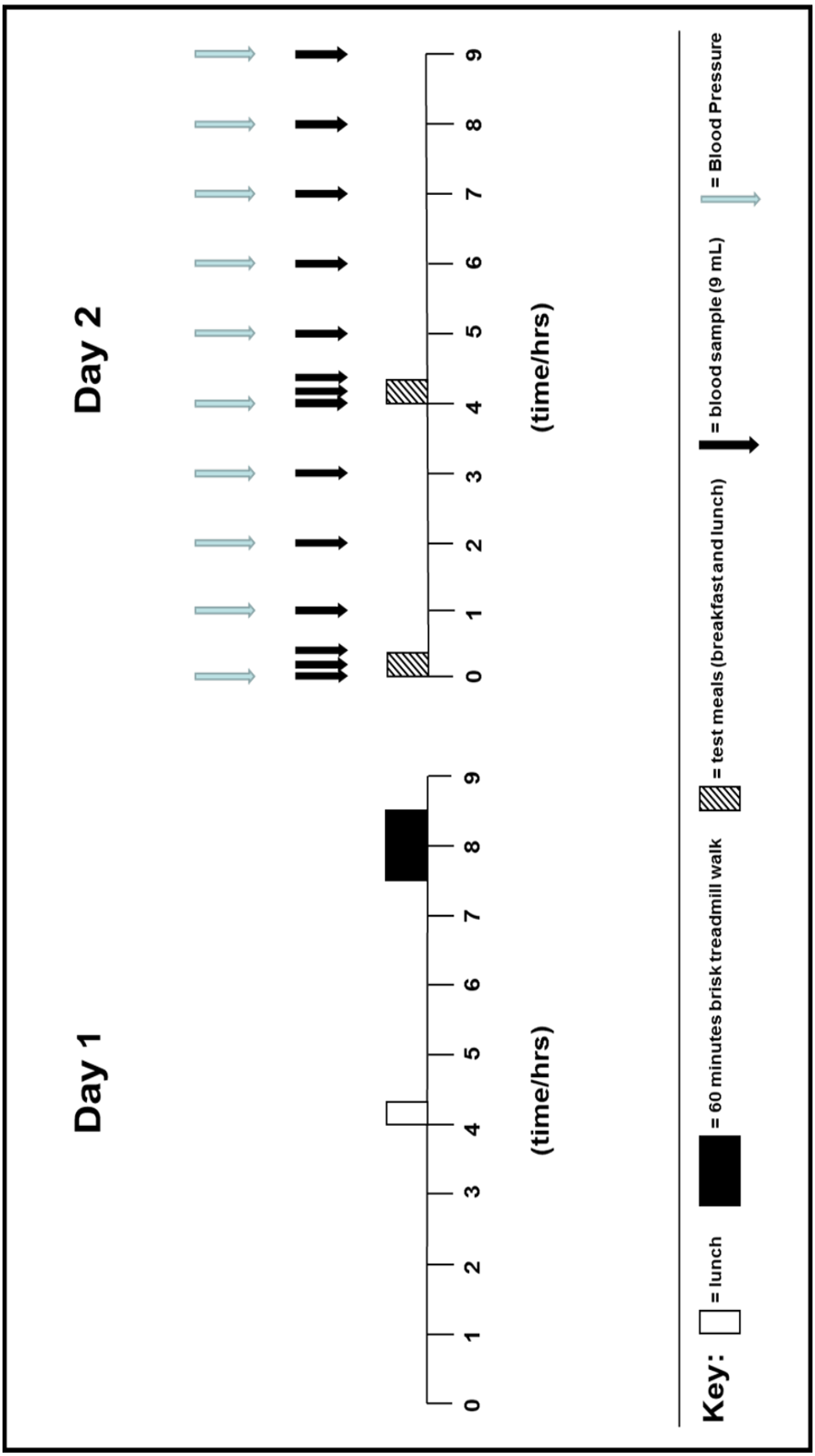

Figure 4.1: A schematic representation of the main trial protocol

4.2.5 Control of diet and exercise

The day before each main trial and on the first day of each main trial, participants recorded their food intake using a weighed food diary. Participants replicated this food intake for the next main trial. Participants were told not to consume coffee, tea or alcohol on the day prior to and during the main trials. Participants were also asked to refrain from strenuous physical activity during the day preceding the main trials and on day 1 and day 2 of the main trials.

4.2.6 Test meals

The test meals consisted of white bread, butter, cheese, mayonnaise, crisps, chocolate milk shake powder and high fat milk. The amount of food consumed was adjusted for each participant based on their body weight and was kept constant throughout the trials. The macronutrient content of the test meal was 57% fat, 32% carbohydrate and 11% protein and each meal provided 60 kJ (14.3 kcal) per kg body mass for a 70 kg participant. Participants consumed each meal within 15 minutes and water was available *ad libitum*.

4.2.7 Blood sampling

Venous blood samples were collected for the measurement of total cholesterol, HDL-C, TAG, glucose and IL-6. Samples were collected at 0, 0.25, 0.5, 1, 2, 3, 4, 4.25, 4.5, 5, 6, 7, 8, 9 hours. Total cholesterol and HDL cholesterol were only measured from baseline samples; IL-6 concentrations were measured from samples collected at 0, 3, 6 and 9 hours, glucose and TAG were measured from all samples. Participants rested in a semi-supine position during blood sampling. Venous blood samples were drawn into pre-cooled 9 mL EDTA monovette tubes (Starstedt, Leicester, United Kingdom) and immediately centrifuged at 1500 x g (3000 revs/min) for 10 minutes in a refrigerated centrifuge (Labofuge 400R, Thermo Scientific, Langenselbold, Germany) at 4ºC. The plasma supernatant was dispensed into eppendorf tubes and stored at -20ºC before analysis. After each blood sample collection 10 mL of non-heparinised saline solution (0.9% (v/w) sodium chloride, Baxter Healthcare Ltd, Norfolk, United Kingdom) was flushed through the cannula to maintain cannula patency. Two mL of blood was drawn into a syringe and discarded at the start of each blood collection to prevent sample contamination from saline.

Prior to the centrifugation of the blood samples at baseline and at nine hours, two 20 µL blood samples were collected from monovettes into micropipettes for the measurement of haemoglobin and three 20 µL blood samples were collected from monovettes into microhaematocrit tubes for the measurement of haematocrit. Haemoglobin and haematocrit values were used to estimate changes in plasma volume across the nine-hour main trial day (Dill and Costill, 1974).

4.2.8 Blood biochemistry

Plasma total cholesterol, HDL cholesterol, TAG and glucose concentrations were determined spectrophotometrically using commercially available kits and a bench top analyser (Pentra 400, HORIBA ABX Diagnostics, Montpellier, France). Enzyme linked immuno sorbent assays (ELISA) assays were used to determine the concentrations of IL-6 (high sensitivity kit; R&D Systems, Abingdon, UK) with the aid of a plate reader (Expert Plus, ASYS, Eugendorf, Austria). To eliminate inter assay variation, samples from each participant were analysed in the same run. Coefficients of variation for each assay were as follows: 0.7% for total cholesterol, 0.7% for HDL cholesterol, 0.7% for TAG, 0.9% for glucose, and 4.3% for IL-6.

4.2.9 Statistical analysis

Data were analysed using Predictive Analytics Software version 18.0 for Windows (SPSS, Inc., Somers, NY, USA). Physical characteristics and exercise responses were compared between South Asians and Europeans using the Students t-test. Three-way repeated measures ANOVA with Bonferroni post-hoc tests was used to examine differences between trials for plasma constituents (TAG, glucose and IL-6) with the three factors being: a) trial (exercise versus control), b) ethnic group (South Asians versus Europeans) and c) time (serial measurements over 9 hours). Effect sizes (Cohen's *d*) were also calculated for each of these variables by dividing the difference between the mean values (exercise versus control or South Asian versus European) with the standard deviation (i.e. the average standard deviation from both trials and ethnic groups combined). Area under the plasma concentration versus time curve (AUC) values were calculated for TAG, glucose and IL-6 using the trapezoidal method. These values were compared using two-way repeated measures ANOVA with the two factors being trial (exercise versus control)

and ethnic group (South Asian versus European). Two-way repeated measures ANOVA was also used to assess between trial and ethnic group differences for fasting plasma metabolite concentrations. Statistical significance was accepted at the 5% level. Results are presented as mean ± SD in the text and tables and as mean ± SEM in figures.

4.3 Results

4.3.1 Participant characteristics

The physical characteristics of the participants are displayed in Table 4.1. There were no significant differences between South Asian and White European participants for weight, resting systolic blood pressure and resting diastolic blood pressure. Age, body mass index, percentage of body fat and waist circumference were significantly higher in South Asian than in White European participants while height and $\dot{V}O_2$ max were significantly lower in South Asian than in White European participants

Table 4.1: Physical characteristics of South Asian and European descent participants measured during the preliminary tests.

Variables	South Asians (n=15)	Europeans (n=14)	*P* value
Age (years)	24.0 ± 2.9	22.0 ± 0.7	0.017
Height (cm)	170.5 ± 8.4	180.2 ± 3.9	0.001
Weight (kg)	74.1 ± 11.5	73.6 ± 8.3	0.903
Body mass index ($kg \cdot m^{-2}$)	25.4 ± 3.3	22.7 ± 2.2	0.013
Body fat (%)	21.7 ± 6.0	12.5 ± 4.6	< 0.001
Waist circumference (cm)	82 ± 9.2	75 ± 5.2	0.037
Resting SBP (mm Hg)	129 ± 10.0	136 ± 13.6	0.103
Resting DBP (mm Hg)	77 ± 7.4	77 ± 6.4	0.859
$\dot{V}O_2$ max ($mL \cdot kg^{-1} \cdot min^{-1}$)	40.7 ± 7.2	49.2 ± 8.0	0.005

All values are in mean ± SD. *P* values for differences between South Asians and Europeans were based on *t* tests for independent samples. SBP, systolic blood pressure; DBP, diastolic blood pressure; $\dot{V}O_2$ max, maximal oxygen uptake.

4.3.2 Responses to treadmill brisk walking

The physiological responses to the 60 minute brisk walking are displayed in Table 4.2. The White Europeans walked significantly faster than the South Asians while the South Asians had a significantly higher average heart rate than White Europeans. There were no significant differences between ethnic groups in $\%\dot{V}O_2$max, energy expenditure, substrate (carbohydrate/fat) utilisation and RPE attained during the brisk walk. There was a tendency for exercise $\dot{V}O_2$ to be slightly higher in White European than South Asian participants.

Table 4.2: Responses during the 60 minute treadmill walk in South Asian and European men.

Variable	**South Asians (n=15)**	**Europeans (n=14)**	***P* value**
Speed ($km \cdot h^{-1}$)	6.4 ± 0.5	7.1 ± 0.3	< 0.001
$\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	21.1 ± 3.3	23.5 ± 3.2	0.073
% $\dot{V}O_2$ max	52.7 ± 8.0	48.3 ± 6.8	0.129
Average heart rate ($beats \cdot min^{-1}$)	145 ± 16.5	126 ± 11.1	0.001
Respiratory exchange ratio	0.95 ± 0.05	0.95 ± 0.05	0.672
Ratings of perceived exertion	11.5 ± 2.2	11.3 ± 1.6	0.853
Exercise energy expenditure ($kJ \cdot h^{-1}$)	1860 ± 3745	2068 ± 364	0.141
Net energy expenditure ($kJ \cdot h^{-1}$)	1555 ± 359	1715 ± 343	0.231
% Energy from fat	18.4 ± 17.6	15.7 ± 17.4	0.676
% Energy from carbohydrate	81.6 ± 17.6	84.3 ± 17.4	0.676

All values are in mean ± SD. *P* values for differences between South Asians and Europeans were based on *t* tests for independent samples. $\dot{V}O_2$, volume of oxygen consumed.

4.3.3 Fasting plasma concentrations

Fasting concentrations of plasma metabolites (on day two of the main trials) are displayed in Table 4.3. There were significant main effects of trial for TAG indicating lower values on the exercise trial for fasting TAG concentration. There was a tendency (P = 0.093) for fasting glucose concentration to be lower on the exercise than the control trial. In addition, there were significant main effects of group for fasting HDL-C , total cholesterol/HDL-C ratio and glucose indicating higher total cholesterol/HDL-C and glucose concentrations in the South Asians than the White Europeans and lower HDL-C concentrations in the South Asians. There was a tendency (P = 0.077) for fasting IL-6 concentrations to be elevated in the South Asians especially after exercise.

Table 4.3: Fasting plasma concentrations and resting blood pressure on day two of the main trials in South Asian and European men.

Variable	South Asians (n = 15)*		Europeans (n = 14)*		*P* trial	*P* group	*P* T v G
	Control	Exercise	Control	Exercise			
TC ($mmol \cdot L^{-1}$)	4.02 ± 0.62	3.98 ± 0.61	3.83 ± 0.59	3.84 ± 0.61	0.786	0.452	0.664
HDL - C ($mmol \cdot L^{-1}$)	0.93 ± 0.18	0.95 ± 0.19	1.22 ± 0.19	1.23 ± 0.24	0.356	0.001	0.653
TC / HDL - C ratio	4.49 ± 1.24	4.37 ± 1.32	3.21 ± 0.76	3.23 ± 0.81	0.269	0.005	0.158
Triacylglycerol ($mmol \cdot L^{-1}$)	1.51 ± 1.16	1.16 ± 0.70	0.94 ± 0.32	0.87 ± 0.26	0.021	0.103	0.105
Glucose ($mmol \cdot L^{-1}$)	5.60 ± 0.25	5.42 ± 0.45	5.22 ± 0.49	5.19 ± 0.36	0.093	0.034	0.209
Interleukin-6 ($pg \cdot mL^{-1}$)	1.27 ± 1.05	1.82 ± 0.71	0.84 ± 1.69	0.87 ± 1.05	0.460	0.077	0.508
SBP (mm Hg)	127 ± 10.3	124 ± 7.3	133 ± 15.6	132 ± 12.9	0.178	0.105	0.260
DBP (mm Hg)	81 ± 7.2	81 ± 7.0	76.4 ± 8.3	77 ± 10.3	0.941	0.256	0.632

All values are mean ± SD. Values were compared using two-way ANOVA. *P* trial, main effect for control v exercise; *P* group, between subjects effect; *P* T v G, main effect for trial x group. *Note that N = 10 in each group for IL-6.

4.3.4 Postprandial plasma metabolite concentrations

Three-way ANOVA revealed main effects of group for TAG (P = 0.031), glucose (P = 0.045) and IL-6 (P = 0.034) indicating higher postprandial TAG, glucose and interleukin-6 in South Asians than White Europeans (Figure 4.2). The effect sizes for these ethnic group comparisons were large for TAG (0.87) and IL-6 (0.82) and medium for glucose (0.67). As body fat percentage was higher in the South Asians than White Europeans it might have confounded the association between ethnicity and plasma metabolite concentrations. Hence, three-way ANOVA was conducted again with body fat added as a covariate to remove its confounding influence. The between group differences for TAG, glucose and IL-6 disappeared after control for percentage body fat.

Three-way ANOVA revealed near main effects of trial for TAG (P = 0.058) indicating that TAG concentration (Figure 4.2) was lower on the exercise trial. The effect size for this TAG comparison was small (0.11). There were main group effects for TAG (P = 0.031), glucose (P = 0.045) and IL-6 (P = 0.34) (Figure 4.3) indicating higher TAG, glucose and IL-6 concentrations in South Asians than White Europeans. Two-way ANOVA for AUC also indicated main effects of group for TAG (P = 0.027), glucose (P = 0.029) and IL-6 (P = 0.040) indicating higher values in South Asians as shown in Table 4.4.

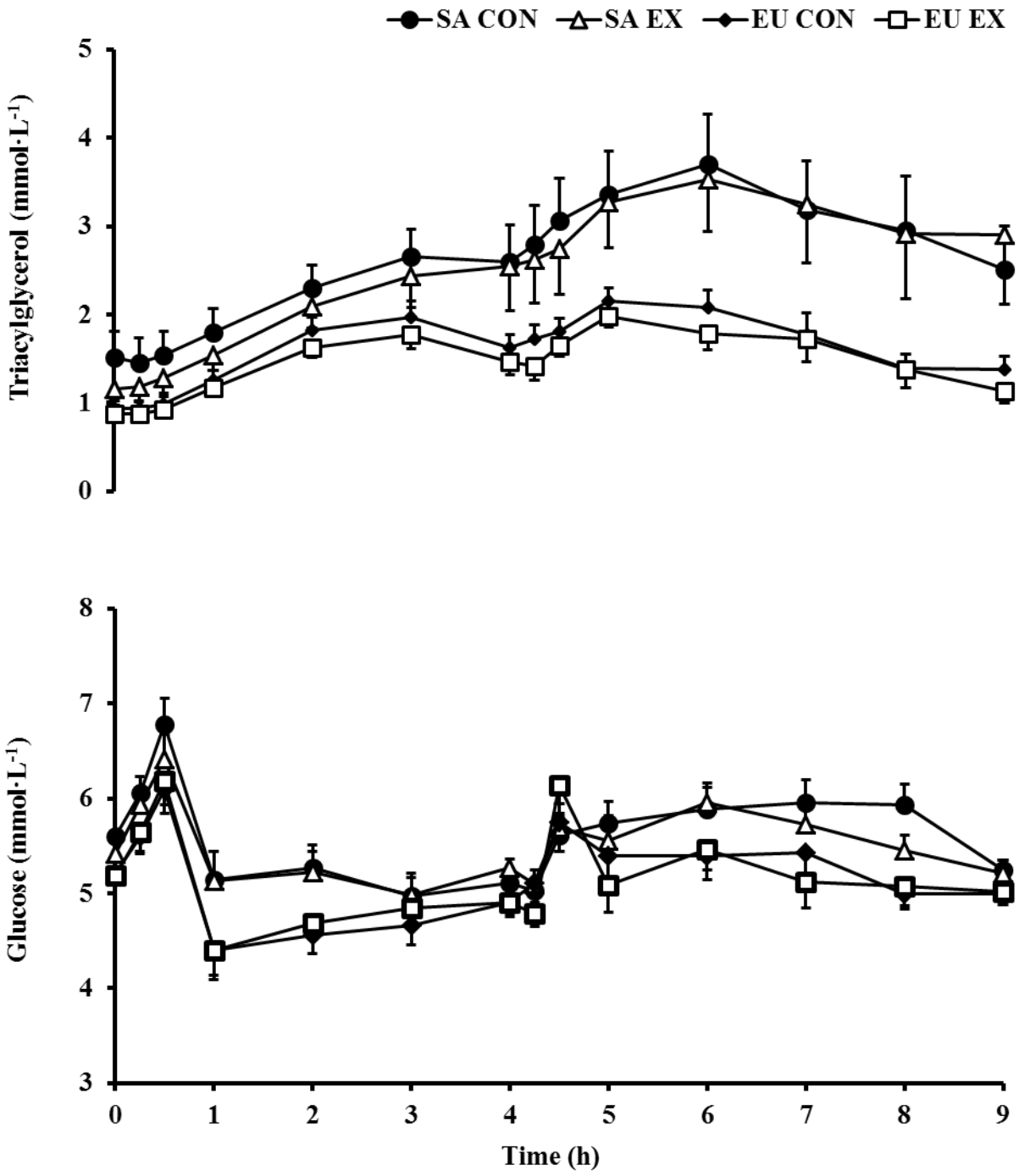

Figure 4.2: Mean (± SEM) postprandial plasma triacylglycerol (top panel) and glucose (bottom panel) concentrations measured on day 2 of the walking and control trials for South Asians (n = 15) and White Europeans (n = 14). Data was analyzed using three-factor ANOVA with repeated-measures followed by a Bonferroni multiple comparisons test. A borderline effect was observed for trial (P = 0.058) in relation to TAG. A main effect of time (P < 0.001) was observed for postprandial plasma TAG and glucose concentrations.

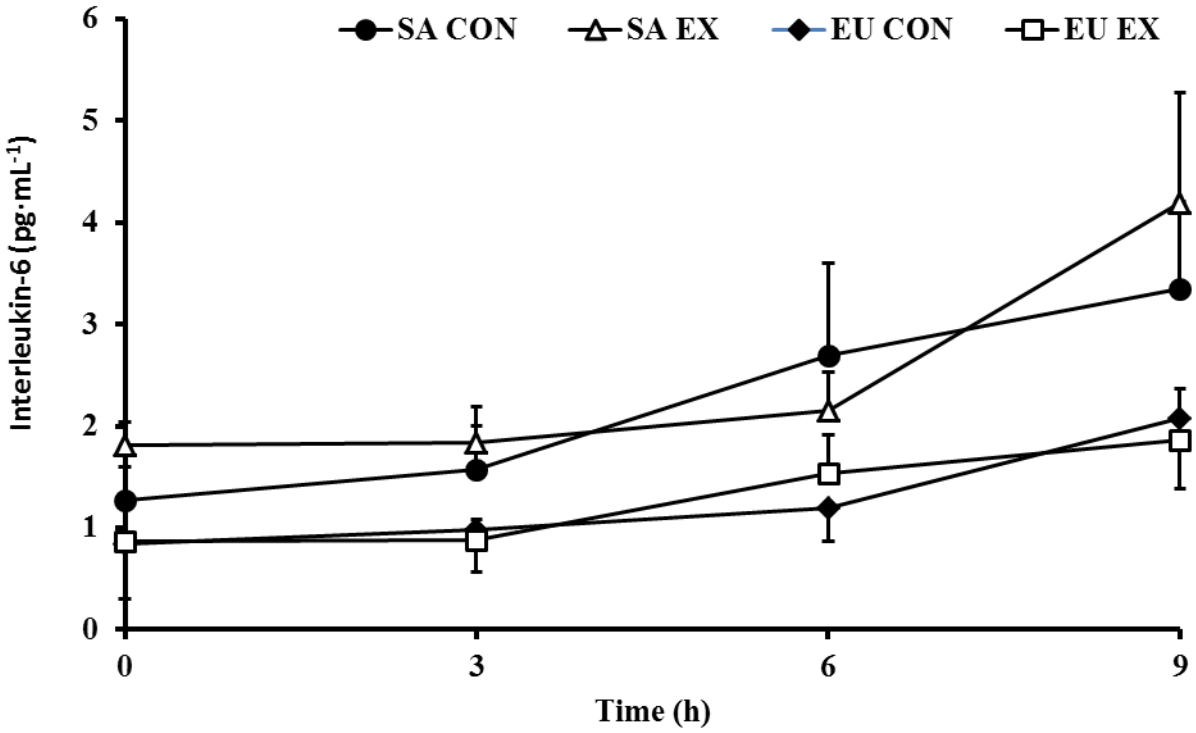

Figure 4.3: Mean (± SEM) postprandial plasma concentrations of interleukin-6 measured on day 2 of the walking and control trials for South Asians (n = 10) and White Europeans (n = 10). Data was analyzed using three-factor ANOVA with repeated-measures followed by a Bonferroni multiple comparisons test. A main effect of time was observed for postprandial plasma interleukin-6 (P = 0.004) concentrations.

Table 4.4: Area under the postprandial concentration versus time curve on day two of the main trials for South Asian and European men.

Variable	South Asians (n = 15)*		Europeans (n = 14)*		*P* trial	*P* group	*P* T v G
	Control	Exercise	Control	Exercise			
TAG (mmol·L^{-1} 9 h)	24.5 ± 14.1	23.5 ± 15.8	15.0 ± 4.6	13.8 ± 4.6	0.158	0.027	0.922
Glucose (mmol·L^{-1} 9 h)	50.1 ± 5.6	49.2 ± 4.9	45.4 ± 5.5	45.8 ± 5.0	0.766	0.029	0.427
IL-6 (pg·mL^{-1} 9 h)	19.7 ± 14.7	21.0 ± 10.3	10.9 ± 10.4	11.4 ± 6.2	0.740	0.040	0.874

All values are mean ± SD. Postprandial concentration calculated as the area under the total concentration versus time curve. Means were compared by using two-way ANOVA followed by a Bonferroni multiple comparisons test. T, Trial; G, group; *P* T v G, main effect for trial x group; TAG, triacylglycerol; IL-6, interleukin-6. *Note that N = 10 in each group for IL-6.

Figure 4.4 displays the difference in the TAG AUC values between the exercise and the control trial for each individual participant. Negative values indicate a lowering of postprandial TAG concentration on the exercise trial compared with the control trial. This figure demonstrates that postprandial TAG concentration was lowered by exercise in eight out of 15 South Asian participants and ten out of 14 European participants.

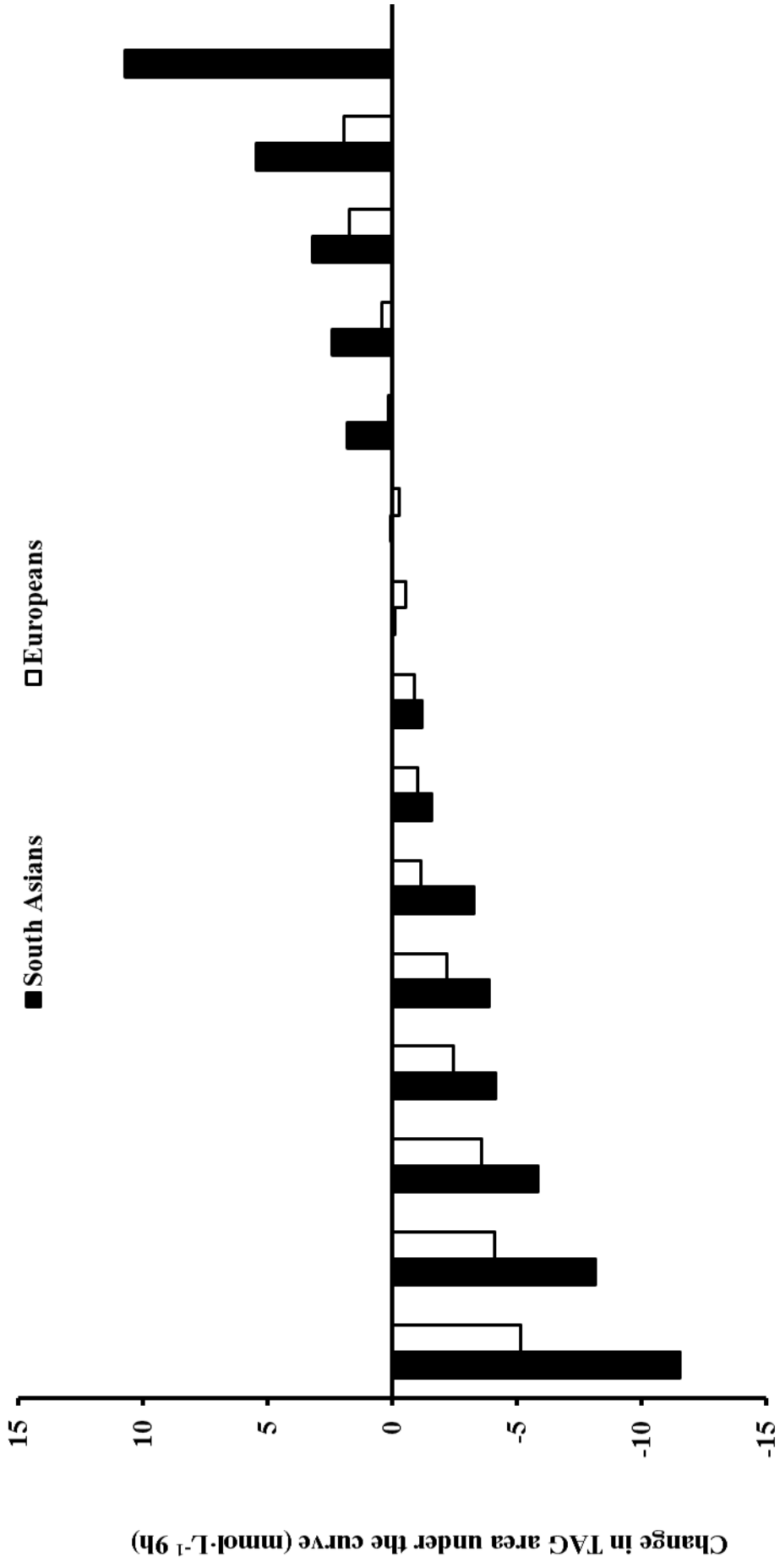

Figure 4.4: Individual changes (exercise minus control) in the total area under the triacylglycerol (TAG) concentration versus time curve in response to the 60 min brisk treadmill walk for South Asian (n=15) and White European males (n=14). Negative values indicate lower concentrations on the exercise trial.

4.3.5 Resting blood pressure responses

Resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) values are shown in Figure 4.5. Baseline resting SBP and DBP measured on day 2 did not differ significantly between trials as shown in Table 4.3. However, a significant effect of time was observed for resting SBP ($P = 0.003$) and DBP ($P < 0.001$). In addition, there was a tendency for SBP ($P = 0.082$) to be lower in South Asians than White Europeans.

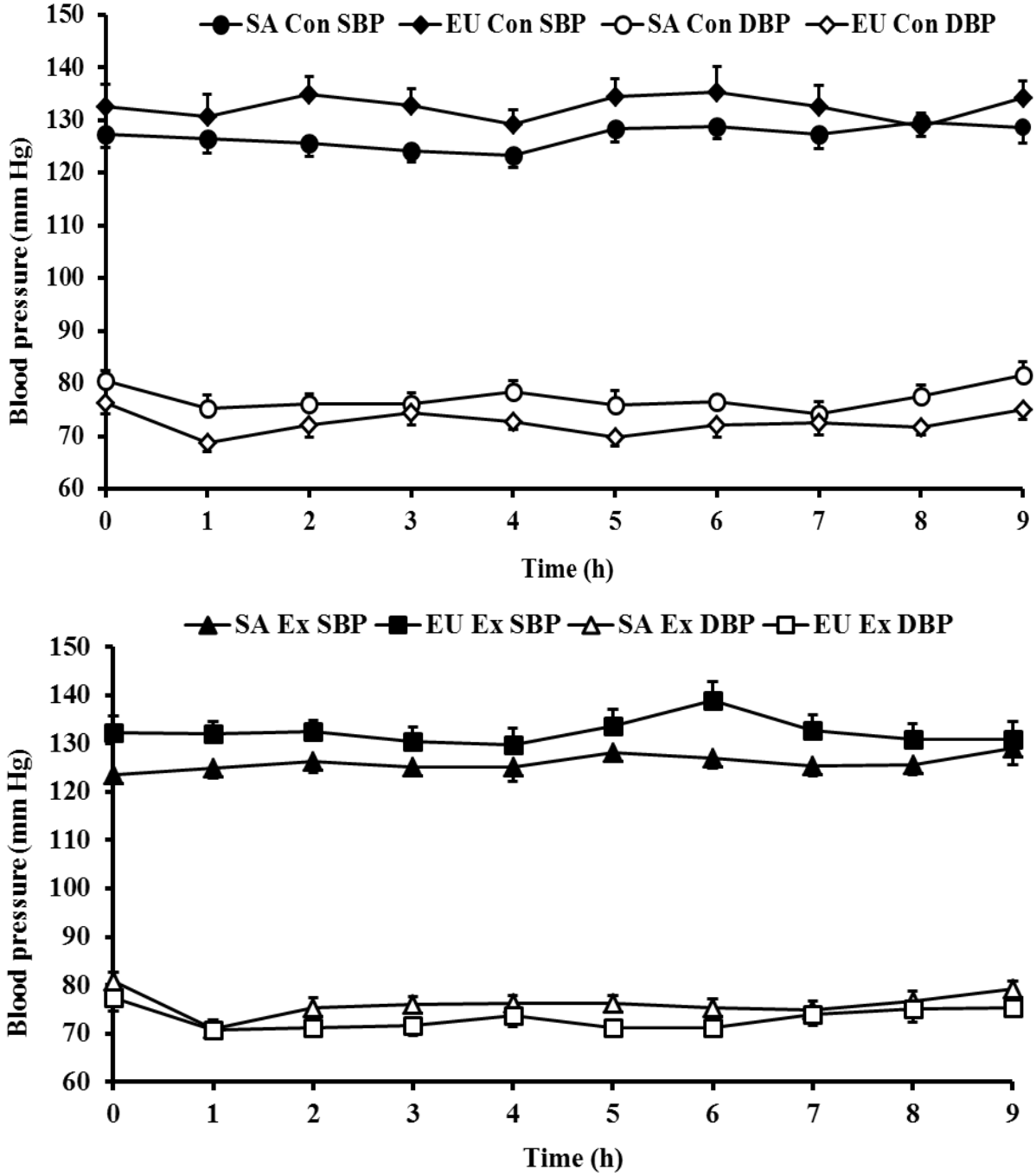

Figure 4.5: Mean (± SEM) systolic blood pressure (SBP) and diastolic blood pressure (DBP) values on day 2 of the control (top panel) and walking (bottom panel) trials for South Asians (n = 15) and White Europeans (n = 14). Data was analyzed using three-factor ANOVA with repeated-measures followed by a Bonferroni multiple comparisons test. A main effect of time was observed for SBP (P = 0.005) and DBP (P < 0.001).

4.3.6 Correlations

The South Asians and White Europeans were combined to assess correlations between baseline measures and trial outcomes. Waist circumference was positively correlated with baseline TAG during both the control ($r = 0.428$, $P = 0.021$) and exercise ($r = 0.462$, $P = 0.012$) trials. Body fat was positively correlated with baseline TAG during both the control ($r = 0.407$, $P = 0.027$) and exercise ($r = 0.454$, $P = 0.013$) trials. Maximal oxygen uptake was negatively correlated with waist circumference ($r = - 0.482$, $P = 0.008$), BMI ($r = - 0.461$, $P = 0.012$) and body fat ($r = - 0.612$, $P < 0.001$). In addition, $\dot{V}O_2$ max was negatively correlated with postprandial TAG on both the control ($r = - 0.402$, $P = 0.031$) and exercise ($r = - 0.477$, $P = 0.009$) trials.

4.4 Discussion

The findings of the present study reveal that South Asians exhibit elevated postprandial plasma TAG concentrations to a much greater extent than White Europeans after consuming high fat meals. Surprisingly exercise had a small, borderline effect on postprandial plasma TAG concentrations in both South Asians and White Europeans. Postprandial plasma glucose and plasma IL-6 concentrations were higher in South Asians than in White Europeans.

The distinctive elevation in postprandial TAG concentrations in response to high fat meals was clearly exhibited in South Asians compared with White Europeans. A few studies have observed higher fasting TAG concentrations in South Asians than in white people (Anand et al, 2000; Tziomalos et al, 2008). Nonetheless, this study is the first to report a difference in postprandial TAG concentrations between these ethnic groups. Only one other study has compared postprandial lipaemia in South Asians and White Europeans and this study did not observe a difference in the lipaemic response to high fat meals although postprandial glucose and insulin concentrations were elevated in South Asians (Cruz et al, 2001). A possible explanation for these different findings is that percentage body fat did not differ between ethnic groups in the study conducted by Cruz and colleagues (2001) but body fat percentage was higher in the South Asians in this study as is often the case (Wang et al, 1994). Although there were between group differences in postprandial lipaemia this was not displayed after controlling for differences in percentage body fat so perhaps the different lipaemic responses were related to the differences in body fat percentage between the two groups. Another possible reason for the disparate findings is the test meals used. The percentage fat provided in the test meals was similar between studies (52% of energy from fat in the study by Cruz and colleagues versus 57% of energy from fat in the present study) but the total amount of food consumed (which is not stated in the paper by Cruz and colleagues 2001) may have differed. Whatever the explanation for the disparity between these studies the contrast in postprandial TAG concentrations between South Asians and White Europeans is very evident in this study and certainly worthy of further investigation.

Another important finding from this study is the (non-significant) tendency for brisk walking to reduce postprandial TAG concentrations. Previous studies have reported that a

single session of prior exercise alleviates postprandial TAG (for reviews see Katsanos 2006; Malkova and Gill, 2006, Miyashita et al, 2008; Hurren, 2011) however this is the first study to report this in South Asians. Surprisingly, studies which examined intermittent (ten, 3 minute bouts) and continuous (30 minutes) walking, running and cycling revealed a significant lowering of postprandial TAG concentrations (Miyashita et al, 2006; 2008; 2008a). In particular, the exercise intensity of the walking study by Miyashita and colleagues (2008) was even lower than that in the present study. The relative percentage of $\dot{V}O_2$ max for intermittent and continuous walking reported by Miyashita et al (2008) was 41 to 42% whereas in the present study it was 53% for the South Asians and 48% for the White Europeans. Even though exercise intensity and duration were greater in the present study there was only a borderline effect for postprandial TAG lowering in both groups. In a study by Tsetsonis and Hardman (1996), it was observed that 1.5 h of walking at 60% of $\dot{V}O_2$ max elicited a significant effect whereas the same duration at 30% of $\dot{V}O_2$ max did not have a significant effect. According to Tsetsonis and Hardman (1996), the energy expenditure of an exercise bout is the main determinant of its potential to reduce postprandial lipaemia. In the present study the exercise energy expenditure was 1860 and 2068 kJ respectively which should have been sufficient to elicit a lowering of postprandial lipaemia based on the previously cited studies.

Whilst it is well established that exercise of a moderate intensity can reduce fasting and postprandial TAG concentrations (for reviews see Katsanos 2006; Malkova and Gill, 2006, Miyashita et al, 2008; Hurren, 2011) studies have also shown that this level of exercise did not lead to significant increases in either leg skeletal muscle lipoprotein lipase (LPL) activity (Herd et al. 2001) or absolute TAG uptake across the leg (Malkova et al. 2000) when these were measured 18 h after exercise. Body tissues other than skeletal leg muscle play a quantitatively important role in whole-body TAG uptake (Jensen 1995; Nguyen et al. 1996). It is possible that there was an insufficient increase in LPL activity in tissues other than the legs and this may explain the borderline TAG attenuation seen after brisk walking in the present study.

The TAG AUC values of the South Asian participants were still 56% higher after exercise than the control trial values displayed by White Europeans. If these findings are translated

into larger samples they would suggest that South Asians are at a much higher risk of experiencing exaggerated postprandial lipaemia in response to high fat meals than White Europeans and this may be a contributing factor to their elevated risk of CHD. In addition to elevated postprandial TAG concentrations, fasting TAG concentrations in the exercise trial were reduced by 23% in South Asians compared with 7% in the Europeans. Fasting glucose concentrations were 6% higher and postprandial glucose concentrations were 9% higher in South Asians than White Europeans. This finding is consistent with the findings of Cruz and colleagues (2001) who observed higher postprandial glucose concentrations in South Asians and also with the finding that fasting glucose concentrations are elevated in those of South Asian descent (Anand et al, 2000). Moreover, it is also postulated that exercise intensity and duration affects glucose uptake. In the post-absorptive state the volume of glucose uptake is critically affected by the exercise intensity. The higher the exercise intensity, the higher the skeletal muscle glucose uptake (Romijin et al, 1993). With a borderline significance, this study did not indicate any differences in trial. Importantly, a moderately elevated glucose concentration is a risk factor for myocardial infarction in non-diabetic South Asians. This may suggest a degree of glucose intolerance in South Asians (Gerstein et al, 1999).

It may also be speculated that hyperinsulinaemia resulting from insulin insensitivity might have decreased LPL activity (Pollare et al, 1991) in this study thereby affecting the mechanisms responsible for removing TAG from the blood (Pollare et al, 1991). This may be a reason for the elevated postprandial lipaemia exhibited in the South Asians in the present study. Prospective epidemiological studies across several populations have indicated that insulin resistance is the central feature of the metabolic syndrome and the primary defect in the development of type 2 diabetes (Misra et al, 2008). Insulin resistance often precedes diabetes by several years and is reported to be a risk factor for development of CVD (Misra et al, 2008).

South Asians exhibited lower fasting HDL cholesterol concentrations and higher fasting total cholesterol/HDL cholesterol ratio values and glucose concentrations than the White Europeans. There was also a tendency for fasting plasma IL-6 concentration to be elevated in the South Asians, especially on the exercise trial. Lowering of fasting TAG concentration in both South Asians and White Europeans was identified on the exercise

trials. Even with this reduction, South Asians exhibited a striking 48% elevation in TAG concentration in comparison with White Europeans. There was also a tendency for fasting glucose to be lowered during the exercise trial.

The differences observed between ethnic groups in this study confirm the findings of previous studies (Anand et al, 2000; Tziomalos et al, 2008) indicating that South Asians have a tendency for higher fasting TAG concentrations, higher fasting total cholesterol to HDL-C ratio values and lower fasting HDL-C concentrations than other ethnic groups. These findings not only expose but also reiterate the greater CHD risk South Asians face (Joshi et al, 2007).

Interleukin-6 was also assessed in the present study as it is an indicator of chronic low grade inflammation and a predictor of future development of CVD and non-insulin dependent diabetes mellitus (NIDDM) (Mathur and Pedersen, 2008). There was a tendency for fasting IL-6 concentrations to be elevated in South Asians and this was also the case with the postprandial IL-6 concentrations. A recent study reported South Asian women to exhibit significantly higher IL-6 concentrations than European women. Thirty per cent of the observed difference in IL-6 was explained by differences in fat distribution (Peters et al, 2012). In similarity, there is an ethnic difference in the present study where body fat percentage is significantly higher in the South Asian men. This could be one possible reason for the elevated IL-6 in South Asians in the present study. In contrast, Peters and colleagues (2013) did not detect an ethnic difference in IL-6 in men. Additionally, a study by Indulekha and colleagues (2011) found high concentrations of IL-6 in Asian Indian men and women with the metabolic syndrome. From these, it is postulated that South Asians may be more susceptible to inflammation and as a result have a tendency to have higher concentrations of IL-6 than others. This susceptibility poses a CVD threat in South Asians.

The present study had a few notable limitations. Firstly, the sample size is small and hence the findings require confirmation with a larger sample. Secondly, it is possible that the group differences observed here are confounded by differences in percentage body fat (although South Asians are known to have a higher body fat percentage for a given BMI, Wang et al, 1994) as well as differences in age, height and fitness level and this may explain in part their elevated CHD risk. Thirdly, most of the participants in the present

study were Indian South Asians and South Asians are a heterogeneous group and hence these findings require confirmation in other South Asian groups (e.g. Bangladeshis, Pakistanis and Nepalese). It would be interesting to examine the postprandial responses to exercise in overweight/obese South Asian participants and in females as well as males. Lastly, the intensity of the brisk walk may not have been optimal hence it would be interesting to examine the effects of a higher intensity of exercise on postprandial TAG in South Asian participants.

In conclusion, the findings of this study indicate notable elevations in postprandial lipaemia in response to high fat meals in South Asians compared with Europeans. Exercise had a borderline influence on postprandial lipaemia in the South Asian and European men examined in the present study. However, bearing in mind the low physical activity levels typical among South Asians and the exaggerated postprandial lipaemia observed here, further research into the potential of exercise for lowering postprandial lipaemia in South Asians would appear to be warranted.

5 The influence of a one hour treadmill run on coronary heart disease risk markers in South Asian and European men

5.1 Introduction

Coronary heart disease (CHD) is responsible for more deaths in the UK (Scarborough et al, 2010), the USA (Roger et al, 2012), and globally (World Health Organisation (WHO, 2011)) than any other single cause and prevention and treatment of CHD remain a public health priority. The prevalence of CHD varies among nations and ethnic groups and one group who are particularly susceptible are South Asians; a heterogeneous group originating from the Indian sub-continent e.g. India, Pakistan, Bangladesh, Sri Lanka and Nepal. Possibly the first to highlight this issue were Danaraj and colleagues (1959) who reported a relatively high prevalence of CHD among Indian compared with Chinese people living in Singapore. More recent reports have confirmed high prevalence rates of CHD among South Asians living in the UK (Wild et al, 2007), the USA (Palaniappan et al, 2004) and Canada (Sheth et al, 1999) and estimates suggest a three to five fold increased risk of myocardial infarction and cardiovascular death among migrant South Asians compared with other ethnic groups (Eapen et al).

A variety of interacting factors may explain the elevated risk of CHD in South Asians and one of these is physical inactivity. In their review of physical activity levels among South Asians living in the UK Fischbacher and colleagues (2004) identifed 12 studies in adults and five in children all of which reported lower levels of physical activity among UK South Asians than the general population. These findings have since been confirmed by data from a diabetes screening programme in Leicester, UK (Yates et al, 2010) and by the Health Survey for England (Williams et al, 2011). Moreover, it has been estimated that physical inactivity explains >20% of the excess CHD mortality experienced by UK South Asians even after adjustment for potential confounders including socioeconomic status, smoking, diabetes and existing cardiovascular disease (CVD) (Williams et al, 2011a). Outside of the UK the INTERHEART study found that only 6.1% of South Asians reported participation in moderate or high intensity exercise compared with 21.6% of participants from other countries

(Joshi et al, 2007). In light of such findings consensus physical activity guidelines for Asian Indians have recently been published in an attempt to promote physical activity among this group (Misra et al, 2012). Despite the high prevalence of CHD and low levels of physical activity among South Asians few studies have examined the effects of physical activity/exercise on CHD or on risk factors for CHD in this group although observational evidence suggests a protective role of physical activity in South Asians (Rastogi et al, 2004).

The study reported in the previous chapter is the first to evaluate the influence of an acute bout of exercise (i.e. brisk walking) on postprandial triacylglycerol (TAG) concentrations in South Asians. This study revealed that South Asians have higher postprandial TAG after a high fat meal than White Europeans. There was a trend for lower postprandial TAG concentrations after walking exercise (in comparison with control conditions) in South Asians but this was not significant. Among the possible reasons for the lack of an exercise effect in the previous study is the mode of exercise which may have provided insufficient energy expenditure to lower postprandial TAG.

Hence the purpose of the present study was to examine the influence of a one-hour run on CVD risk markers in South Asian and European men to see if the higher energy expenditure elicited by the run would have any effect. The primary outcome variable in this study was postprandial TAG concentration but several other disease risk markers were examined including total cholesterol, high density lipoprotein cholesterol (HDL-C), glucose, insulin, interleukin-6 (IL-6) and soluble intercellular adhesion molecule-1 (sICAM-1).

5.2 Methods

5.2.1 Participants

With the approval of Loughborough University's Ethics Advisory Committee 10 South Asian men and 10 men of white European descent were recruited and they gave their written informed consent to participate in this study. G Power (version 3.1.3, Franz Faul, Universitat Kiel, Germany) was used to calculate the study sample size and this indicated that 10 participants per group would be sufficient to detect a difference in TAG AUC (the primary outcome variable) with a power of 0.8 and a 5% level of significance. When calculating power using G-power, postprandial AUC TAG values were used in preference to fasting TAG values. This was done due to the strong correlation between postprandial TAG levels and elevated risk of developing cardiovascular disease. Participants were healthy and recreationally active and ranged in age from 20 to 28 years. Participants were non-smokers, with no personal history of CVD or metabolic disease, and none of them reported taking medication. Participants had a BMI < 30 $kg \cdot m^{-2}$. They were not dieting and did not have any extreme dietary habits. To verify ethnicity each South Asian participant completed a form providing details of their place and country of birth, their mother tongue language, their religion and race, the country of their parents' birth and their family history of migration. This revealed that seven of the participants were Indian nationals, two were UK Indians and one was from Pakistan.

5.2.2 Anthropometry

Prior to the main trials participants attended the laboratory for a screening and familiarization visit lasting approximately two hours. During this visit they completed a participant information form and questionnaires assessing health status, usual physical activity and ethnicity (South Asians only). Subsequently, weight was measured to the nearest 0.01 kg using a digital scale (Seca Ltd, Germany) and height was measured to the nearest 0.1 cm using a stadiometer (Avery Industrial Ltd, Leicester, UK). Skinfold thickness was measured with calipers (Harpenden, Burgess Hill, U.K.) on the right hand side of the body at the biceps, triceps, subscapular and suprailiac. The sum of these four skinfold measurements was used to determine body density (Durnin and Womersley, 1974) and body fat percentage (Siri, 1956). In addition, waist circumference was determined at the narrowest part of the torso

above the umbilicus and below the xiphoid process using a measuring tape. Lastly, blood pressure was measured using a digital monitor (Omron M5-1, Matsusaka Co., Ltd, Japan).

5.2.3 Preliminary exercise tests

After familiarization with motorized treadmill running (RUNRACE, Techno gym, Gambettola, Italy) participants completed two preliminary exercise tests: a submaximal, incremental treadmill running test (to determine the relationship between running speed and oxygen uptake) and a maximal oxygen uptake ($\dot{V}O_2$ max) test. The submaximal test was performed on a level treadmill and involved four, four-minute stages of increasing intensity. Initial running speed was set between 6 and 9.5 km·h^{-1} and the speed was increased by 0.5 or 1 km·h^{-1} (depending on each participant's level of fitness) at the end of each stage. After a 30 minute recovery, $\dot{V}O_2$ max was determined with the use of an incremental uphill protocol at a constant speed until participants reached volitional exhaustion (Taylor et al, 1955). The initial treadmill gradient was set at 3.5% for this test and the gradient was increased by 2.5% every 3 minutes. Short range telemetry (Sports tester PE_{3000}, Polar Electro, Finland) was used to evaluate heart rate throughout both tests. Ratings of perceived exertion (RPE) were assessed periodically during these tests using the Borg scale (Borg, 1973).

Expired air samples were collected into Douglas bags (Plysu Protection Systems, Milton Keynes, United Kingdom) during both of the preliminary exercise tests. An O_2/CO_2 analyser (Servomex 1440, Crowborough, Sussex, United Kingdom) was used to measure the oxygen and carbon dioxide percentages within the expired air samples. The analysers were calibrated using gases of known concentration prior to testing. A dry gas meter (Harvard Apparatus, Edenbridge, United Kingdom) was used to measure expired air volumes which were corrected to standard temperature and pressure dry. The oxygen consumption values from the two preliminary exercise tests were used together to determine the running speed required to elicit 70% of each participant's $\dot{V}O_2$ max.

5.2.4 Main trials

Participants completed two, two day trials (exercise and control) in a random order separated by an interval of at least one week. Trials were undertaken in block random order (block size

of two) using software available at http://www.randomization.com/. On day one of the exercise trial, participants arrived at the laboratory between 8.00 and 9.00 am and rested (reading, working at a computer, watching television, listening to music or playing video games) throughout the day until 5.00 pm. Participants consumed a standardized lunch at approximately 12.00 pm. At 3.30 pm, participants performed a 60 minute run at a speed predicted to elicit 70% of their $\dot{V}O_2$ max. One minute samples of expired air were collected at 15 minute intervals during the run to monitor the exercise intensity i.e. minutes 14-15, 29-30, 44-45 and 59-60 during the run. If necessary adjustments were made to the treadmill speed to ensure that participants were at the correct intensity. Heart rate and RPE were also monitored during the run. During day one of the control trial procedures were exactly the same as on day one of the exercise trial except that no running was performed and four, five-minute resting expired air samples were collected at the time when running was performed on day 1 of the exercise trial. Oxygen consumption and carbon dioxide production were calculated from expired air samples as described previously. Energy expenditure was estimated from oxygen consumption and carbon dioxide production values using stoichiometric equations (Frayn, 1983).

On day two of the main trials participants arrived at the laboratory between 7.45 and 8.00 am having fasted overnight (no food or drink except water) for 10 hours. On arrival at the laboratory, participants sat on a bed in a semi-supine position for 5 minutes while a cannula (BD Ven-flon, Becton-Dickinson, Helsingborg, Sweden) was inserted into an antecubital vein and a baseline blood sample was collected. Participants then consumed a prescribed test meal (see below) for breakfast. A clock was started the moment they commenced their meal and this was identified as the 0 hour. The trial continued on for nine hours during which a total of 14 (including the fasting sample), 9 mL venous blood samples were collected. At 4 hours, a second test meal, identical to the first, was served to participants. Participants rested throughout day two of both the control and exercise trials and hence day two of these trials was identical. A schematic representation of the main trial protocol is displayed in Figure 5.1.

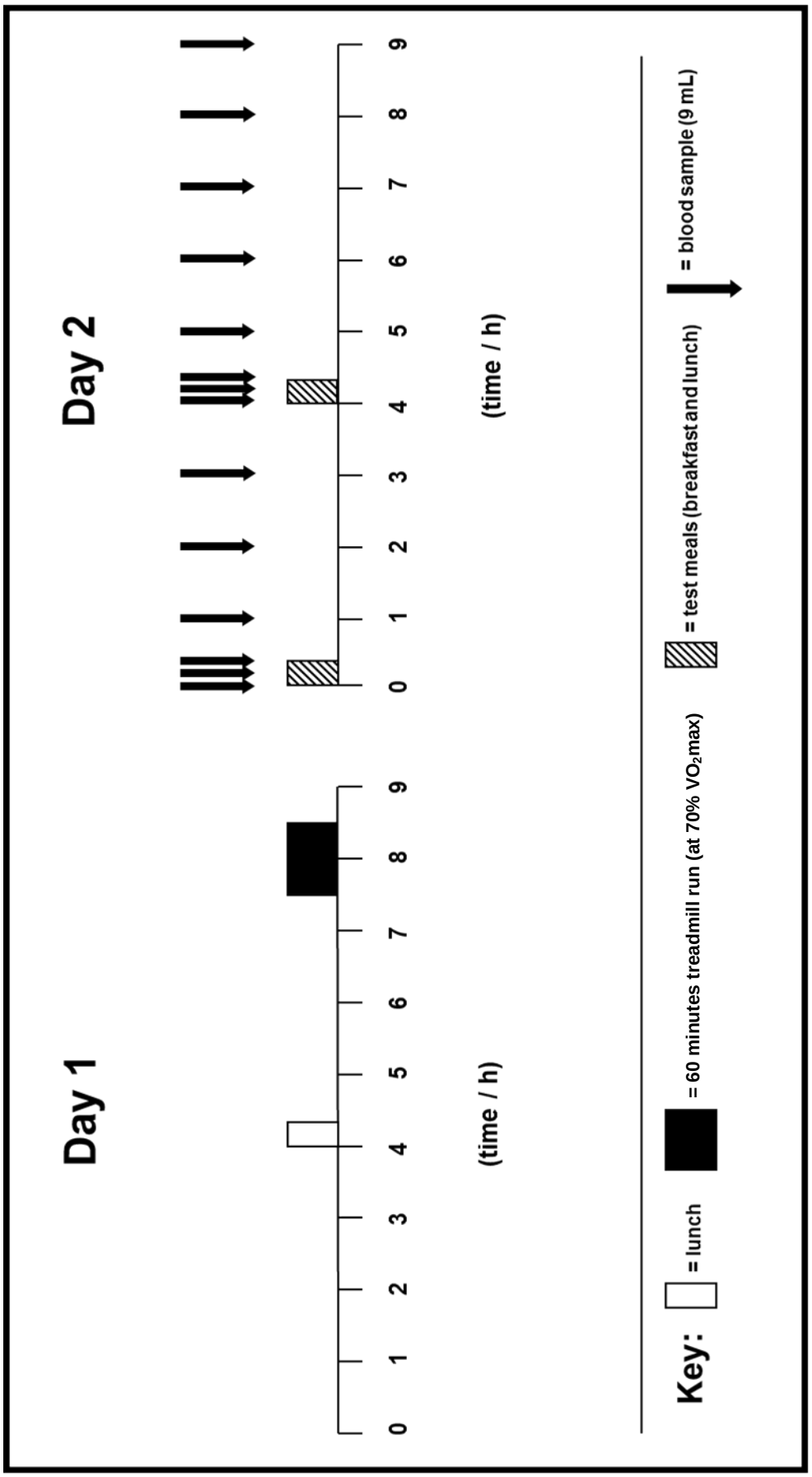

Figure 5.1: A schematic representation of the main trial protocol.

5.2.5 Control of diet and exercise

The day before each main trial and on the first day of each main trial, participants recorded their food intake using a weighed food diary. Participants replicated this food intake for the next main trial. Participants were told not to consume tea, coffee, or alcohol on the day prior to and during the main trials. Participants were also asked to refrain from strenuous physical activity during the day preceding the main trials and on day 1 and day 2 of the main trials.

5.2.6 Test meals

The test meals consisted of white bread, butter, cheese, mayonnaise, crisps, chocolate milk shake powder and high fat milk. The amount of food consumed was adjusted for each participant based on their body weight and was kept constant throughout the trials. The macronutrient content of the test meal was 57% fat, 32% carbohydrate and 11% protein and each meal provided 60 kJ (14.3 kcal) per kg body mass for a 70 kg participant. Participants consumed each meal within 15 minutes and water was available *ad libitum*.

5.2.7 Blood sampling

Venous blood samples were collected for the measurement of total cholesterol, high density lipoprotein (HDL) cholesterol, TAG, glucose, insulin, IL-6 and sICAM-1. Samples were collected at 0, 0.25, 0.5, 1, 2, 3, 4, 4.25, 4.5, 5, 6, 7, 8, 9 hours. Total cholesterol and HDL cholesterol were only measured from baseline samples; IL-6 and sICAM-1 concentrations were measured from samples collected at 0, 3, 6 and 9 hours; glucose, insulin and TAG were measured from all samples. Participants rested in a semi-supine position during blood sampling. Venous blood samples were drawn into pre-cooled 9 mL EDTA monovette tubes (Starstedt, Leicester, United Kingdom) and immediately centrifuged at 1500 x g (3000 revs/min) for 10 minutes in a refrigerated centrifuge (Burkard, Hertfordshire, United Kingdom) at 4ºC. The plasma supernatant was dispensed into eppendorf tubes and stored at -80ºC before analysis. After each blood sample collection 10 mL of non-heparinised saline solution (0.9% (v/w) sodium chloride, Baxter Healthcare Ltd, Norfolk, United Kingdom) was flushed through the cannula to maintain cannula patency. Two mL of blood was drawn into a syringe and discarded at the start of each blood collection to prevent sample contamination

from saline. Haemoglobin and haematocrit values were used to estimate changes in plasma volume across the nine-hour main trial day (Dill and Costill, 1974).

5.2.8 Blood biochemistry

Plasma total cholesterol, HDL-C, TAG and glucose concentrations were determined spectrophotometrically using commercially available kits and a bench top analyser (Pentra 400, HORIBA ABX Diagnostics, Montpellier, France). Enzyme linked immuno sorbent assays (ELISA) assays were used to determine the concentrations of plasma insulin (Mercodia, Sylveniusgatan, Uppsala, Sweden), IL-6 (high sensitivity kit; Diaclone, Besançon, France) and sICAM-1 (Diaclone, Besançon, France) with the aid of a plate reader (Expert Plus, ASYS, Eugendorf, Austria). To eliminate inter assay variation, samples from each participant were analysed in the same run. Coefficients of variation for each assay were as follows: 0.7% for total cholesterol, 0.7% for HDL-C, 3.0% for TAG, 0.5% for glucose, 6.0% for insulin, 3.4% for IL-6 and 4.9% for sICAM-1.

5.2.9 Statistical analysis

Data were analysed using Predictive Analytics Software version 18.0 for Windows (SPSS, Inc., Somers, NY, USA). Physical characteristics and exercise responses were compared between South Asians and Europeans using Students t-tests for independent samples. Three-way repeated measures ANOVA with Bonferroni post-hoc tests was used to examine differences between trials for plasma constituents (TAG, glucose, insulin, IL-6 and sICAM-1) with the three factors being: a) trial (exercise versus control), b) ethnic group (South Asians versus Europeans) and c) time (serial measurements over 9 hours). Effect sizes (Cohen's *d*) were also calculated for each of these variables by dividing the differences between the mean values (exercise versus control or South Asian versus European) with the standard deviation (i.e. the average standard deviation from both trials and ethnic groups combined). Area under the plasma concentration versus time curve (AUC) values were calculated for TAG, glucose, insulin, IL-6 and sICAM-1 using the trapezoidal method. These values were compared using two-way repeated measures ANOVA with the two factors being trial (exercise versus control) and ethnic group (South Asian versus European). Two-way repeated measures ANOVA was also used to assess between trial and ethnic group differences for fasting plasma

concentrations. Statistical significance was accepted at the 5% level. Results are presented as mean ± SD in the text and tables and as mean ± SEM in figures.

5.3 Results

5.3.1 Participant characteristics

The physical characteristics of the participants are displayed in Table 5.1. There were no significant differences between South Asian and European participants for age, height, weight, BMI, waist circumference and resting diastolic blood pressure. Percentage body fat was higher in South Asians than Europeans while resting systolic blood pressure and $\dot{V}O_2$ max were lower in South Asians than in Europeans.

Table 5.1: Participant characteristics.

Variable	**South Asians (n = 10)**	**Europeans (n = 10)**	***P* value**
Age (years)	22.3 ± 1.3	23.2 ± 2.0	0.259
Height (cm)	173.0 ± 5.7	177.0 ± 6.0	0.133
Weight (kg)	76.3 ± 9.1	79.2 ± 8.6	0.471
Body mass index ($kg \cdot m^{-2}$)	25.4 ± 2.5	25.2 ± 1.6	0.818
Body fat (%)	23.0 ± 4.4	16.4 ± 4.2	0.003
Waist circumference (cm)	82.8 ± 4.9	80.0 ± 3.3	0.144
Resting SBP (mm Hg)	128 ± 8	138 ± 11	0.032
Resting DBP (mm Hg)	75 ± 8	76 ± 6	0.757
$\dot{V}O_2$ max ($mL \cdot kg^{-1} \cdot min^{-1}$)	48.2 ± 7.3	56.6 ± 6.7	0.015

All values are mean ± SD. Means were compared using independent samples Student's t-tests. SBP, systolic blood pressure; DBP, diastolic blood pressure; $\dot{V}O_2$ max, maximal oxygen uptake.

5.3.2 Responses to treadmill running

The physiological responses to the 60 minute treadmill run are displayed in Table 5.2. The White European participants ran significantly faster and expended more energy during the run than the South Asian participants. There were no significant differences between groups in % $\dot{V}O_2$ max, average heart rate, average RPE or substrate (carbohydrate/fat) utilisation attained during the run. There was a tendency for exercise $\dot{V}O_2$ to be slightly higher in White Europeans than South Asians.

Table 5.2: Responses to treadmill running.

Variable	**South Asians (n = 10)**	**Europeans (n = 10)**	***P* value**
Running speed ($km \cdot h^{-1}$)	7.6 ± 1.4	9.6 ± 1.6	0.008
$\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	35.5 ± 5.6	39.9 ± 4.4	0.061
% $\dot{V}O_2$ max ($mL \cdot kg^{-1} \cdot min^{-1}$)	73.5 ± 4.5	70.6 ± 2.2	0.087
Average heart rate ($beats \cdot min^{-1}$)	172 ± 14	172 ± 20	0.958
Rating of perceived exertion	12 ± 2	12 ± 1	0.347
Respiratory exchange ratio	0.93 ± 0.06	0.97 ± 0.06	0.300
Exercise energy expenditure ($kJ \cdot h^{-1}$)	3313 ± 623	3901 ± 473	0.029
% Energy from fat	22.2 ± 20.3	11.6 ± 20.8	0.265
% Energy from carbohydrate	77.8 ± 20.3	88.4 ± 20.8	0.265

All values are mean ± SD. Means were compared using independent samples Student's t-tests. $\dot{V}O_2$, volume of oxygen consumed; SBP, systolic blood pressure; DBP, diastolic blood pressure; $\dot{V}O_2$ max, maximal oxygen uptake.

5.3.3 Fasting plasma concentrations

There were significant main effects of trial for fasting total cholesterol, TAG and sICAM-1 indicating lower values on the exercise trial for fasting total cholesterol and TAG and higher values for fasting sICAM-1 (Table 5.3). There were significant main effects of group for fasting plasma insulin, HDL-C and the ratio of total cholesterol/HDL-C indicating higher insulin and total cholesterol/HDL-C concentrations in the South Asian than the European participants and lower HDL-C concentrations in the South Asian participants. There was a tendency ($P = 0.074$) for fasting TAG to be elevated in the South Asian participants.

Table 5.3: Fasting plasma concentrations on day two of the main trials.

Variable	South Asians (n = 10)		Europeans (n = 10)		*P* for trial	*P* for group	*P* for T v G
	Control	Exercise	Control	Exercise			
TC ($mmol \cdot L^{-1}$)	3.85 ± 0.45	3.77 ± 0.50	3.80 ± 0.83	3.58 ± 0.61	0.045	0.649	0.348
HDL-C ($mmol \cdot L^{-1}$)	0.96 ± 0.19	0.95 ± 0.19	1.27 ± 0.21	1.23 ± 0.27	0.399	0.005	0.719
TC / HDL-C ratio	4.13 ± 0.90	4.09 ± 0.81	3.08 ± 0.90	3.06 ± 0.97	0.617	0.017	0.864
TAG ($mmol \cdot L^{-1}$)	1.42 ± 0.49	1.18 ± 0.34	1.04 ± 0.40	0.92 ± 0.40	0.021	0.074	0.402
Glucose ($mmol \cdot L^{-1}$)	5.03 ± 0.30	4.94 ± 0.44	5.15 ± 0.47	5.00 ± 0.47	0.087	0.632	0.672
Insulin ($\mu U \cdot mL^{-1}$)	16.6 ± 23.6	15.2 ± 20.9	2.4 ± 1.6	3.2 ± 5.8	0.952	0.014	0.834
sICAM-1 ($ng \cdot mL^{-1}$)	446 ± 56	516 ± 114	452 ± 79	529 ± 70	0.001	0.770	0.859
IL-6 ($pg \cdot mL^{-1}$)	1.31 ± 1.11	1.49 ± 1.21	1.25 ± 0.80	0.80 ± 0.76	0.590	0.313	0.223

All values are mean ± SD. Comparisons were made using two-way ANOVA. T, trial (exercise versus control); G, group (South Asian versus European); TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; TAG, triacylglycerol; sICAM-1, soluble intercellular adhesion molecule-1; IL-6, interleukin-6.

5.3.4 Postprandial plasma concentrations

Three-way ANOVA revealed main effects of group for TAG ($P < 0.001$), insulin ($P < 0.010$) and glucose ($P < 0.05$) indicating higher postprandial TAG and insulin values in South Asian participants and higher postprandial glucose values in European participants (Figure 5.2). The effect sizes for these ethnic group comparisons were all large: 1.22, 1.06 and 0.85 respectively. Body fat percentage was higher in the South Asian participants than the European participants and this might confound the relationship between ethnicity and plasma concentrations, therefore, three-way ANOVA was conducted a second time with body fat added as a covariate to remove its confounding influence. Between group differences remained significant for TAG and glucose but were not significant for insulin after control for percentage body fat.

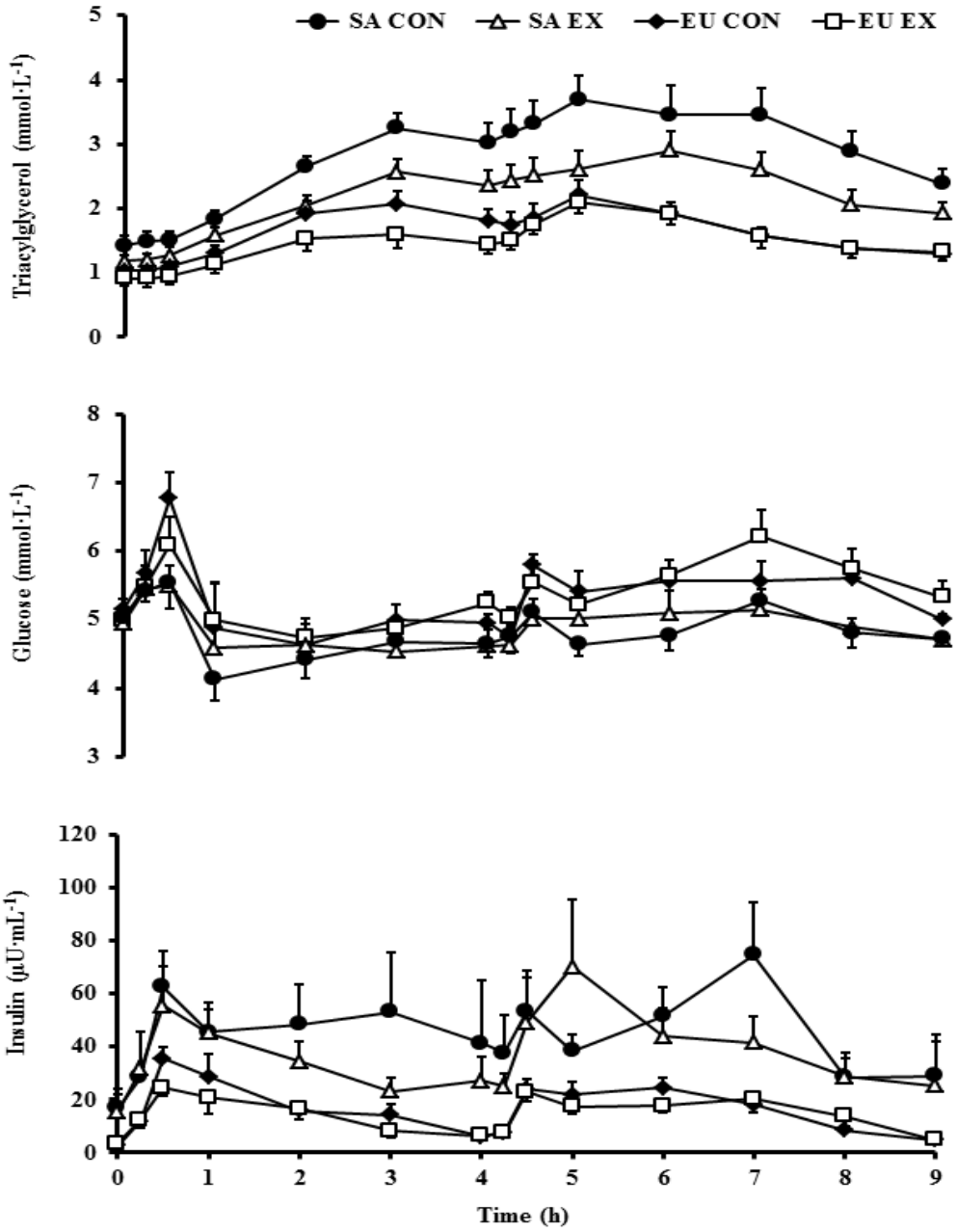

Figure 5.2: Mean ± (SEM) postprandial plasma triacylglycerol (top panel), glucose (middle panel) and insulin (bottom panel) concentrations measured on day two of the exercise and control trials for South Asian (n=10) and European (n=10) men. Data were analysed using three-way repeated measures ANOVA. There were significant main effects of trial (P = 0.001) for triacylglycerol and significant main effects of ethnicity for triacylglycerol (P = 0.001), glucose (P = 0.043) and insulin (P = 0.010). There was also a trial x ethnicity effect for triacylglycerol (P = 0.031).

Three-way ANOVA revealed main effects of trial for TAG ($P < 0.001$), IL-6 ($P < 0.003$) and sICAM-1 ($P < 0.001$) indicating that TAG (Figure 5.2) and IL-6 (Figure 5.3) concentrations were lower on the exercise trial while sICAM-1 concentrations were higher on the exercise trial (Figure 5.3). The effect size for these comparisons (based on AUC values) was medium for TAG (0.52) and IL-6 (0.55) and large for sICAM-1 (1.04).

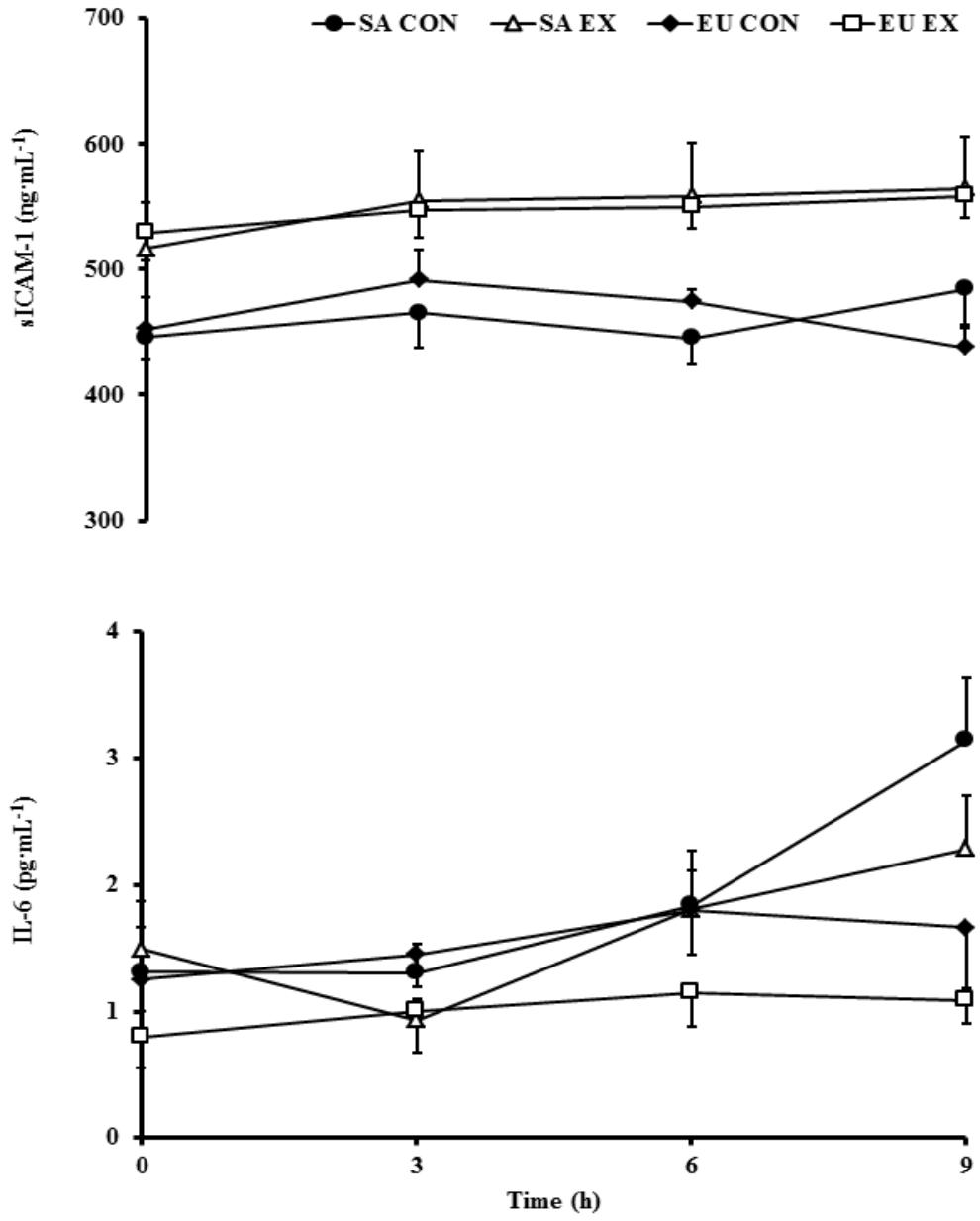

Figure 5.3: Mean ± (SEM) postprandial plasma concentrations of soluble intercellular adhesion molecule-1 (sICAM-1) and interleukin-6 (IL-6) measured on day two of the exercise and control trials for South Asian (n=10) and European (n=10) men. Data were analysed using three-way repeated measures ANOVA. A main effect of trial was observed for sICAM-1 ($P < 0.001$) and IL-6 ($P = 0.003$). There were no main effects for ethnicity.

Trial and ethnic group differences were confirmed when assessing AUC values using two-way ANOVA (Table 5.4). Again plasma TAG and insulin concentrations were higher in South Asian participants while plasma glucose concentrations were higher in European participants. The TAG and IL-6 lowering effects of exercise were also confirmed as was the exercise induced elevation in sICAM-1. Finally, a significant trial by group interaction effect was observed for TAG indicating a greater decrease after exercise in the South Asian men than the European men (22% versus 10%).

Table 5.4: Area under the postprandial concentration versus time curve values on day two of the main trials.

Variable	South Asians (n = 10)		Europeans (n = 10)		*P* for trial	*P* for group	*P* for T v G
	Control	Exercise	Control	Exercise			
TAG (mmol·L^{-1} 9 h)	26.1 ± 7.1	20.2 ± 5.2	15.2 ± 3.9	13.7 ± 3.7	0.001	0.001	0.026
Glucose (mmol·L^{-1} 9 h)	43.0 ± 4.8	43.8 ± 5.2	47.7 ± 4.4	48.5 ± 5.4	0.307	0.037	0.967
Insulin (μU·mL^{-1} 9 h)	419 ± 326	341 ± 215	151 ± 77	133 ± 76	0.126	0.012	0.331
sICAM-1 (ng·mL^{-1} 9 h)	4125 ± 643	4960 ± 1119	4233 ± 433	4921 ± 511	<0.001	0.900	0.679
IL-6 (pg·mL^{-1} 9 h)	16.1 ± 6.9	13.9 ± 6.4	14.1 ± 5.5	9.3 ± 6.0	0.004	0.212	0.249

All values are mean ± SD. Comparisons were made using two-way ANOVA. T, trial (exercise versus control); G, group (South Asian versus European); TAG, triacylglycerol; sICAM-1, soluble intercellular adhesion molecule-1; IL-6, interleukin-6.

Figure 5.4 displays the difference in the TAG AUC values between the exercise and the control trials for each participant. Negative values indicate a lowering of postprandial TAG concentration on the exercise trial. This figure demonstrates that postprandial TAG concentration was lower on the exercise trial in nine out of 10 South Asian participants and eight out of 10 European participants. It is also clear from the figure that the TAG lowering effect of exercise is greater in the South Asian than in the European participants.

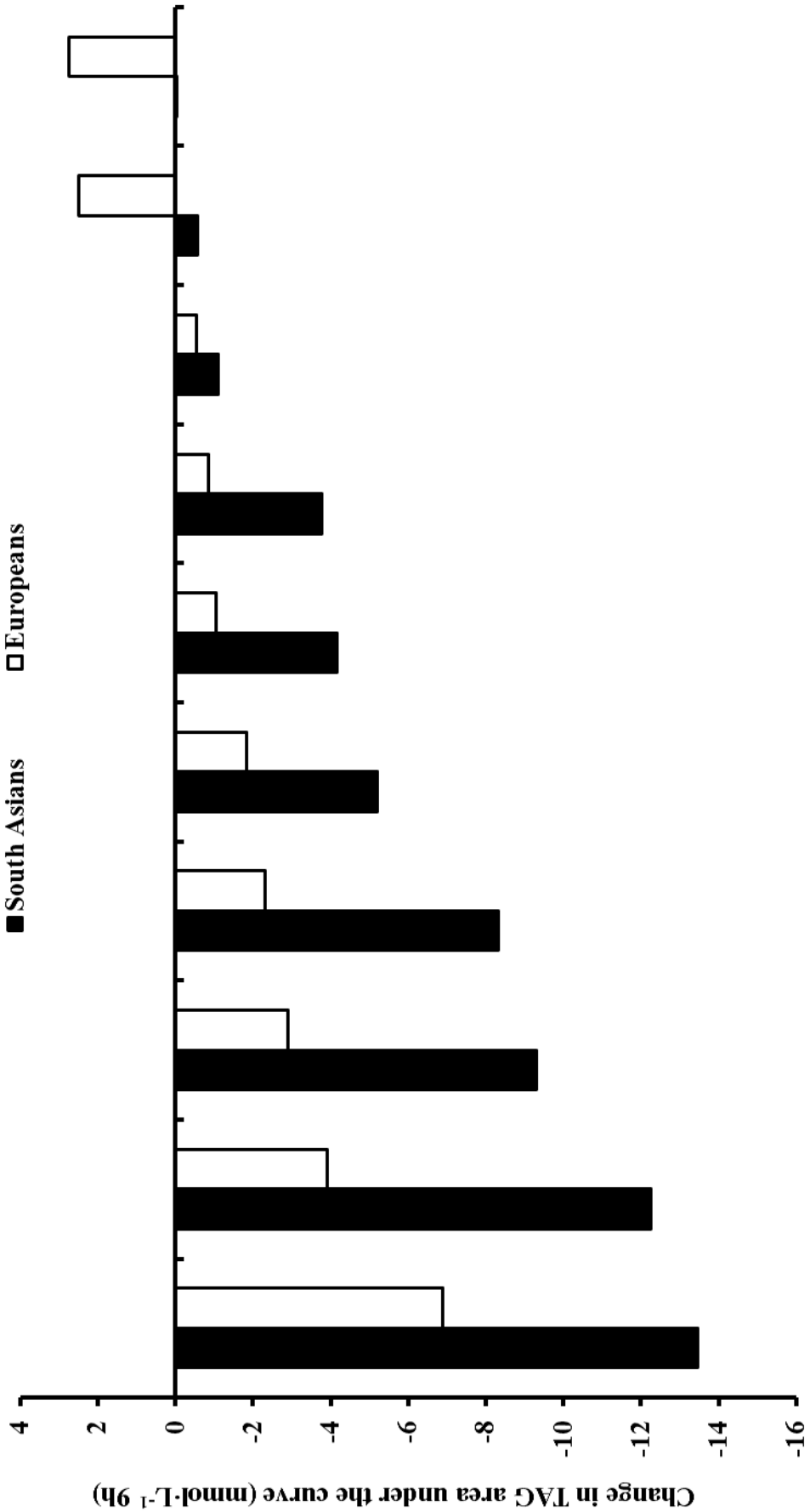

Figure 5.4: Individual changes (exercise minus control) in the total area under the TAG concentration versus time curve in response to the 60 min treadmill run for South Asian (n=10) and European (n=10) men. Negative values indicate lower concentrations on the exercise trial

5.4 Discussion

The novel findings arising from this study are: 1) postprandial plasma TAG concentrations were elevated to a much greater extent in the South Asian men than in the European men in response to high fat meals; 2) exercise was equally effective if not more so for lowering postprandial plasma TAG concentrations in the South Asian men than in the European men. Another key finding arising from this study is that postprandial plasma insulin concentrations were higher in the South Asian men than in the European men. No ethnic group differences were apparent for IL-6 and sICAM-1 but postprandial plasma IL-6 concentrations were lower after exercise while postprandial sICAM-1 concentrations were higher.

The most striking finding from this study is the clear elevation in postprandial TAG concentrations in response to high fat meals in the South Asian participants compared with the White European participants. Previous studies have observed higher fasting TAG concentrations in South Asians than in white people (Anand et al, 2000; Tziomalos et al, 2008) but there are no published reports of exaggerated postprandial TAG in response to high fat meals in South Asians. The findings in the present study are consistent with those reported in the previous chapter. Importantly, individuals with exaggerated postprandial TAG are more susceptible to CVD and the findings of the present study suggest that exaggerated postprandial lipaemia may be prevalent among South Asian people exposed to high fat diets. Interestingly, one other study which has compared postprandial lipaemia in South Asians and Europeans did not observe a difference in the lipaemic response to high fat meals although postprandial glucose and insulin concentrations were elevated in South Asians (Cruz et al, 2001). A possible explanation for these different findings is that percentage body fat did not differ between ethnic groups in the study conducted by Cruz and colleagues (2001) whereas body fat percentage was higher in the South Asian participants in the present study as is often the case (Wang et al, 1994). Nevertheless, between group differences in postprandial lipaemia remained significant in the present study even after controlling for differences in percentage body fat. Another possible explanation for the disparate findings is the test meals used. The percentage fat provided in the test meals was similar between studies (52% of energy from fat in the study by Cruz and colleagues (2001) versus 57% of energy from fat in the present study) but the total amount of food consumed (which is not stated in the paper by Cruz and colleagues) may have differed.

Another important finding from the present study is the effectiveness of running exercise for lowering postprandial TAG concentrations in the South Asian participants. The finding that postprandial TAG concentrations are lowered by a single session of prior exercise has been reported in many previous studies (for a review see Katsanos (2006)) but the present study is the first to report this in South Asians. Exercise was particularly effective in the South Asian group eliciting a 22% reduction in the TAG AUC values compared with only a 10% reduction in the European participants. This difference in the apparent effectiveness of exercise may have been due to the elevated TAG values in the South Asian participants i.e. higher values may provide a greater potential for reductions. Despite the effectiveness of exercise in the South Asian participants it is important to note that their TAG AUC values were still 33% higher after exercise than the control trial values exhibited by the European participants. If these findings are replicated in larger samples they would suggest that South Asians are at a much higher risk of experiencing exaggerated postprandial lipaemia in response to high fat meals than Europeans and this may be a contributing factor to their elevated risk of CHD.

In addition to elevated postprandial TAG concentrations, fasting insulin concentrations were nearly six times higher and postprandial insulin concentrations were nearly three times higher in the South Asian versus the European participants. These differences suggest a degree of insulin resistance in the South Asian participants and this is consistent with the findings of Cruz and colleagues (2001). Insulin resistance is thought to be a major contributor to the increased risk of type 2 diabetes and CHD experienced by those of South Asian descent (Sandeep et al, 2011; Tziomalos et al, 2008). Hyperinsulinaemia resulting from insulin resistance is thought to decrease muscle lipoprotein lipase activity (Pollare et al, 1991) and this would impair one of the major mechanisms for removal of TAG from blood. Thus, it is possible that the elevated postprandial lipaemia exhibited by the South Asian participants in the present study is linked to their elevated plasma insulin concentrations.

Surprisingly, and in contrast to the differences noted for insulin, there was a small but significant difference in postprandial plasma glucose concentrations between ethnic groups with higher values in the European participants. This finding conflicts with that of Cruz and colleagues (2001) who observed higher postprandial glucose concentrations in South Asian participants and also with the finding that fasting glucose concentrations are elevated in those

of South Asian descent (Anand et al, 2000). It is possible that the difference observed in the present study is a random (chance) finding. Aside from this finding the other differences observed between ethnic groups are consistent with previous research (Anand et al, 2000, Tziomalos et al, 2008) i.e. South Asian participants in the present study had a tendency for higher fasting TAG concentrations, higher fasting total cholesterol to HDL-C ratio values and lower fasting HDL-C concentrations. These findings indicate a higher risk of CHD in the South Asian participants (Joshi et al, 2007).

Interleukin-6 and sICAM-1 were assessed in the present study because both are indicative of chronic low grade inflammation which in turn is associated with an increased risk of type 2 diabetes and CHD (Hwang et al, 1997; Libby et al, 2002; Ridker et al, 1998). It has been suggested that an increased predisposition to chronic low grade inflammation, due to higher visceral and overall adiposity, might explain the elevated CHD risk in South Asians but the evidence to support this proposal is equivocal (Tziomalos et al, 2008). There were no differences in IL-6 and sICAM-1 between the South Asian and European men in the present study but IL-6 concentrations were suppressed the day after exercise while sICAM-1 concentrations were elevated. It is well documented that exercise causes a transient increase in the myokine IL-6 and this is known to stimulate an anti-inflammatory cascade involving increased concentrations of IL-10 and IL-1 receptor antagonist (Petersen and Pedersen, 2005; Gleeson et al, 2011). The lower IL-6 concentrations observed the day after exercise are possibly reflective of an anti-inflammatory effect of exercise subsequent to an initial increase in IL-6. The elevated sICAM-1 concentrations are probably related to an increased blood shear stress during exercise and it is clear that this elevation lasts for at least 24 h although the significance of this elevation is uncertain. Finally, there was a small but significant reduction in fasting total cholesterol concentration the day after exercise in the present study. If genuine this represents a beneficial influence of exercise but this is not a consistent finding in the literature and hence caution is warranted when interpreting this outcome.

This study had three notable limitations. Firstly, the sample size is small and hence these findings require confirmation with a larger sample. Secondly, it is possible that the group differences observed here are confounded by the differences in percentage body fat although South Asians are known to have a higher body fat percentage for a given BMI (Wang et al, 1994) and this may explain in part their elevated CHD risk. Thirdly, most of the participants

in the present study were Indian South Asians and South Asians are a heterogeneous group and hence these findings require confirmation in other South Asian groups (e.g. Bangladeshis and Pakistanis) and also in South Asian females.

In conclusion; the findings of this study indicate striking elevations in postprandial lipaemia in response to high fat meals in South Asian men. This study also demonstrates that running exercise is effective for lowering postprandial lipaemia in South Asian men. The relationship between elevated postprandial lipaemia and CHD risk in South Asians and the role of exercise in lowering postprandial lipaemia and CHD risk in South Asians should be a priority for future research.

6 The effects of a single bout of running versus three consecutive days of running on postprandial lipaemia in men of South Asian descent

6.1 Introduction

Cardiovascular disease is a major cause of death in the UK (British Heart Foundation, 2010), the USA (American Heart Association, 2012) and globally (World Health Organisation, 2011). South Asians regardless of where they live experience a higher rate of CHD than the general population. High morbidity and mortality rates from CVD/CHD in South Asians have been identified in Singapore (Danaraj et al, 1959), South Africa (Adelstein, 1963), Canada (Sheth et al, 1999), the USA (Palaniappan et al, 2004), and the UK (Wild et al, 2007). Estimates suggest a three to five fold increased risk of myocardial infarction and cardiovascular death among migrant South Asians compared with other ethnic groups (Eapen et al, 2009) and South Asians are generally younger when affected by CVD (Ramaraj & Chellappa, 2008). The reasons for these are uncertain.

Genetics and/or environment (diet, physical activity, psychosocial, socio-economic conditions, etc.) may act as catalysts inducing CVD in South Asians. One under researched environmental factor is physical inactivity which represents an independent vascular risk factor (Yusuf et al, 2004; Rastogi et al, 2004; Mohan et al, 2005; Rao et al, 2012) and can assist in preventing CVD and promoting and maintain health (Pearson et al, 2002; Haskell et al, 2007). Lower physical activity levels have been recorded in South Asian compared with white populations (Fischbacher et al, 2004, Owen et al, 2009; Yates et al, 2010; Williams et al, 2011; Misra et al, 2012). Levels of physical activity are inversely correlated with BMI, waist circumference, glucose and insulin levels in South Asians and Europeans (Hayes et al, 2002). Yet, there remains little evidence of successful exercise interventions among South Asians.

It is not uncommon for people in industrialised nations to spend considerable time each day in a postprandial state and this is critical because high TAG concentrations are a strong and

independent predictor for CVD risk (Nordestgaard et al, 2007; Bansal et al, 2007). The vascular complications associated with exaggerated postprandial lipaemia and its clinical relevance, given that the development of atherosclerosis is initiated at a young age, is vital in addressing CVD (Sternby et al, 1999; McGill et al, 2000).

Studies have shown that a single bout of aerobic exercise reduces postprandial lipaemia (Miyashita et al, 2006; Miyashita et al, 2008; Miyashita et al, 2008a; MacEneaney et al, 2009; Hurren et al, 2011). However, this reduction appears to be transient since detraining leads to a prompt elevation in postprandial lipaemia (Hardman et al, 1998). Therefore, for continued benefit exercise must be performed regularly. In addition, insulin action is enhanced in people who exercise regularly and vigorously and a reversal of this action takes place when individuals stop exercising (Leblanc et al, 1979). The exercise induced improvement in insulin action and glucose tolerance lasts for approximately 3 days (King et al, 1995).

Only one study has compared the effect of a single bout of exercise with that of bouts of exercise on three consecutive days on postprandial lipaemia and this study was conducted in overweight/obese European men (Farah et al, 2010). The exercise duration ranged from 65 minutes to 110 minutes per participant in this study and the investigators observed a reduction in postprandial TAG in both exercise trials compared with a control trial. Hence, the present study sought to examine this exercise protocol in men of South Asian descent using an exercise duration of 30 minutes (as recommended by the American College of Sports Medicine and the American Heart Association (Haskell et al, 2007)). In addition, this study also examined the effects of exercise on fasting and postprandial glucose concentrations, and on fasting total cholesterol, fasting high density lipoprotein cholesterol (HDL-C), fasting low density lipoprotein cholesterol (LDL-C), the fasting total cholesterol/HDL-C ratio and resting systolic and diastolic blood pressure.

6.2 Methods

6.2.1 Participants

With the approval of Loughborough University's Ethics Advisory Committee 11 South Asian men were recruited and they gave their written informed consent to participate in this study. The study sample size was calculated using G Power (version 3.1.3, Franz Faul, Universitat Kiel, Germany) which indicated that for the primary outcome variable (TAG) 14 participants would be sufficient to detect a difference in TAG with a power of 0.8 and a 5% level of significance. When calculating power using G-power, postprandial AUC TAG values were used in preference to fasting TAG values. This was done due to the strong correlation between postprandial TAG levels and elevated risk of developing cardiovascular disease. Participants were healthy and recreationally active and ranged in age from 18 to 28 years. Participants were non-smokers, with no personal history of CVD or metabolic disease, and none of them reported taking medication. They had a BMI < 30 $kg \cdot m^{-2}$. Participants were not dieting and did not have any extreme dietary habits. To verify ethnicity each South Asian participant completed a form providing details of their place and country of birth, their mother tongue language, their religion and race, the country of their parents' birth and their family history of migration. This revealed that six of the participants were Indian nationals, three were UK Indians and two were Sri Lankans from Sri Lanka.

6.2.2 Anthropometry

Prior to the main trials participants attended the laboratory for a screening and familiarization visit lasting approximately two hours. During this visit they completed a participant information form and questionnaires assessing health status, usual physical activity and ethnicity. Subsequently, weight was measured to the nearest 0.01 kg using a digital scale (Seca Ltd, Germany) and height was measured to the nearest to 0.1 cm using a stadiometer (Avery Industrial Ltd, Leicester, UK). Skinfold thickness was measured with calipers (Harpenden, Burgess Hill, U.K.) on the right hand side of the body at the biceps, triceps, subscapular and suprailliac. The sum of these four skinfold measurements was used to determine body density (Durnin & Wormersley, 1974) and body fat percentage (Siri,

1956). In addition, waist circumference was determined as the narrowest part of the torso above the umbilicus and below the xiphoid process using a measuring tape.

6.2.3 Preliminary exercise tests

After familiarization with motorized treadmill running (RUNRACE, Techno gym, Gambettola, Italy) participants completed two preliminary exercise tests: a submaximal, incremental treadmill running test (to determine the relationship between running speed and oxygen uptake) and a maximum oxygen uptake ($\dot{V}O_2$ max) test. The submaximal test was performed on a level treadmill and involved four, four-minute stages of increasing intensity. Initial running speed was set between 5.5 and 8 $km \cdot h^{-1}$ and the speed was increased by 0.5 or 1 $km \cdot h^{-1}$ (depending on each participant's level of fitness) at the end of each stage. After a 30 minute recovery, $\dot{V}O_2$ max was determined with the use of an incremental uphill protocol at a constant speed until participants reached volitional exhaustion (Taylor, Buskirk and Henschel, 1955). The initial treadmill gradient was set at 3.5% for this test and the gradient was increased by 2.5% every 3 minutes. Short range telemetry (Polar T31; Polar Electro, Kempele, Finland) was used to evaluate heart rate throughout both tests. Ratings of perceived exertion (RPE) were assessed periodically during these tests using the Borg scale (Borg, 1973).

Expired air samples were collected into Douglas bags (Plysu Protection Systems, Milton Keynes, United Kingdom) during both of the preliminary exercise tests. An O_2/CO_2 analyser (Servomex 1440, Crowborough, Sussex, United Kingdom) was used to measure the oxygen and carbon dioxide percentages within the expired air samples. The analysers were calibrated using gases of known concentration prior to testing. A dry gas meter (Harvard Apparatus, Edenbridge, United Kingdom) was used to measure expired air volumes which were corrected to standard temperature and pressure dry. The oxygen consumption values from the two preliminary exercise tests were used together to determine the running speed required to elicit 70% of each participant's $\dot{V}O_2$ max.

6.2.4 Main trials

Participants completed three main experimental trials each over 4 days. These were: one-day exercise (1-D Ex), three-day exercise (3-D Ex) and resting (control). These trials were conducted in a random order and separated by an interval of at least one week. Trials were undertaken in block random order (block size of one) using software available at http://www.randomization.com/. During the 1-D Ex trial, participants rested on days 1 and 2. On day 3, they arrived at the laboratory at 2.30 pm. After resting for an hour participants performed a 30 minute treadmill run at a speed predicted to elicit 70 % of their $\dot{V}O_2$ max. A 30 minute treadmill duration was chosen because this duration has been shown to be effective for lowering postprandial lipaemia in European participants (Miyashita et al, 2006) and also to minimise the potential for injury with longer bouts. One minute samples of expired air were collected at 10 minute intervals during the run to monitor the exercise intensity i.e. minutes 9-10, 19-20 and 29-30 during the run. If it was necessary adjustments were made to the treadmill speed to ensure that participants were at the correct intensity. Heart rate and RPE were also monitored during the run. During the control trial, participants rested from day 1 to day 3 and on day 3, procedures were exactly the same as on day 3 of the 1-D Ex trial except that no running was performed. Two, five minute resting expired air samples were collected at the time when running was performed on day 3 of the 1-D Ex trial i.e. between 3.30 pm and 4.00 pm equivalent to minutes 10-15 and 25-30. The 3-D Ex procedures were also identical to the 1-D Ex trial with the addition of 30 minute runs on days 1 and 2. Oxygen consumption and carbon dioxide production were determined from expired air samples as described for the preliminary exercise trials. Energy expenditure was estimated from oxygen consumption and carbon dioxide production values using stoichiometric equations (Frayn, 1983).

On day 4 of each main trial participants arrived at the laboratory by 8.30 am having fasted overnight (no food or drink except water) for 10 hours. On arrival, participants' body mass was measured. They then sat on a bed in a semi-supine position for 10 minutes after which a 5 minute expired air sample was collected. After the baseline expired air sample a cannula (BD Ven-flon, Becton-Dickinson, Helsingborg, Sweden) was inserted into an antecubital vein and a baseline blood sample was collected. After this, baseline resting blood pressure was measured using a digital monitor (Omron M5-1, Matsusaka Co., Ltd,

Japan). Participants then consumed a prescribed test meal for breakfast (see details below). A clock was started the moment participants commenced their meal and this was identified as 0 hour. The trial continued on for seven hours during which a total of 10 (including the fasting sample), 9 mL venous blood samples were collected. At 3 hours, a second test meal, identical to the first, was served to participants. Further measurements of blood pressure were performed at hourly intervals for 7 hours after the start of breakfast. Additional 5 minute expired air samples were collected at 1 h, 3 h, 4 h and 7 h). Participants rested throughout day four of the main trials and hence the final day of each experimental trial was identical. A schematic representation of the main trial protocol is displayed in Figure 6.1.

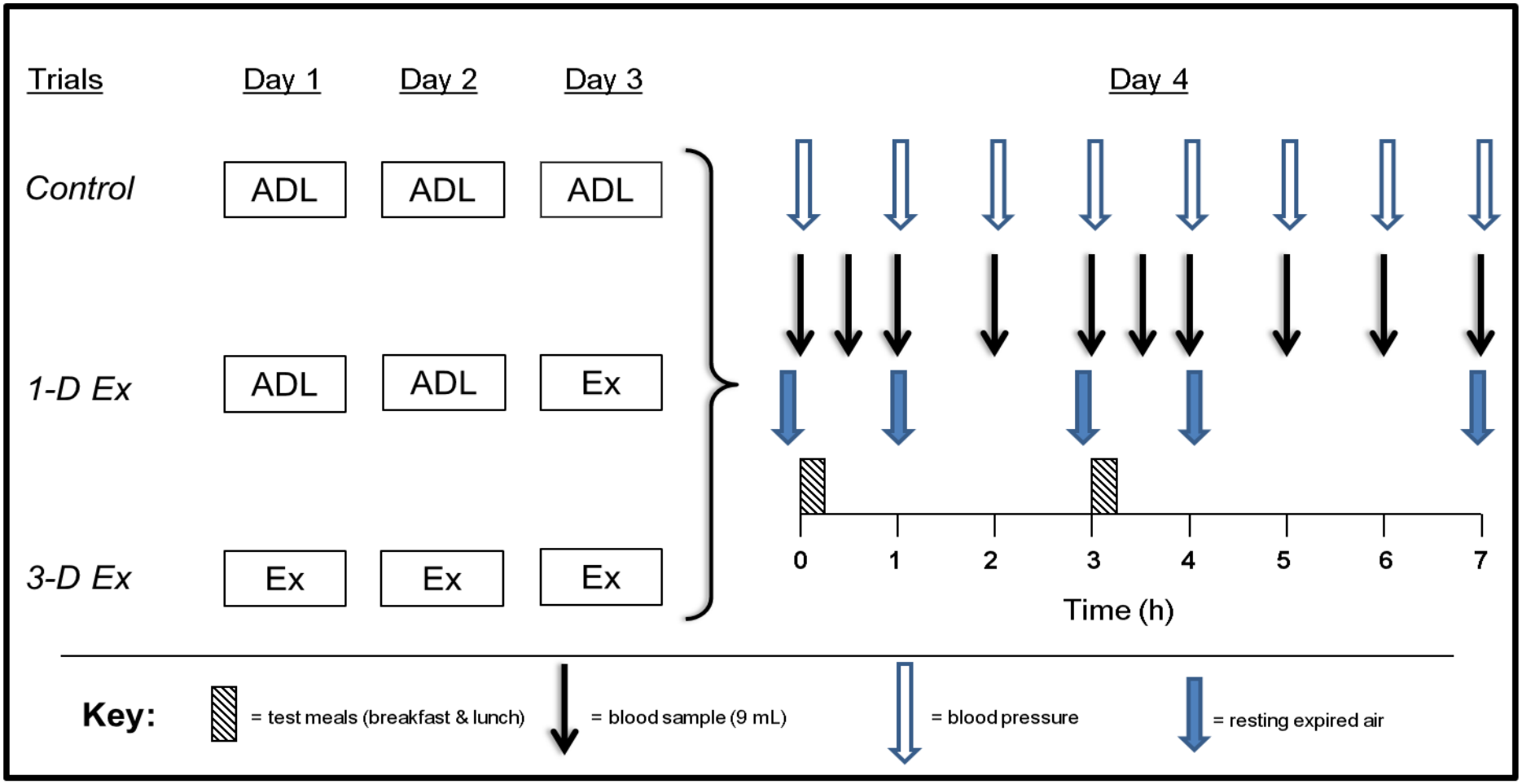

Figure 6.1: Schematic representation of the main trial protocol.

Control: no exercise and resting expired air measured from 10 - 15 and 25 - 30 min on day 3; **1-D Ex:** 30 minutes treadmill run at 70% of $\dot{V}O_2max$ on day 3; **3-D Ex:** 30 minutes treadmill run at 70% of $\dot{V}O_2max$ on days 1, 2 and 3. Expired air samples were collected during exercise trials between minutes 9-10, 19-20 and 29-30 of each run. **ADL:** activities of daily living.

6.2.5 Control of diet and exercise

The day before day 4 of each main trial participants recorded their food intake using a weighed food diary. Participants replicated this food intake on the day prior to each of the subsequent main trials. Participants were told not to consume coffee, tea or alcohol on the day prior to and during the main trials. They were also asked to refrain from strenuous physical activity (other than that performed as part of the study) on the day prior to and on all four days of each main trial).

6.2.6 Test meals

The meals consisted of white bread, butter, cheese, mayonnaise, crisps, chocolate milk shake powder and high fat milk. The amount of food consumed was adjusted for each participant based on their body weight and was kept constant throughout the trials. The macronutrient content of the test meal was 57% fat, 32% carbohydrate and 11% protein and each meal provided 60 kJ (14.3 kcal) per kg body mass for a 70 kg participant. Participants consumed each meal within 20 minutes and water was available *ad libitum*.

6.2.7 Blood sampling

Venous blood samples were collected for the measurement of total cholesterol, high density lipoprotein cholesterol (HDL-C), TAG and glucose. Samples were collected at 0, 0.5, 1, 2, 3, 3.5, 4, 5, 6 and 7 hours. Total cholesterol and HDL-C were only measured from baseline samples; TAG and glucose were measured from all samples. Participants rested in a semi-supine position during blood sampling. Venous blood samples were drawn into pre-cooled 9 mL EDTA monovette tubes (Starstedt, Leicester, United Kingdom) and immediately centrifuged at 1500 x g (3000 revs/min) for 10 minutes in a refrigerated centrifuge (Labofuge 400R, Thermo Scientific, Langenselbold, Germany) at 4ºC. The plasma supernatant was dispensed into eppendorf tubes and stored at -20ºC before analysis. After each blood sample collection 10 mL non-heparinised saline solution (0.9% (v/w) sodium chloride, Baxter Healthcare Ltd, Norfolk, United Kingdom) was flushed through the cannula to maintain cannula patency. Two mL of blood was drawn into a syringe and discarded at the start of each blood collection to prevent sample contamination from saline. Prior to the centrifugation of the blood samples at baseline and at seven hours, two 20 µL

blood samples were collected from monovettes into micropipettes for the measurement of haemoglobin and three 20 µL blood samples were collected from monovettes into microhaematocrit tubes for the measurement of haematocrit. Haemoglobin and haematocrit values were used to estimate changes in plasma volume across the seven-hour main trial day (Dill and Costill, 1974).

6.2.8 Blood biochemistry

Plasma total cholesterol, HDL-C, TAG and glucose concentrations were determined spectrophotometrically using commercially available kits and a bench top analyser (Pentra 400, HORIBA ABX Diagnostics, Montpellier, France). To eliminate inter assay variation, samples from each participant were analysed in the same run. Coefficients of variation for each assay were as follows: 1.9% for total cholesterol, 3.1% for HDL-C, 3.2% for LDL-C, 2.8 % for TAG and 0.6 % for glucose.

6.2.9 Statistical analysis

Data was analysed using Predictive Analytics Software version 18.0 for Windows (SPSS Inc., Somers, NY, USA). Exercise responses were compared between the two experimental trials using *t* - tests for paired samples. Two-way repeated measures ANOVA was used to examine differences between trials for plasma constituents (TAG and glucose) and blood pressure with the two factors being: a) trial (exercise 1-D, exercise 3-D and control) and b) time: (serial measurements over 7 hours). Effect sizes (Cohen's *d*) were also calculated for each of these variables by dividing the difference between the mean values (exercise versus control) with the average standard deviation from the respective trials combined). Area under the plasma concentration versus time curve (AUC) values were calculated for TAG and glucose using the trapezoidal method. These values were compared using one-way repeated measures ANOVA. One-way repeated measures ANOVA was also used to assess between trial differences for fasting plasma metabolite concentrations. Statistical significance was accepted at the 5% level. Results are presented as mean ± SD in the text and tables and as mean ± SEM in figures.

6.3 Results

6.3.1 Participant characteristics

The physical characteristics of the participants are displayed in Table 6.1.

Table 6.1: Physical characteristics of South Asian men .

Variables	**South Asians (n=11)**		
Age (years)	22.3	±	2.8
Height (cm)	175.3	±	7.2
Weight (kg)	73.1	±	11.4
Waist circumference (cm)	77.2	±	8.5
Body mass index ($kg \cdot m^{-2}$)	23.8	±	3.2
Body fat (%)	18.4	±	5.3
Resting SBP (mm Hg)	124	±	9
Resting DBP (mm Hg)	74	±	8
$\dot{V}O_2$ max ($mL \cdot kg^{-1} \cdot min^{-1}$)	52.4	±	5.8

Data are displayed as mean ± SD. SBP = systolic blood pressure; DBP = diastolic blood pressure; $\dot{V}O_2$ max = maximum oxygen uptake.

6.3.2 Responses to treadmill running

The physiological responses to the 30 minute runs during the 1-D Ex and 3-D Ex trials are displayed in Table 6.2. Participants ran significantly faster during the 3-D Ex than the 1-D Ex trials. A few of the participants experienced a 'training effect' and thus their running speed had to be increased to elicit 70% of $\dot{V}O_2$ max. There was also a tendency for exercise $\dot{V}O_2$, percentage $\dot{V}O_2$ max and energy expenditure to be slightly higher during the 3-D Ex trial than the 1-D Ex trial. There were no significant differences between exercise trials for respiratory exchange ratio, substrate (carbohydrate/fat) utilization, average heart rate and RPE.

Table 6.2: Responses during the 30 minute treadmill runs (n = 11).

Variable	1-Day Ex	3-Day Ex	P value
Speed ($km \cdot h^{-1}$)	8.0 ± 1.0	8.3 ± 1.2	0.022
$\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	35.7 ± 3.8	37.1 ± 4.1	0.067
% $\dot{V}O_2$ max	68.4 ± 5.1	70.9 ± 2.8	0.071
Respiratory Exchange ratio	0.95 ± 0.05	0.95 ± 0.04	0.690
Energy Expenditure ($kJ \cdot h^{-1}$)	1571 ± 195	1632 ± 200	0.092
Net Energy Expenditure ($kJ \cdot h^{-1}$)	1396 ± 169	1458 ± 173	0.091
% Energy Fat	16.8 ± 16.7	18.0 ± 14.2	0.736
% Energy Carbohydrate	83.2 ± 16.7	82.0 ± 14.2	0.736
Average Heart Rate ($beats \cdot min^{-1}$)	174 ± 10.1	172 ± 11.9	0.508
Rating of Perceived Exertion	11.3 ± 2.0	11.9 ± 2.0	0.237

Data are displayed as mean ± SD. For the 3-Day Ex trial the mean of three values was used. P values for differences between one day exercise and three day exercise trials are based on paired samples *t* tests. $\dot{V}O_2$ = volume of oxygen consumed.

6.3.3 Fasting plasma metabolite concentrations

Fasting concentrations of plasma metabolites (on day four of the main trials) are displayed in Table 6.3. There were no significant differences between trials for total cholesterol, HDL-C, LDL-C, total cholesterol/HDL-C, TAG or glucose.

Table 6.3: Fasting plasma concentrations and resting blood pressure on day four of the main trials (n = 11).

Variable	Control	1-Day Exercise	3-Day Exercise	P value
TC ($mmol \cdot L^{-1}$)	3.77 ± 0.64	3.82 ± 0.65	3.89 ± 58	0.384
HDL-C ($mmol \cdot L^{-1}$)	1.15 ± 0.14	1.15 ± 0.20	1.16 ± 0.20	0.958
LDL-C ($mmol \cdot L^{-1}$)	2.14 ± 0.46	2.17 ± 0.39	2.25 ± 0.48	0.356
TC / HDL-C	3.28 ± 0.43	3.33 ± 0.32	3.44 ± 0.72	0.526
TAG ($mmol \cdot L^{-1}$)	0.76 ± 0.21	0.74 ± 0.26	0.67 ± 0.23	0.292
Glucose ($mmol \cdot L^{-1}$)	5.31 ± 0.21	5.21 ± 0.36	5.10 ± 0.56	0.335
SBP (mm Hg)	125 ± 7.2	123 ± 6.7	123 ± 8.0	0.271
DBP (mm Hg)	74 ± 5.4	72 ± 3.4	73 ± 4.2	0.107

Data are displayed as mean ± SD. Values were compared using one-way analysis of variance. TC = total cholesterol; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; TAG = triacylglycerol; SBP = systolic blood pressure; DBP = diastolic blood pressure.

6.3.4 Postprandial plasma metabolite concentrations

Two-way ANOVA did not reveal any differences between trials for plasma TAG and glucose but a significant ($P < 0.001$) effect of time was observed for both these metabolites (Figure 6.2, Table 6.4). The effect sizes for TAG were small for all comparisons ≤ 0.24. Likewise, the effect sizes for glucose were small for all comparisons ≤ 0.06.

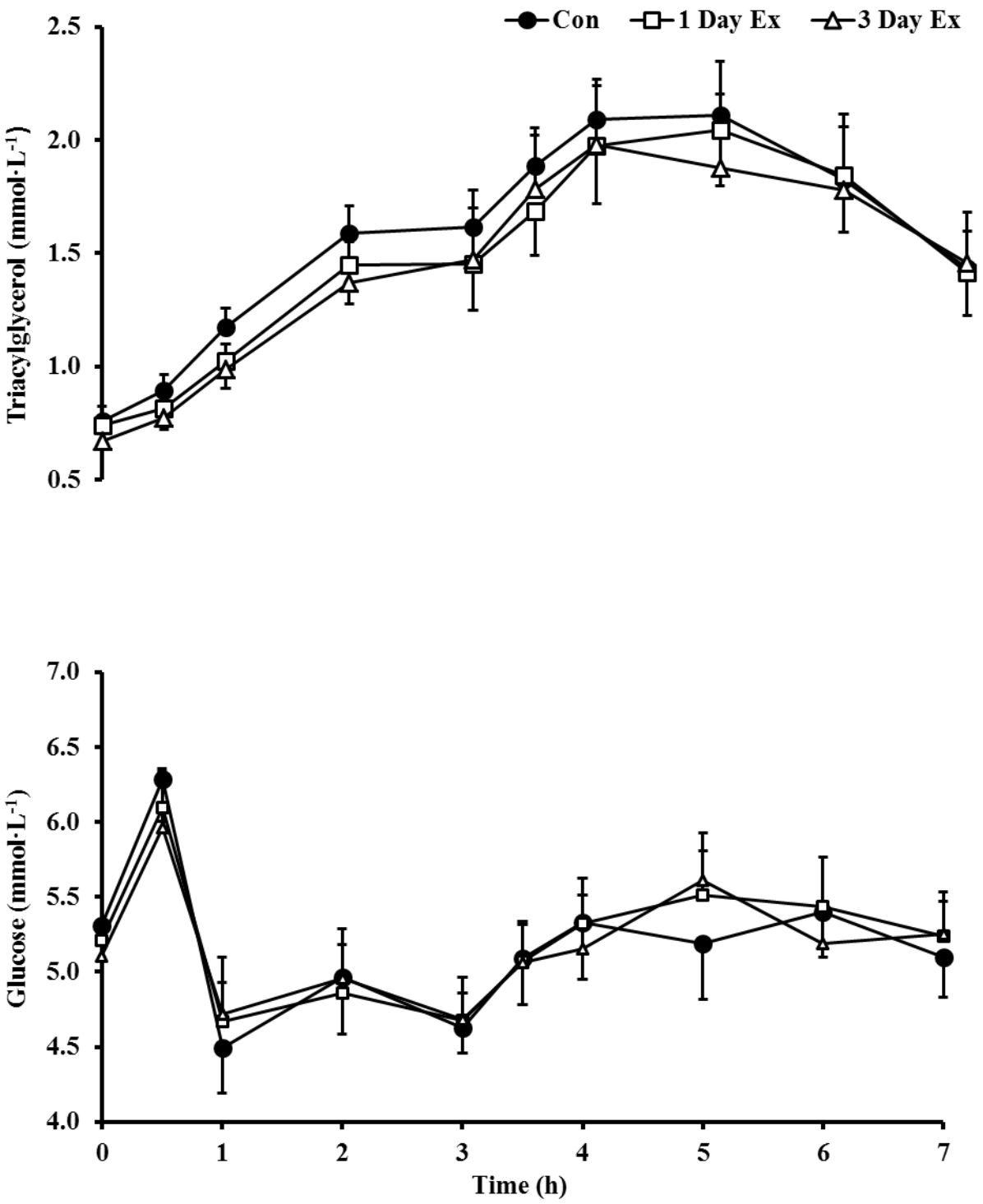

Figure 6.1: Postprandial plasma triacylglycerol (top panel) and glucose (bottom panel) concentrations measured on day four of the exercise and control trials (n=11). Data are displayed as mean ± SEM.

Table 6.4: Area under the postprandial concentration versus time curve values on day four of the main trials (n = 11).

Variable	Control	1-Day Exercise	3-Day Exercise	P value
TAG (mmol·L^{-1} 7 h)	11.4 ± 3.2	10.8 ± 4.2	10.5 ± 5.0	0.652
Glucose (mmol·L^{-1} 7 h)	35.7 ± 5.5	36.3 ± 5.4	36.1 ± 5.8	0.727

Data are displayed as mean ± SD. Values were compared using one-way analysis of variance; TAG = triacylglycerol.

Figure 6.3 displays the difference in the TAG AUC values between the 1-D Ex and control trials and the 3-D Ex and control trials for each individual participant. Negative values indicate a lowering of postprandial TAG concentration on the exercise trial compared with the control trial. This figure demonstrates that postprandial TAG concentration was lowered in 6 out of 11 participants in the 1-D Ex trial and 8 out of 11 participants in the 3-D Ex trial.

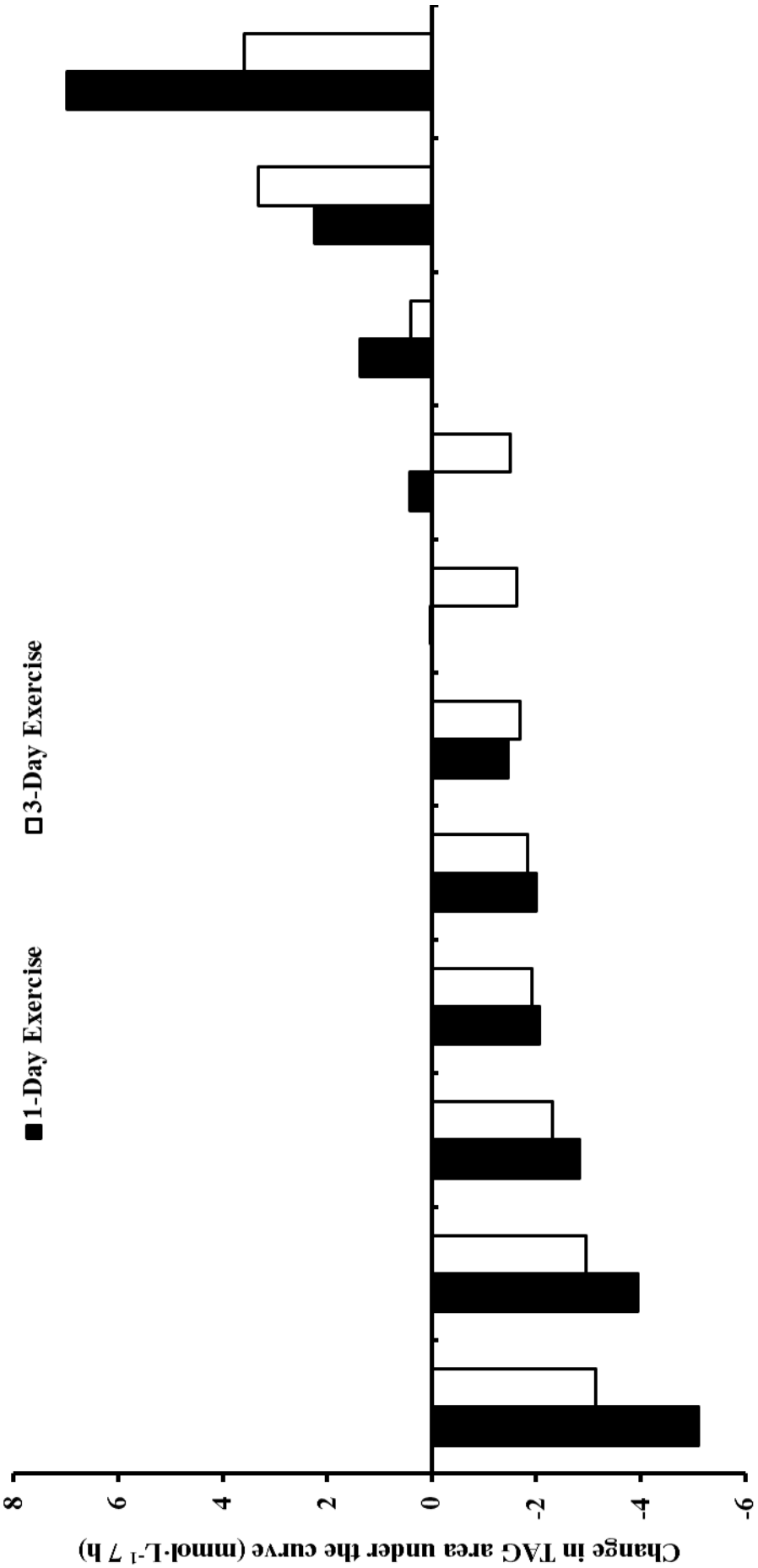

Figure 6.2: Individual changes (exercise minus control) in the total area under the TAG concentration versus time curve in response to the 30 minute treadmill runs (n=11). Negative values indicate lower concentrations on the exercise trials compared with the control trial.

6.3.5 Resting blood pressure responses

Resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) values are shown in Figure 6.4. Two-way ANOVA did not reveal any main effects of trial for SBP or DBP but a significant effect of time was observed for both: P = 0.006 for SBP and P = 0.024 for DBP.

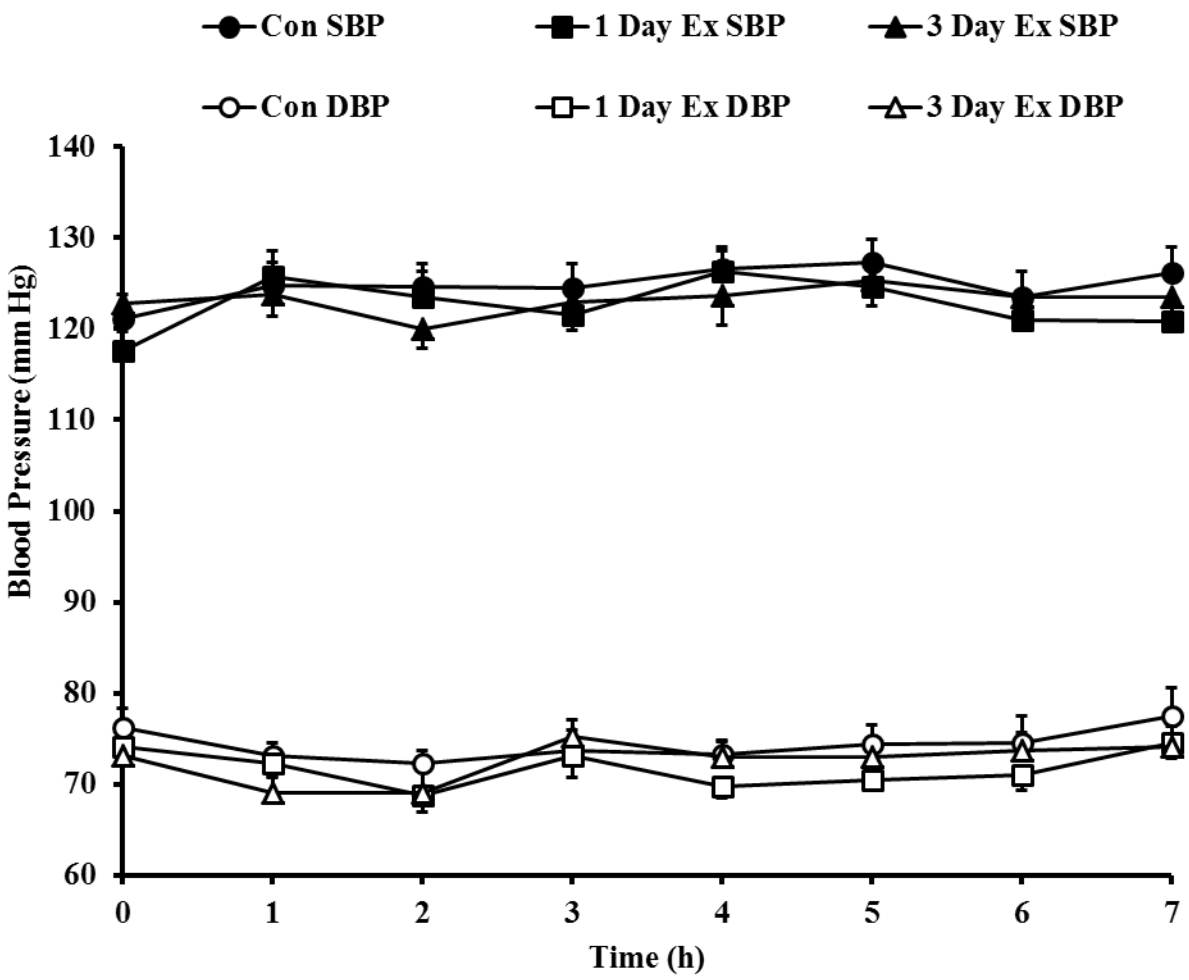

Figure 6.3: Resting systolic and diastolic blood pressure measured on day four of the exercise and control trials (n=11). Data are displayed as mean ± SEM.

6.3.6 Resting energy expenditure during main trials (day 4)

There were no differences in resting energy expenditure or substrate oxidation during day four of the 1-D Ex and 3-D Ex trials when compared with the control trial.

6.4 Discussion

The main finding in the present study is that neither a single bout of exercise nor three consecutive days of exercise influenced postprandial TAG in response to high fat meals when compared with the response on a control trial. These findings are in contrast to a study by Farah and colleagues (2010) who examined the effects of exercise on postprandial responses to ad libitum feeding in overweight/obese men and observed that TAG total AUC was 27% lower in 1-D Ex and 25% lower in 3-D Ex trials compared with a control. The present study also failed to identify differences in fasting plasma TAG and fat oxidation in either exercise trials in comparison with the control trial. These results are also in conflict with those of Farah and colleagues (2010). Fasting TAG were 17% lower in 1-D Ex and 15% lower in 3-D Ex trials, whereas, fat oxidation was 16% higher in 1-D Ex and 39% higher in 3-D Ex trials in comparison with the control trial (Farah et al, 2010).

These findings indicate that the duration of the aerobic exercise, 30 minutes of treadmill running at 70% $\dot{V}O_2$ max, may not have been effective considering the adiposity and lipid profile of the South Asian participants. South Asians are known to have a higher body fat percentage for a given body mass index (Wang et al, 1994) and for their predisposition to an adverse lipid profile (Tziomalos et al, 2008). In Farah and colleagues' (2010) study, the participants exercised at 50% of $\dot{V}O_2$ max for between 65 and 110 minutes expending 33.5 $kJ \cdot kg^{-1}$ body mass. Another study showed a significantly greater reduction in postprandial plasma TAG (23%) after a 2 hour exercise bout compared with a 1 hour exercise bout (9%) at 50% of $\dot{V}O_2$ max (Gill et al, 2002) indicating that the duration of exercise is an important factor determining the reduction in postprandial lipaemia. It was thought that a higher intensity of exercise may have compensated for the shorter exercise duration in the present study but this does not appear to be the case. Thus, perhaps the South Asians in the present study did not expend sufficient energy to elicit a reduced lipaemic response. In the present study average energy expenditure during the 30 minute exercise bouts was 1571 kJ in the 1 D Ex trial and 1632 kJ in the 3 D Ex trial. In previous studies examining the acute effects of exercise on postprandial lipaemia, the average gross energy expenditure found to attenuate the lipaemic response ranged from 1500 kJ to 7200 kJ (Petitt & Cureton, 2003). Confirming this, the study presented in the previous chapter

demonstrated a significant lowering of postprandial TAG after a 60 minute treadmill run in South Asians. The exercise energy expenditure of the South Asians in the study reported in the previous chapter was 3313 kJ which is over twice as high as the energy expenditure in the present study.

Many studies have demonstrated significantly lower postprandial TAG responses after an acute bout of exercise (Tsetsonis et al, 1996; Gill et al, 2001; 2003; 2004; Miyashita et al, 2006; Miyashita et al, 2008; Miyashita et al, 2008a; MacEneaney et al, 2009; Farah et al, 2010; Hurren et al, 2011). Similarly, Farah and colleagues' 3-D Ex trial elicited a significant lowering of postprandial plasma TAG. Thus, the disparate findings of the present study where there was no difference between the exercise trials and the control trial is perplexing. However, some previous studies have failed to show a lowering of postprandial lipaemia in response to exercise. For example, attenuation of postprandial lipaemia was not evident 60 hours after exercise in individuals with normal fasting plasma TAG (Herd et al, 2000) or even 24 hours after exercise in individuals with elevated fasting plasma TAG (Zhang et al, 2004). Muscle TAG and LPL activity have been shown to return to pre-exercise values within 42 hours after exercise. Thus, the TAG lowering effects of exercise on the first two days of the 3-D Ex trial may not have persisted until the main trial (day 4). Perhaps the energy expenditure threshold for lowering TAG was not reached. Ferguson and colleagues (1998) identified an exercise induced change in blood lipid and lipoprotein concentrations and demonstrated that the lowering in fasting TAG concentrations 24 h after an exercise bout was similar after exercise bouts expending between 3300 and 6300 kJ. Hence, an energy expenditure threshold may exist and it is even possible that different exercise thresholds exist for different populations. A final possibility is that a lack of monitoring/control for activities of daily living explains these finding i.e. participants may have expended more energy in activities of daily living in the control and 1-D Ex trials than they did in the 3-D Ex trial and this may explain the lack of overall difference in postprandial lipaemia (Hamilton et al, 2007; Latouche et al 2013).

Exercise intensity and duration also affects glucose uptake. In the post-absorptive state the volume of glucose uptake is affected by the exercise intensity. The higher the intensity, the higher the skeletal muscle glucose uptake (Romijin et al, 1993). Again, these factors may

have influenced postprandial glucose and perhaps the exercise intensity was insufficient to elicit reductions in postprandial glucose concentration.

It is reasonable to speculate that hyperinsulinaemia resulting from insulin insensitivity might have decreased LPL activity. Pollare and colleagues (1991) demonstrated that insulin itself or the increased glucose uptake in muscle cells during hyperinsulinaemia downregulates LPL activity. Regulation of muscle LPL activity is not insulin resistant and thus it is downregulated in a hyperinsulinaemic state (Pollare et al, 1991) and therefore the non-significant postprandial TAG response in the present study may be related to this factor. The accumulation of both hepatically derived TAG-rich VLDL and intestinally derived chylomicrons after a fat rich meal (Levy and Zoltowska, 1999) may be another possible reason for the non-significant findings reported here. Individuals with insulin resistance often demonstrate high TAG or amplified TAG (Zhang et al, 2006) and this is also described as the common underlying mechanism that causes the metabolic syndrome and the development of type 2 diabetes (Misra et al, 2008). Insulin resistance often precedes diabetes by several years and it is reported to be a risk factor for the development of CVD (Misra et al, 2008).

Whilst it is well established that exercise of a moderate intensity can reduce fasting and postprandial TAG concentrations (Katsanos 2006; Malkova and Gill, 2006; Miyashita et al, 2006; Hurren et al, 2011), studies have shown that this level of exercise did not lead to significant increases in either leg skeletal LPL activity (Herd et al. 2001) or absolute TAG uptake across the leg (Malkova et al. 2000) when these were measured 18 h after exercise. However, as body tissues other than leg skeletal muscle play a quantitatively important role in whole-body TAG uptake (Jensen 1995; Nguyen et al. 1996), it is possible that there was an insufficient increase in LPL activity in tissues other than the leg and hence there was no TAG attenuation after the running exercise in the present study.

As mentioned earlier some previous studies have also failed to demonstrate a significant reduction in postprandial TAG after exercise. An investigation involving a single bout of resistance exercise in European participants did not reveal any reduction in postprandial TAG in comparison with a no exercise control trial (Burns et al, 2005). Similarly, Zhang and colleagues (2007) also failed to identify a reduction in postprandial TAG after 30

minutes of treadmill running at 60% of $\dot{V}O_2$ peak in ten sedentary male participants with the metabolic syndrome. Interestingly, 45 minute and 60 minute duration treadmill runs in the same participants resulted in significant reductions in postprandial TAG (Zhang et al, 2007). Moreover, Zhang and colleagues (2007) also observed a significant lowering of fasting plasma insulin and a reduced plasma insulin response to a high fat meal (Zhang et al, 2007).

In addition, in view of the lack of change in postprandial lipaemia in response to 30 minutes of daily exercise in the present study, it is interesting to note that recent consensus guidelines on physical activity for Asian Indians (Misra et al, 2012) have recommended one hour of activity every day comprising 30 minutes of moderate-intensity aerobic activity, 15 minutes of work-related activity and 15 minutes of muscle-strengthening exercise. This would be an addition of 30 minutes to the general guidelines recommended by the American College of Sports Medicine and American Heart Association which recommend 30 minutes of moderate-intensity physical activity 5 days a week or 20 minutes of vigorous activity 3 days a week or a mixture of both (Haskell et al, 2007). The World Health Organisation (WHO) recommends 150 minutes of moderate-intensity aerobic physical activity throughout the week or at least 75 minutes of vigorous-intensity aerobic physical activity for adults (WHO, 2010). It may be presumed that the prescription for Asian Indians (Misra et al 2012) has arisen as a result of South Asians' strong CVD burden and the growing awareness of the pivotal role of physical activity/exercise in counteracting CVD. Though Misra and colleagues' (2012) guidelines send out a clear message in addressing CVD/CHD in South Asians, the recommendations may be a 'tall order' to follow for this ethnic group who are already struggling to meet the ACSM/AHA guidelines.

It is important to acknowledge that there were limitations to the present study. Firstly, the sample size was small and hence possibly underpowered to detect significant changes although some previous studies have detected exercise induced changes in TAG with similar sample sizes to that used in the present study. Secondly, a comparison with White European participants would have revealed whether the lack of an exercise effect was related specifically to ethnicity or was evident in Europeans also. Thirdly, a limitation of the study design was that total physical activity outside the lab was not quantified.

In conclusion, the findings of the present study are at odds with those of the only other study which has examined the relationship between a single bout of exercise and cumulative bouts of exercise on postprandial lipaemia. Further research is required to clarify whether this non-significant finding is due to the nature of the participants (i.e. South Asians) or to an insufficient exercise stimulus. It is important to clarify this because individuals with exaggerated postprandial TAG are more susceptible to CVD and this may apply to many South Asians. Hence, fully characterizing the optimal exercise mode, volume, intensity and duration for lowering postprandial lipaemia in South Asians is an important challenge for future research.

7 A comparison of fasting and postprandial cardiovascular disease risk markers in South Asian and White European men

7.1 Introduction

High coronary heart disease rates and mortality are common among South Asian groups of different geographical origin, religion and language (McKeigue et al 1989). In England and Wales, male and female migrants from the Indian sub-continent (India, Pakistan, Bangladesh, Nepal, Sri Lanka) have higher morbidity and mortality from cardiovascular disease (CVD) than the local population (McKeigue et al, 1991; Wild et al, 2007). Thus, the control measures, proven effective in other populations have clearly failed to address CVD related morbidity and mortality and its rise among South Asians in the UK and elsewhere (Mallika et al, 2007).

Increasing urbanization, industrialization and energy consumption in the form of concentrated calories and fat in developing countries have resulted in an increased prevalence of obesity, metabolic syndrome and diabetes which are contributing factors for CVD (Srikanthan et al, 2008). Hypercholesterolaemia is a known risk factor for CVD and the typical lipid profile in South Asians varies from that in other populations. High concentrations of triacylglycerol and low density lipoprotein cholesterol (LDL-C), together with low concentrations of high density lipoprotein cholesterol (HDL-C), increased visceral fat, hypertension, and insulin resistance are more prevalent among South Asians (McKeigue et al, 1989; McKeigue et al, 1993; Miller et al, 1989; Anand et al, 2000; Ahmad & Frossard, 2006; Tziomalos et al, 2008).

In addition to the actual concentrations of these lipids, particle size appears to be an important predictor of CVD risk. The LDL-C particle size in South Asians tends to be smaller. This small particle size increases the susceptibility of LDL-C to oxidation, thereby rendering these particles more atherogenic than the larger ones (Kulkarni et al, 1999). South Asians are also reported to have lower values of HDL-C and higher concentrations

of small particles that are less protective (Superko et al, 2005). This type of HDL-C has also been observed in South Asians who have normal HDL-C values (Bhalodkar et al, 2004).

Physical inactivity is another well-established risk factor for CVD (Wannamethee & Shaper, 2001; Rastogi et al, 2004; Mohan et al, 2005; Rao et al, 2012). Unfortunately, several studies have documented low physical activity levels in South Asians compared with other populations (Kamath et al, 1999; Fischbacher et al, 2004; Owen et al, 2009; Williams et al, 2011; Yates et al, 2010; Misra et al, 2012). There is substantial, consistent and strong evidence that physical activity is effective for lowering the risk of several forms of CVD (Fletcher et al, 1992; Haskell et al, 2007). Yet, few, if any, studies have addressed the acute effect of exercise in South Asians.

Hence, the purpose of this chapter is twofold: 1) this chapter seeks to clarify ethnic group differences in a variety of CVD risk markers by combining data from the first three experimental chapters in this thesis to provide a larger sample size; 2) this chapter seeks in the same way to clarify the acute effects of exercise on several fasting and postprandial CVD risk markers by again combining the data from the first three experimental chapters.

7.2 Methods

7.2.1 Participants and procedures

These analyses are based on the data presented in Chapters four, five and six which have been merged here into one dataset. The outcome variables examined in this chapter are as follows: fasting total cholesterol (TC), fasting HDL-C, fasting TC/HDL-C, fasting LDL-C, fasting TAG, fasting glucose, fasting IL-6, postprandial TAG, postprandial glucose and postprandial IL-6, resting systolic blood pressure (SBP) and resting diastolic blood pressure (DBP). For the fasting variables data was used from all three of the previous experimental chapters yielding a sample size of 30 South Asians and 24 Europeans. For postprandial TAG, glucose and IL-6 concentrations only data from Chapters 4 and 5 was used because the protocols employed involved nine hour postprandial observation periods whereas the protocol employed in Chapter 6 involved a seven hour postprandial observation period which was not directly comparable with the other data. Although all our participants from these studies were recruited from the University's student population based on convenience it was made sure that each participant included in this chapter was unique (i.e. if a participant completed more than one study they are only included once here).

7.2.2 Statistical analysis

Data were analysed using Predictive Analytics Software version 18.0 for Windows (SPSS, Inc., Somers, NY, USA). Physical characteristics were compared between South Asians and Europeans using independent samples Students *t*-tests. Two-way repeated measures ANOVA with Bonferroni post-hoc tests was used to examine differences between trials for fasting plasma constituents (total cholesterol, HDL-C, LDL-C, total cholesterol/HDL-C, TAG, glucose, IL-6) and resting blood pressure with the two factors being: a) trial (exercise versus control) and b) ethnic group (South Asian versus European). Area under the plasma concentration versus time curve (AUC) values were calculated for postprandial TAG, glucose and IL-6 using the trapezoidal method. These values were also compared using two-way repeated measures ANOVA with the two factors being trial (exercise versus control) and ethnic group (South Asian versus European). Effect sizes (Cohen's *d*) were calculated by dividing the difference between the mean values (exercise versus control or South Asian versus European) with the standard deviation (i.e. the average standard

deviation from both trials and ethnic groups combined). Statistical significance was accepted at the 5% level. Results are presented as mean ± SD in the text and tables and as mean ± SEM in figures.

7.3 Results

7.3.1 Participant characteristics

The physical characteristics of the participants are displayed in Table 7.1. There were no significant differences between South Asian and White European participants for age, weight, body mass index, waist circumference and resting diastolic blood pressure. Height and resting systolic blood pressure were lower while percentage body fat was higher in the South Asians than the White Europeans.

Table 7.1: Physical characteristics of South Asian and European participants.

Variables	**South Asians (n = 30)**	**Europeans (n = 24)**	***P* value**
Age (years)	23.0 ± 2.7	22.5 ± 1.5	0.392
Height (cm)	172.6 ± 7.6	178.9 ± 5.0	0.001
Weight (kg)	73.9 ± 10.4	76.0 ± 8.7	0.441
Body mass index ($kg \cdot m^{-2}$)	24.8 ± 3.1	23.7 ± 2.3	0.165
Body fat (%)	20.9 ± 5.6	14.1 ± 4.8	< 0.001
Waist circumference (cm)	80.3 ± 7.7	77.3 ± 5.0	0.107
Resting SBP (mm Hg)	128 ± 10	137 ± 12	0.003
Resting DBP (mm Hg)	75 ± 8	77 ± 6	0.468

Data are displayed as mean ± SD. *P* values for differences between South Asians and Europeans are based on independent samples *t* tests. SBP = systolic blood pressure; DBP = diastolic blood pressure.

7.3.2 Fasting plasma metabolite concentrations and resting blood pressure

Fasting concentrations of plasma metabolites and resting blood pressure are displayed in Table 7.2. There were significant main effects of trial for TAG, and glucose indicating lower values on the exercise trial. The effect sizes for each of these were small: TAG 0.3, and glucose 0.3. In addition, there were significant main effects of ethnic group for HDL-C, total cholesterol/HDL-C, IL-6 and SBP indicating lower values of HDL-C and SBP and higher values of total cholesterol/HDL-C and IL-6 in South Asian than White European participants. The effect sizes for these ethnic group comparisons were large for HDL-C (1.0), TC/HDL-C (0.8), IL-6 (0.5) and SBP (0.8). Finally, a significant trial by group effect was observed for DBP indicating a decrease in DBP in response to exercise in South Asians which did not occur in White Europeans.

Table 7.2: Fasting plasma metabolite concentrations and baseline blood pressure in South Asians and Europeans.

Variable	South Asians (n = 30)*		Europeans (n = 24)*		*P* for Trial	*P* for Group	*P* for T v G
	Control	Exercise	Control	Exercise			
TC ($mmol \cdot L^{-1}$)	3.8 ± 0.5	3.8 ± 0.6	3.8 ± 0.7	3.7 ± 0.6	0.334	0.653	0.342
HDL-C ($mmol \cdot L^{-1}$)	1.0 ± 0.2	1.0 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	0.889	< 0.001	0.424
TC / HDL-C ratio	4.0 ± 1.0	3.9 ± 0.9	3.2 ± 0.8	3.2 ± 0.9	0.420	0.002	0.426
LDL-C ($mmol \cdot L^{-1}$)	2.3 ± 0.6	2.4 ± 0.6	2.2 ± 0.7	2.2 ± 0.7	0.266	0.400	0.857
TAG ($mmol \cdot L^{-1}$)	1.3 ± 0.8	1.0 ± 0.5	1.0 ± 0.4	0.9 ± 0.3	0.004	0.170	0.161
Glucose ($mmol \cdot L^{-1}$)	5.3 ± 0.4	5.2 ± 0.5	5.2 ± 0.5	5.1 ± 0.4	0.008	0.362	0.348
IL-6 ($pg \cdot mL^{-1}$)	1.4 ± 1.1	1.7 ± 1.0	1.0 ± 1.3	0.8 ± 0.9	0.731	0.026	0.221
SBP (mm Hg)	126 ± 8	124 ± 7	133 ± 12	132 ± 10	0.229	0.022	0.330
DBP (mm Hg)	76 ± 6	74 ± 5	73 ± 5	73 ± 6	0.228	0.204	0.021

Data are displayed as mean ± SD. Comparisons were made using two-way ANOVA. T: trial (exercise versus control); G: group (South Asian versus European). ANOVA = analysis of variance; TC = total cholesterol; HDL-C = high density lipoprotein cholesterol; TAG = triacylglycerol; IL-6 = interleukin-6; SBP = systolic blood pressure; DBP = diastolic blood pressure.

* Note IL-6 values represent n = 18 South Asians and n = 20 White Europeans

* Note SBP and DBP values represent n = 22 South Asians and n = 14 White Europeans

7.3.3 Postprandial plasma metabolite concentrations

Postprandial concentrations of plasma metabolites are displayed in Table 7.3. There was a significant main effect of trial for AUC TAG indicating lower values on exercise trial. The effect size was small for AUC TAG 0.2. Additionally, there were significant main effects of ethnic group for AUC TAG and AUC IL-6 indicating higher values of AUC TAG and AUC IL-6 in South Asian than White European participants. The effect size for these ethnic group comparisons was large for AUC TAG (0.9), and small for AUC IL-6 (0.2).

Table 7.3: Area under the postprandial concentration versus time curve for South Asian and European men.

Variable	South Asians*		Europeans*		*P* for Trial	*P* for Group	*P* for T v G
	Control	Exercise	Control	Exercise			
AUC TAG (mmol·L^{-1} 9 h)	25.1 ± 11.6	22.2 ± 12.5	15.1 ± 4.2	13.8 ± 4.1	0.001	0.001	0.201
AUC Glucose (mmol·L^{-1} 9 h)	47.2 ± 6.3	47.1 ± 5.6	46.3 ± 5.1	46.9 ± 5.2	0.727	0.706	0.515
AUC IL-6 (pg·mL^{-1} 9 h)	18.9 ± 11.5	18.0 ± 9.3	12.5 ± 8.3	10.3 ± 6.0	0.277	0.008	0.670

Data are displayed as mean ± SD. Comparisons were made using two-way ANOVA. T: trial (exercise versus control); G: group (South Asian versus European). ANOVA = analysis of variance; TAG = triacylglycerol; AUC = area under curve; IL-6 = interleukin-6.

* Note AUC TAG and AUC glucose values represent n = 25 South Asians and n = 24 White Europeans

* Note AUC IL-6 values represent n = 18 South Asians and n = 20 White Europeans

7.3.4 Correlations

Table 7.4 displays some of the more notable correlations identified in this study. Total cholesterol was positively correlated to TC/HDL-C, TAG and SBP in both ethnic groups. Of these, the correlation between TC and TC/HDL-C was very high in the White European participants. HDL-C was negatively correlated with TC/HDL-C, TAG and percentage body fat (this latter correlation only applying in South Asians). A high negative correlation was seen between HDL-C and TC/HDL-C in both groups. In both South Asians and White Europeans a positive correlation was observed between TC/HDL-C and TAG. However, TC/HDL-C was positively correlated with percentage body fat and DBP only in the South Asians. A positive correlation between TAG and waist circumference and between TAG and percentage body fat was also seen in the South Asians only. Body composition variables (weight, BMI, waist circumference and percentage body fat) were highly correlated with each other in both ethnic groups. Systolic and DBP were correlated only in South Asians.

Table 7.4: Correlation coefficients describing the relationship between plasma metabolites, blood pressure and anthropometric measurements

Variables		South Asians (n = 30)		White Europeans (n = 24)	
		r value	P value	r value	P value
TC	TC/HDL-C	0.518	0.003	0.827	< 0.001
	TAG	0.391	0.032	0.450	0.027
	SBP	0.371	0.044	0.441	0.031
HDL-C	TC/HDL-C	- 0.720	< 0.001	- 0.744	< 0.001
	TAG	- 0.449	0.013	- 0.476	0.019
	Percentage body fat	- 0.396	0.030	- 0.038	0.859
TC/HDL-C	TAG	0.680	< 0.001	0.560	0.004
	Percentage body fat	0.365	0.047	0.219	0.305
	DBP	0.460	0.010	0.134	0.534
TAG	Waist Circumference	0.439	0.015	0.121	0.574
	Percentage body fat	0.462	0.010	0.252	0.235
Weight	BMI	0.787	< 0.001	0.868	< 0.001
	Waist Circumference	0.897	< 0.001	0.823	< 0.001
	Percentage body fat	0.618	< 0.001	0.622	0.001
BMI	Waist Circumference	0.878	< 0.001	0.867	< 0.001
	Percentage body fat	0.807	< 0.001	0.683	< 0.001
Waist circumference	Percentage body fat	0.801	< 0.001	0.789	< 0.001
SBP	DBP	0.444	0.014	0.064	0.767

TC = total cholesterol; HDL-C = high density lipoprotein cholesterol; TAG = triacylglycerol; SBP = systolic blood pressure; DBP = diastolic blood pressure.

NB: Correlations were computed using mean values for each variable i.e. exercise trial value plus control trial value divided by 2.

7.4 Discussion

This cross-sectional study identified the following: a) exercise appears to be effective in lowering fasting TAG and glucose and postprandial TAG; b) HDL-C concentrations and resting SBP were significantly lower in the South Asian than the White European participants; c) total cholesterol/HDL-C, postprandial TAG and fasting and postprandial IL-6 concentrations were significantly higher in South Asian than White European participants; and d) exercise appeared to result in a small lowering of resting diastolic blood pressure in South Asian participants but not in White European participants.

Importantly, this study revealed the effectiveness of exercise in lowering postprandial TAG in South Asian and White European participants. Many studies have reported that a single bout of exercise lowers postprandial TAG concentrations (Katsanos, 2006; Miyashita et al, 2006; Miyashita et al, 2008; McEneaney et al, 2009; Hurren et al, 2011) and the present study confirms these findings. Exercise was slightly more effective in South Asian participants eliciting a 12% reduction in TAG AUC values compared with a 9% reduction in White European participants. Despite the effectiveness of exercise in the South Asian participants it is important to note that their TAG AUC values were still nearly 50% higher after exercise than the control trial values shown by the White European participants. In addition, exercise also reduced fasting TAG concentrations by 23% in South Asians and 10% in White Europeans. Fasting glucose concentrations were reduced by 2% in both ethnic groups. Blood glucose concentrations even at the higher end of the normal range are associated with an increased risk of CVD in South Asians (Pais et al, 1996). Higher fasting TAG and glucose in South Asians have been documented in several studies (Anand et al, 2000; Tziomalos et al, 2008) and the findings of the present study confirm this.

South Asians have a higher susceptibility to CVD morbidity and mortality (McKeigue et al, 1991; Wild et al, 2007) and this susceptibility may be exacerbated by their low physical activity levels (Fischbacher et al, 2004, Williams et al, 2011, Yates et al, 2010). The findings of the present study suggest that regular exercise may serve to partially offset the elevated postprandial TAG experienced by South Asians. Observational evidence also suggests a cardio-protective role of physical activity for CHD and CHD risk markers in South Asians (Rastogi et al, 2004; Mohan et al, 2005; Rao et al, 2012). In Western

populations, regular moderate intensity exercise is associated with a 30% to 50% reduction in the risk of CHD, obesity, diabetes and stroke (Wannamethee et al, 2000; Batty, 2002). Further research is required to establish the effectiveness of exercise for lowering the risk of these conditions in South Asians.

Another key finding in the present study is the significant ethnic group difference in postprandial TAG. Mean postprandial TAG concentrations (the average value across the two trials) were 64% higher in South Asian than White European participants. This is concerning for South Asians and reiterates their vulnerability to CVD. South Asians exhibited lower fasting HDL-C concentrations and resting systolic blood pressure than the White European participants. Baseline HDL-C is a significant predictor of subsequent CHD events (Gotto et al, 2000) and recent epidemiological studies have confirmed the inverse relationship between HDL-C and CHD risk (Barter, 2011).

Total cholesterol/HDL-C ratio values and fasting and postprandial IL-6 concentrations were elevated in the South Asians. Fasting IL-6 concentrations were 55% higher and postprandial IL-6 concentrations were 72% higher in the South Asians than the White Europeans. These differences observed between ethnic groups in the present study confirm the findings of previous studies (Anand et al, 2000; Peters et al, 2013; Tziomalos et al, 2008) indicating that South Asians have a tendency for higher fasting TAG and IL-6 concentrations, higher fasting total cholesterol to HDL-C ratio values, and lower fasting HDL-C concentrations than other ethnic groups. Thus, these findings confirm and extend previous research demonstrating adverse CVD risk factor profiles in South Asians (Joshi et al, 2007).

In conclusion, the findings of the present study confirm previous reports that South Asian ethnicity is related to an adverse CVD risk factor profile. Moreover, the present findings demonstrate that an acute bout of exercise is effective for modifying several CVD risk markers in South Asians – at least transiently. Further research is required to examine the effects of exercise training on CVD risk markers in South Asians. Further research is also required to determine if these findings hold true in female South Asians.

8 General discussion

This chapter aims to integrate and reflect on the major findings of the investigations in this thesis. Previous research suggests that acute exercise attenuates postprandial lipaemia in mostly European participants. The main aim of this thesis was to examine the effect of acute bouts of exercise on postprandial lipaemia and several other cardiovascular disease (CVD) risk markers in South Asian participants and to compare their responses with those of White European participants. There is growing body of evidence suggesting that South Asians are predisposed to CVD. In the recent past, studies have been 'unearthing' the high susceptibility of South Asians to CVD related morbidity and mortality (Gupta et al, 2006; Tziomalos et al, 2008; Rao et al, 2012).

The first experimental chapter of this thesis (the walking study) revealed that South Asians exhibit elevated postprandial plasma triacylglycerol (TAG) concentrations to a much greater extent than White Europeans after consuming high fat meals. Brisk walking for 60 minutes at 48% to 52% of $\dot{V}O_2$ max exhibited a borderline effect, eliciting a small lowering of postprandial plasma TAG concentrations in both South Asians and White Europeans. Postprandial plasma glucose and plasma interleukin-6 (IL-6) concentrations were higher in South Asians than in White Europeans.

In the second experimental chapter, a one hour run, elicited a significant lowering of postprandial TAG in South Asians and White Europeans with the reduction being greater in the South Asians than the Europeans. The exercise was prescribed at 70% of $\dot{V}O_2$ max in this study. As the exercise was prescribed according to individual ability and fitness, the least fit participants performed less exercise in absolute terms than their fitter counterparts but, importantly, most of these participants experienced substantial reductions in plasma TAG concentrations. Consistent with the findings of the walking study, the running study also demonstrated a greater elevation in postprandial plasma TAG concentration in response to high fat meals in the South Asian men compared with the White European men.

The South Asian men also had higher postprandial plasma insulin concentrations than the White European men in the running study. No ethnic group differences were apparent for IL-6 and soluble intercellular adhesion molecule-1 (sICAM-1) but postprandial plasma IL-6 concentrations were lower after exercise while postprandial sICAM-1 concentrations were higher. The lower IL-6 concentrations observed the day after exercise in the running study are possibly reflective of an anti-inflammatory effect of exercise subsequent to an initial increase in IL-6. The elevated sICAM-1 concentrations are probably related to an increased blood shear stress during exercise and it is clear that this elevation lasts for at least 24 h although the significance of this elevation is uncertain.

In the third experimental chapter, a thirty minute run at 70 % of $\dot{V}O_2$ max performed on one day and three consecutive days did not influence postprandial TAG in response to high fat meals in either of the trials. Additionally, fasting TAG and fat oxidation were not influenced by exercise in this study. A limitation of this study is that there was no European participant group with which to compare responses. The findings of the third study are in contrast to the findings of the study by Farah and colleagues' (2010) which has employed a similar protocol in overweight/obese Europeans.

In combining the first three studies, Chapter 7 gained a greater sample size and this helped to clarify the effects of an acute exercise. This data identified that fasting TAG and glucose concentrations are significantly reduced by an acute bout of exercise in South Asians and additionally that postprandial TAG concentrations are significantly reduced by exercise. This data also revealed significant main effects of ethnic group confirming that South Asians have lower fasting high density lipoprotein cholesterol (HDL-C) and resting systolic blood pressure and higher fasting total cholesterol/HDL-C and IL-6 concentrations than Europeans. Additionally, the significant main effects of ethnic group also showed South Asians to have higher postprandial TAG and IL-6 concentrations.

In general, all experimental chapters except Chapter 6 (where there was no comparison group) revealed that South Asians have markedly higher postprandial TAG than White European participants. This confirms the findings of many studies which have shown South Asians to have high fasting TAG concentrations in comparison with other populations (Anand et al, 2000; Tziomalos et al, 2008). Importantly, exaggerated postprandial TAG, a

strong predictor for CVD morbidity and mortality (Bansal et al, 2007; Nordestgaard et al, 2007) may play a causative role in the premature atherosclerosis observed in South Asians (Gupta and Brister, 2006). It is possible that genetically susceptible individuals develop abdominal obesity and insulin resistance when exposed to an unfavourable environment of reduced energy expenditure and increased caloric consumption. This trend is increasingly observed in parallel with urbanisation, suggesting that the increased risk in South Asians may be preventable through lifestyle interventions to attain optimal levels of blood pressure, lipids and glucose (Gupta and Brister, 2006).

South Asians have a higher risk of developing CVD at a younger age in comparison with other ethnic groups (Ramaraj and Chellappa, 2008). This somewhat relates to the South Asian participants assessed in this thesis who were all relatively young and displayed higher values for postprandial TAG than White Europeans. It is also important to acknowledge that TAG-rich particles are produced mainly postprandially (Castro et al, 2001).

The data from Chapters 5 and 7 have shown that acute exercise has a beneficial effect on postprandial lipaemia in both South Asian and White European participants. This adds to the body of evidence which suggests that exercise, both walking and running, can attenuate postprandial lipaemia (Gill et al, 2004; Miyashita et al, 2006, Miyashita et al, 2008). This is particularly relevant in South Asians who are at an increased risk of CVD. These metabolic improvements are likely to contribute to the reduced CHD risk often observed in physically active individuals but additional longitudinal research will be required to confirm this. Despite the effectiveness of exercise in the South Asian participants it is important to note that their postprandial TAG concentrations were still markedly higher after exercise than the control trial values shown by the White European participants. Therefore, South Asians are at a much higher risk of experiencing exaggerated postprandial lipaemia in response to high fat meals than Europeans and this may be a contributing factor to their elevated risk of CHD.

Even though moderate intensity exercise did not significantly attenuate postprandial TAG in the South Asian and White European participants in Chapter 4, (60 minute brisk walk) and in South Asians in Chapter 6 (30 minutes run on one day or on three consecutive days),

it cannot be used as a yardstick to generalise that exercise would not attenuate postprandial TAG. In contrast, the 60 minute running study (Chapter 5) clearly demonstrated a significant effect of exercise, especially in the South Asian participants. Possibly, the exercise duration and intensity may have been optimal in this study. Moreover, fasting hypertriglyceridaemia could have a number of underlying causes and moderate intensity exercise might have a substantial impact on fasting and postprandial plasma TAG concentrations in some individuals and a minimal effect in others.

The reason for the insignificant results displayed in Chapter 4 (60 minutes brisk walking) and Chapter 6 (30 minutes run on one day or on three consecutive days) may also be related to intramuscular TAG (IMTG) concentrations. South Asians have been reported to have 30% higher IMTG concentrations than BMI matched Europeans (Forouhi et al, 1999). Thus, the elevated IMTG in South Asians is suggestive of a deficiency in skeletal muscle lipid metabolism. Accumulating evidence indicates that deficits in skeletal muscle oxidative capacity and low rates of skeletal muscle lipid oxidation are likely to contribute to skeletal muscle lipid accumulation and consequent insulin resistance (Kelley and Goodpaster, 2001; Bruce and Hawley, 2004; Kelley et al, 1999), even though the underlying mechanisms are unknown.

Furthermore, available evidence indicates that South Asians have lower $\dot{V}O_2$ max values, an index of oxidative capacity at the whole-body level, than matched European counterparts (Davey et al, 2000; Hardy and Eston, 1985) and $\dot{V}O_2$ max is a strong independent predictor of whole body insulin sensitivity (Bruce et al, 2003, Nyholm et al, 2004). While it is known that cardiorespiratory fitness is closely associated with skeletal muscle lipid oxidative capacity (Sahlin et al, 2007; Venables et al, 2005; Helge et al, 2006), it is not known whether capacity for lipid oxidation is reduced in South Asians compared with Europeans or whether these factors contribute to increased insulin resistance in South Asians.

Taking all of the experimental studies together, exercise attenuated postprandial lipaemia in 21 out of 30 South Asian and 18 out of 24 White European participants. This suggests that exercise could be an instrument for the improvement of TAG metabolism. Numerous

studies have demonstrated the effect of exercise on postprandial lipaemia in White Europeans (Gill et al, 2002; Miyashita et al, 2008; Hurren et al, 2011). The experimental studies in this thesis are a first step in addressing the acute effects of exercise in South Asians.

It is important to note that approximately one third of participants examined in this thesis showed a non-beneficial response to exercise i.e. their postprandial TAG was not lowered or was even increased. A recent study by Bouchard and colleagues (2012) showed that some people get worse with exercise compared to others (adverse responders versus non-adverse responders). The insulin, TAG, SBP values in their study were higher after exercise while the HDL-C values were lower (Bouchard et al, 2012). The prevalence of adverse responders appeared to be similar at low and high doses of exercise. However, the researchers did not know whether some adverse responders would revert to a more positive response pattern if exposed to different exercise doses or exercise modalities. They did not find any evidence for differences in the prevalence of adverse responders between Blacks and Whites or between men and women. Moreover, the adverse responder traits are not explained by prior health status of subjects, age, amount of exercise imposed by the program, or lack of improvement in cardiorespiratory fitness. Thus, some individuals experience adverse responses when exposed to regular exercise, but the causes of the phenomenon are unknown at this time (Bouchard et al, 2012).

In addition to postprandial TAG, the experimental studies described in this thesis also suggest that South Asians have lower HDL-C, higher fasting TAG, and a higher ratio of total cholesterol/HDL-C than White Europeans which are indicative of an adverse lipid profile. This is consistent with previous studies (Anand et al, 2000; Enas et al, 2005; Gupta et al, 2006; Tziomalos et al, 2008). Concentrations of HDL-C are inversely related to CHD incidence consistent with its role in reverse cholesterol transport (Fielding and Fielding, 1995). As a result of low HDL-C, South Asians have a higher ratio of total cholesterol/HDL-C. Having a low HDL-C is also an indicator of insulin resistance and is associated with high fasting TAG values (Tziomalos et al, 2008).

In addition, South Asians exhibited marked elevations in insulin concentrations in the fasting and postprandial state in comparison with White Europeans (Chapter five) which is

consistent with the findings of Cruz and colleagues (2001). Insulin resistance is thought to be a major contributor to the increased risk of type 2 diabetes and CHD experienced by those of South Asian descent (Sandeep et al, 2011; Tziomalos et al, 2008). Insulin has significant functional effects on the vasculature, including dilation of large and small vessels and recruitment of skeletal muscle capillaries to increase nutritive flow (Clark et al, 2003). Recent data indicate that loss of endothelial-specific insulin signalling reduces whole body and skeletal muscle insulin stimulated glucose uptake (Kubota et al, 2011), illustrating the broader importance of insulin's endothelial effects. Furthermore, the vasodilatory effects of insulin are attenuated in subjects with impaired endothelial function and type 2 diabetes, in that insulin-stimulated nutritive flow to skeletal muscle is largely reduced in the insulin resistant state (Laakso et al, 1990; Clark et al, 2008). Thus, endothelial cells can effectively become desensitized to insulin, and this endothelial insulin resistance occurs in close association with the development of insulin resistance in downstream tissues (e.g. skeletal muscle). Exercise is believed to help maintain appropriate glucose and insulin metabolism (Holloszy et al, 2005; Kelly et al, 2012; Rogers et al, 1988).

Chronically, elevated levels of IL-6 perturb endothelial function, haemostatic and lipid pathways, and may also promote insulin resistance (Yudkin et al, 1999). In the experimental chapters IL-6 was examined with varying outcomes. In chapters 4, 5 and 7 there was no effect of exercise on fasting IL-6 concentrations. Comparing ethnic group values in the walking study (Chapter 4) revealed a tendency for fasting IL-6 concentrations to be elevated in South Asians compared with the Europeans. This was not supported by the findings of the running study (Chapter 5) but was confirmed in the combined cross-sectional data examined in Chapter 7. Moreover, for postprandial IL-6 concentrations there were significant ethnic group differences in Chapters 4 and 7, supporting that South Asians have elevated IL-6 concentrations although again this was not observed in the running study (Chapter 5). Chapter 5 did reveal a significant exercise induced lowering of IL-6 but this was not observed in Chapters 4 and 7. Thus, these IL-6 findings are somewhat ambiguous and require further study with a larger sample of South Asian and European participants. If the elevated IL-6 concentrations in South Asians are confirmed this suggests another mechanism by which they are at increased risk of CVD.

A limitation of the study design in the third study (Chapter 6) is that total physical activity outside the lab was not quantified. Breaking up postprandial sedentary time with short activity bouts (2 minutes of activity time for every 20 minutes of sitting) is associated with changes in the expression of skeletal muscle genes involved in cellular development, growth and proliferation and lipid and carbohydrate metabolism (Latouche et al, 2013). Activities of daily living also have the potential to alter LPL activity hence altering postprandial lipaemia (Hamilton et al 2007). Thus lack of adequate control for activities of daily living in the 1-D Ex versus 3-D Ex study may explain the lack of significance in postprandial TAG values.

Lastly, according to McKeigue and colleagues (1989) and Eapen and colleagues (2009), South Asians are a heterogeneous population. In this respect, most of our participants were Indians and there was not equal representation of Pakistanis, Bangladeshis, Sri Lankans and Nepalese. Hence the extent to which these findings are applicable to all South Asians is uncertain. In addition, the participants included in this thesis are a young and healthy population which is not representative of the general South Asian population.

Importantly, the present findings demonstrate that acute bouts of exercise are effective for modifying several CVD risk factors in South Asians – at least transiently. Further research is required to examine a variety of issues related to the potential of exercise to lower CVD risk in South Asians. Below are a few suggestions for research questions which require attention in the immediate future.

- To what extent are the differences in postprandial lipaemia between South Asians and White Europeans generalizable i.e. can the findings reported in this thesis be confirmed with larger sample sizes?
- Do South Asian females exhibit elevated postprandial lipaemia in response to high fat meals in the same way as South Asian males?
- Does an acute bout of exercise lower postprandial lipaemia in South Asian females?
- What is the optimal intensity and duration of exercise for lowering postprandial lipaemia in South Asian men and women?
- What is the postprandial lipaemia response to high fat meals in older South Asian men and women?

- Is exercise effective for lowering postprandial lipaemia in older South Asian men and women?
- What effect does resistance exercise have on postprandial lipaemia in South Asian men and women?
- Do South Asian children and adolescents have elevated postprandial lipaemia in response to high fat meals?
- Is exercise effective for lowering postprandial lipaemia in South Asian children and adolescents?
- How effective is exercise training for lowering postprandial lipaemia in South Asian men and women?
- How does acute and chronic exercise influence lipoprotein lipase activity in South Asians?
- Will exercise induced reductions in postprandial lipaemia lead to a reduction in the risk of CVD/CHD in South Asians?
- How effective will combined diet and exercise intervention be for reducing postprandial lipaemia in South Asians?
- What mechanisms are responsible for the exaggerated postprandial lipaemia in South Asians?
- What exercise intervention strategies are effective for encouraging South Asians to be more active?

Although CVD is a fatal disease, it is predictable, preventable and treatable and exercise/physical activity is one factor which may help in this regard. Using the findings of this thesis as baseline knowledge of acute exercise and its effect on CVD risk markers in South Asians, it is important that work now continues to enhance knowledge and understanding of the role of exercise in modifying CVD risk factors in South Asians. Moreover, it is equally if not more important that this work is publicised among the South Asian community and that physical activity promotion and intervention schemes are widely implemented in South Asians.

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10 Appendices

10.1 Appendix A: Participant information

School of Sport, Exercise and Health Sciences

The effect of prior walking on postprandial lipaemia and resting blood pressure in South Asian versus European European men

Investigators

Mr Saravana Pillai Arjunan, Miss Alice Rogan Miss Pattida Achakulwisut, Miss Andrea Smith, Mr Aled Hills,and Dr David Stensel: School of Sport, Exercise and Health Sciences, Loughborough University.

Background

South Asian men living in the UK have a higher than average risk of cardiovascular disease (CVD). The reasons for this are uncertain. Physical inactivity is known to increase the risk of CVD and it is possible that the prevalence of physical inactivity is higher in South Asian men than in men of European descent. Alternatively, physical activity may be less effective in preventing CVD in South Asian men than in other men. The proposed study will compare the effects of a single bout of exercise on CVD risk markers (blood lipids, markers of inflammation) in South Asian men and white men.

Inclusion Criteria

Volunteers will:

(i) be male
(ii) aged 18-40 y
(iii) have no personal history of cardiovascular disease, metabolic disease or dyslipidaemia,
(iv) not be dieting or have any extreme dietary habits
(v) not be taking drugs known to affect digestion or metabolism – medical or illegal (for example anabolic steroids, marijuana, amphetamines, thyroid prescription drugs).

Study Demands

If you volunteer to participate in this study you will be required to attend the Exercise and Health laboratory (HE111) in the Clyde Williams building for a screening/familiarisation visit lasting approximately two hours and then you will perform two main trials in the laboratory at least one week apart. Each main trial will be conducted over two-days and you will be in the laboratory from 8.00 am to 5.00 pm on each of these days. You will be required to weigh and record all food and drink consumed in the 24 h prior to each main trial and to abstain from alcohol, caffeine and structured physical activity during this time.

Preliminary Procedures

During the screening/familiarisation visit we will:

- Explain the objectives of the study and its requirements
- Ask you to complete a confidential questionnaire regarding your health
- Familiarise you with the testing procedures and equipment
- Familiarise you with dietary recording
- Answer any questions you may have

After this we will collect the physiological/anthropometric measurements listed below:

- Resting blood pressure
- Height
- Weight
- Skinfold thickness at four sites (to estimate body fat percentage)
- Waist and hip circumferences

You will then complete a submaximal walking test on a treadmill and (once you have recovered from this test) a maximum oxygen uptake test.

Main Trials

There will be two main trials each conducted over two days (8.00 am to 5.00 pm on each day). These will be assigned in a random order and separated by at least one week.

<u>Exercise trial</u>

On day one of the exercise trial you will report to the laboratory at 8.00 am after a 10 h overnight fast. You will rest in the laboratory (reading, working at a computer, watching television, listening to music etc) throughout day 1 until 5.00 pm. We will provide you with lunch on day 1. At 3.30 pm you will perform a 60 minute walk at 70% of your walking maximum oxygen uptake. At 5.00 pm on day 1 you will leave the laboratory. You will consume a standardised meal at home in the evening, fast overnight for 10 h and return to the laboratory on day 2.

On day 2 of the exercise trial you will report to the laboratory just before 8.00 am. A cannula will be inserted into a vein in your arm when you arrive at the laboratory. You will rest in the laboratory (reading, working at a computer, watching television, listening to music etc) throughout day 2 until 5.00 pm. You will be fed standardised meals for breakfast (8.00 am) and lunch (12.00 pm). Fourteen, 9 mL venous blood samples will be collected from you via the cannula at the following times: 08.00, 08.15, 08.30, 09.00, 10.00, 11.00, 12.00, 12.15, 12.30, 13.00, 14.00, 15.00, 16.00 and 17.00. In total 126 mL of blood will be collected on day 2 and this equates to just over one-quarter of a standard blood donation.

Control trial

The control trial will be identical to the exercise trial with the exception of the 60 minute walk on day 1. On the control trial you will perform no exercise on day 1 and remain resting in the laboratory. Other than this the trials are identical.

Preparation for the tests

Recording your diet

You will be asked to weigh and record everything you eat and drink for 24 hours prior to the first main trial. You will then consume identical amounts of the same food and drink prior to your second main trial. Alcohol and caffeine must not be consumed on the days when you are recording your diet. These points are very important in order to prevent extraneous variables influencing the study findings and we will discuss this with you in depth prior to the main trials.

Controlling physical activity

No strenuous physical activity should be performed during the day preceding main trials.

Overnight fast

You will finish eating by 10:00 pm on the evenings before main trials. You may however continue to drink water after this time. You will report to the laboratory at 8:00 am the next morning without having eaten breakfast. We will provide you with breakfast and lunch on both day one and day two of each main trial.

Travelling to the laboratory

If you live within one mile of the laboratory you should walk in slowly on the morning of each main trial. Please do not run or cycle. If you live more than one mile from the laboratory then you should drive in. If you do not have access to a car please tell us and we will arrange for you to be collected.

How much time will it take?

- Screening visit: approximately 2 hours**.**
- Two main trials each conducted over two days: nine hours per day, 18 hours per trial, 36 hours in total.

You will be encouraged to bring work and reading material with you for the main trials. Alternatively you may watch television/movies, listen to music or work at a computer (internet enabled).

Possible risks and discomforts

High intensity exercise will cause breathlessness. In a tiny minority of individuals, even in young adults, the possibility exists that such exercise triggers disturbances to normal physiology: these include abnormal blood pressure, fainting or a change in the normal rhythm of the heart. There is also a risk of musculoskeletal injury but this is minimal and measures will be taken to prevent any occurrences.

Venous cannulation can cause air or plastic embolism (occlusion of a blood vessel) but good practice minimises this risk and the personnel conducting the procedure have been trained and are highly experienced. Cannulation can also lead to local thrombophlebitis (inflammation) in a superficial vein but the absolute level of risk is low.

Benefits of the study

The study should lead to greater understanding about the effects of exercise on the cardiovascular disease risk markers in relation to males of South Asian descent and white European males. In so doing it will contribute to an expanding body of evidence concerning the role of exercise in the prevention of cardiovascular disease.

We will give you feedback on your own results and we will be happy to discuss this with you.

Confidentiality

Although information will be stored on computer, each participant will be entered as a number rather than by name, in accordance with the Data Protection Act. The information linking participant names to their number will be kept for no longer than five years. Data will be used for research purposes only and confidentiality will be maintained in any publications arising from the study. Participant data will not be kept longer than is necessary for the purposes of this investigation. Blood plasma samples collected during this investigation will be kept for no longer than three years. Samples will be disposed of via bio-hazard waste collection bags.

Right to withdraw

If you volunteer to participate in this study you hold the right to withdraw at any stage without having to inform the investigators of your reasons for doing so.

Contacts

Please feel free to ask any questions, at any stage. Contact information for the staff involved in this study is as follows:

Mr Saravana Pillai Arjunan
S.P.Arjunan@lboro.ac.uk
Telephone 01509 226351

Dr David Stensel
D.J.Stensel@lboro.ac.uk
Telephone: 01509 226344

School of Sport, Exercise and Health Sciences

The influence of a one hour treadmill run on coronary heart disease risk markers in South Asian and European men

Investigators

Mr Saravana Pillai Arjunan, Mr James King, Miss Lucy Wasse, Miss Taru Irene Saarinen, Miss Victoria Rose Paley and Dr David Stensel: School of Sport, Exercise and Health Sciences, Loughborough University.

Background

South Asian men living in the UK have a higher than average risk of cardiovascular disease (CVD). The reasons for this are uncertain. Physical inactivity is known to increase the risk of CVD and it is possible that the prevalence of physical inactivity is higher in South Asian men than in men of European descent. Alternatively, physical activity may be less effective in preventing CVD in South Asian men than in other men. The proposed study will compare the effects of a single bout of exercise on CVD risk markers (blood lipids, markers of inflammation) in South Asian men and white men.

Inclusion Criteria

Volunteers will:

(vi) be male
(vii) aged 18-40 y
(viii) have no personal history of cardiovascular disease, metabolic disease or dyslipidaemia,
(ix) not be dieting or have any extreme dietary habits
(x) not be taking drugs known to affect digestion or metabolism – medical or illegal (for example anabolic steroids, marijuana, amphetamines, thyroid prescription drugs).

Study Demands

If you volunteer to participate in this study you will be required to attend the Exercise and Health laboratory (HE111) in the Clyde Williams building for a screening/familiarisation

visit lasting approximately two hours and then you will perform two main trials in the laboratory at least one week apart. Each main trial will be conducted over two-days and you will be in the laboratory from 8.00 am to 5.00 pm on each of these days. You will be required to weigh and record all food and drink consumed in the 24 h prior to each main trial and to abstain from alcohol, caffeine and structured physical activity during this time.

Preliminary Procedures

During the screening/familiarisation visit we will:

- Explain the objectives of the study and its requirements
- Ask you to complete a confidential questionnaire regarding your health
- Familiarise you with the testing procedures and equipment
- Familiarise you with dietary recording
- Answer any questions you may have

After this we will collect the physiological/anthropometric measurements listed below:

- Resting blood pressure
- Height
- Weight
- Skinfold thickness at four sites (to estimate body fat percentage)
- Waist and hip circumferences

You will then complete a 16 minute submaximal running test on a treadmill and (once you have recovered from this test) a maximum oxygen uptake test.

Main Trials

There will be two main trials each conducted over two days (8.00 am to 5.00 pm on each day). These will be assigned in a random order and separated by at least one week.

Exercise trial

On day one of the exercise trial you will report to the laboratory at 8.00 am after a 10 h overnight fast. You will rest in the laboratory (reading, working at a computer, watching television, listening to music etc) throughout day 1 until 5.00 pm. We will provide you with breakfast and lunch on day 1. At 3.30 pm you will perform a 60 minute run at 70% your maximum oxygen uptake. At 5.00 pm on day 1 you will leave the laboratory. You will consume a standardised meal at home in the evening, fast overnight for 10 h and return to the laboratory on day 2.

On day 2 of the exercise trial you will report to the laboratory just before 8.00 am. A cannula will be inserted into a forearm or antecubital vein when you arrive at the laboratory. You will rest in the laboratory (reading, working at a computer, watching television, listening to music etc) throughout day 2 until 5.00 pm. You will be fed standardised meals

for breakfast (8.00 am) and lunch (12.00 pm). Fourteen, 9 mL venous blood samples will be collected from you via the cannula at the following times: 08.00, 08.15, 08.30, 09.00, 10.00, 11.00, 12.00, 12.15, 12.30, 13.00, 14.00, 15.00, 16.00 and 17.00. (126 mL of blood collected in total on day 2).

Control trial

The control trial will be identical to the exercise trial with the exception of the 60 minute run on day 1. On the control trial you will perform no exercise on day 1 and remain resting in the laboratory. Other than this the trials are identical.

Preparation for the tests

Recording your diet

You will be asked to weigh and record everything you eat and drink for 24 hours prior to the first main trial. You will then consume identical amounts of the same food and drink prior to your second main trial. Alcohol and caffeine must not be consumed on the days when you are recording your diet. These points are very important in order to prevent extraneous variables influencing the study findings and we will discuss this with you in depth prior to the main trials.

Controlling physical activity

No strenuous physical activity should be performed during the day preceding main trials.

Overnight fast

You will finish eating by 10:00 pm on the evenings before main trials. You may however continue to drink water after this time. You will report to the laboratory at 8:00 am the next morning without having eaten breakfast. We will provide you with breakfast and lunch on both day one and day two of each main trial.

Travelling to the laboratory

If you live within 400 metres of the laboratory you should walk in slowly on the morning of each main trial. Please do not run or cycle. If you live more than 400 metres from the laboratory then you should drive in. If you do not have access to a car please tell us and we will arrange for you to be collected.

How much time will it take?

- Screening visit: approximately 2 hours**.**
- Two main trials each conducted over two days: nine hours per day, 18 hours per trial, 36 hours in total.

You will be encouraged to bring work and reading material with you for the main trials. Alternatively you may watch television/movies, listen to music or work at a computer (internet enabled).

Possible risks and discomforts

High intensity exercise will cause breathlessness. In a tiny minority of individuals, even in young adults, the possibility exists that such exercise triggers disturbances to normal physiology: these include abnormal blood pressure, fainting or a change in the normal rhythm of the heart. There is also a risk of musculoskeletal injury but this is minimal and measures will be taken to prevent any occurrences.

Venous cannulation can cause air or plastic embolism (occlusion of a blood vessel) but good practice minimises this risk and the personnel conducting the procedure have been trained and are highly experienced. Cannulation can also lead to local thrombophlebitis (inflammation) in a superficial vein but the absolute level of risk is low.

Benefits of the study

The study should lead to greater understanding about the effects of exercise on the cardiovascular disease risk markers in relation to males of South Asian descent and white European males. In so doing it will contribute to an expanding body of evidence concerning the role of exercise in the prevention of cardiovascular disease.

We will give you feedback on your own results and we will be happy to discuss this with you.

Confidentiality

Although information will be stored on computer, each participant will be entered as a number rather than by name, in accordance with the Data Protection Act. The information linking participant names to their number will be kept for no longer than five years. Data will be used for research purposes only and confidentiality will be maintained in any publications arising from the study. Participant data will not be kept longer than is necessary for the purposes of this investigation. Blood plasma samples collected during this investigation will be kept for no longer than three years. Samples will be disposed of via bio-hazard waste collection bags.

Right to withdraw

If you volunteer to participate in this study you hold the right to withdraw at any stage without having to inform the investigators of your reasons for doing so.

Contacts

Please feel free to ask any questions, at any stage. Contact information for the staff involved in this study is as follows:

Mr Saravana Pillai Arjunan
S.P.Arjunan@lboro.ac.uk
Telephone 01509 226351

Dr David Stensel
D.J.Stensel@lboro.ac.uk
Telephone: 01509 226344

School of Sport, Exercise and Health Sciences

The effects of a single bout of running versus three consecutive days of running on postprandial lipaemia in men of South Asian descent

Investigators

Mr Saravana Pillai Arjunan, Ms Emma Smith, Mr Daniel Teran, Ms Sara Treacy, Mr James Whiting, and Dr David Stensel

Background

South Asian men living in the UK have a higher than average risk of cardiovascular disease (CVD). The reasons for this are uncertain but physical inactivity may play a role. Alternatively, physical activity may be less effective in lowering the risk of CVD in South Asian men than in other men. Previous research from our laboratory has demonstrated that a single bout of exercise is effective for lowering blood lipid (triglyceride) concentrations after meals. This is important because high triglyceride concentrations are a marker for CVD risk. The proposed study will examine whether exercise performed on three consecutive days is more effective for lowering blood triglyceride concentrations than a single bout of exercise in men of South Asian descent. In addition to assessing the effects of exercise on blood triglyceride concentrations this study will also examine the effects of exercise on markers of inflammation in the blood because inflammatory markers may also be of use in predicting CVD risk.

Inclusion Criteria

Volunteers will:

(xi) be male
(xii) aged 18-40 y
(xiii) have no personal history of cardiovascular disease, metabolic disease (e.g. diabetes) or dyslipidaemia (e.g. high blood cholesterol)
(xiv) not be dieting or have any extreme dietary habits
(xv) not be taking drugs known to affect digestion or metabolism – medical or illegal (for example anabolic steroids, marijuana, amphetamines, thyroid prescription drugs).

Study Demands

If you volunteer to participate in this study you will be required to attend the Exercise and Health laboratory (1.11) in the Clyde Williams building for a screening/familiarisation visit lasting approximately two hours and then you will perform three main trials in the laboratory at least one week apart. These trials are 1) control (resting), 2) one-day exercise, 3) three-days exercise. The time commitments required for each of these trials are as follows:

1) Control (resting): 1 hour in the lab on day 1 and 7 hours in the lab on day 2 (8 hours)
2) One-day exercise: 1 hour in the lab on day 1 and 7 hours in the lab on day 2 (8 hours)
3) Three-day exercise: 1 hour in the lab on days 1, 2 and 3 and 7 hours in the lab on day 4 (10 hours)

In total participants will need to visit the lab on 9 occasions which will require 28 hours of their time

Preliminary Procedures

During the screening/familiarisation visit we will:

- Explain the objectives of the study and its requirements
- Ask you to complete a confidential questionnaire regarding your health
- Familiarise you with the testing procedures and equipment
- Familiarise you with dietary recording
- Ask you about your food tolerances and preferences
- Answer any questions you may have

After this we will collect the physiological/anthropometric measurements listed below:

- Resting blood pressure
- Height
- Weight
- Skinfold thicknesses at four sites (to estimate body fat percentage)
- Waist and hip circumferences

You will then complete a submaximal running test on a treadmill and (once you have recovered from this test) a maximum oxygen uptake test.

Main Trials

The three main trials will be assigned in a random order and separated by at least one week.

<u>One-day exercise trial</u>

On day one of this trial you will report to the laboratory at 3.00 pm. After a brief warm up you will complete a 30 minute treadmill run at 70% of maximum oxygen uptake. After completing the run you will warm down and leave the laboratory. You will consume a

standardised meal at home in the evening, fast overnight for 10 h and return to the laboratory on day 2.

On day 2 of this exercise trial you will report to the laboratory just before 9.00 am. A cannula will be inserted into a vein in your arm. You will rest in the laboratory (reading, working at a computer, watching movies, listening to music etc) throughout day 2 until 4.00 pm. You will be fed standardised meals for breakfast (9.00 am) and lunch (12.00 pm). Ten, 9 mL venous blood samples will be collected during the day. The timing of these collections is as follows: 09.00, 09.30, 10.00, 11.00, 12.00, 12.30, 13.00, 14.00, 15.00, and 16.00. In total 90 mL of blood will be collected on day 2 and this equates to less than one-fifth of a standard blood donation.

Three-day exercise trial

For this trial you will visit the lab in the afternoon for 3 consecutive days to complete a 30 minute treadmill run at 70% of maximum oxygen uptake. The procedures on the fourth day will be identical to those outlined for day 2 of the one-day exercise trial.

Control trial

The control trial will be identical to the one-day exercise trial with the exception of the 30 minute run. On the control trial you will perform no exercise on day 1 and remain resting in the laboratory for an hour. Several expired air samples will be collected into Douglas bags during this time.

NB It is important that you are free of illness for all lab visits and we will check this with you at the start of each visit.

Preparation for the tests

Recording your diet

You will be asked to weigh and record everything you eat and drink for 24 hours prior to the first main trial. You will then consume identical amounts of the same food and drink prior to the other main trials. Alcohol and caffeine must not be consumed on the days when you are recording your diet. These points are very important in order to prevent extraneous variables influencing the study findings and we will discuss this with you in depth prior to the main trials. For the three-day exercise trial we will ask you to keep a record of your food intake over days one to three of the trial.

Controlling physical activity

No strenuous physical activity should be performed during the days preceding main trials.

Overnight fast

You will finish eating by 11:00 pm on the evenings before the final day of each trial. You may however continue to drink water after this time. You will report to the laboratory at

9:00 am the next morning without having eaten breakfast. We will provide you with breakfast and lunch on the final day of each main trial.

Travelling to the laboratory

If you live within one mile of the laboratory you should walk in slowly on the morning of each main trial. Please do not run or cycle. If you live more than one mile from the laboratory then you should drive in. If you do not have access to a car please tell us and we will arrange for you to be collected.

Possible risks and discomforts

High intensity exercise will cause breathlessness. In a tiny minority of individuals, even in young adults, the possibility exists that such exercise triggers disturbances to normal physiology: these include abnormal blood pressure, fainting or a change in the normal rhythm of the heart. There is also a risk of musculoskeletal injury but this is minimal and measures will be taken to prevent any occurrences.

Venous cannulation can cause air or plastic embolism (occlusion of a blood vessel) but good practice minimises this risk and the personnel conducting the procedure have been trained and are highly experienced. Cannulation can also lead to local thrombophlebitis (inflammation) in a superficial vein but the absolute level of risk is low.

Benefits of the study

The study should lead to greater understanding about the effects of exercise on the CVD risk markers in relation to males of South Asian descent. In so doing it will contribute to an expanding body of evidence concerning the role of exercise in the prevention of CVD. We will give you feedback on your own results and we will be happy to discuss this with you.

Confidentiality

Although information will be stored on computer, each participant will be entered as a number rather than by name, in accordance with the Data Protection Act. The information linking participant names to their number will be kept for no longer than five years. Data will be used for research purposes only and confidentiality will be maintained in any publications arising from the study. Participant data will not be kept longer than is necessary for the purposes of this investigation. Blood plasma samples collected during this investigation will be kept for no longer than three years. Samples will be disposed of via bio-hazard waste collection bags.

Right to withdraw

If you volunteer to participate in this study you hold the right to withdraw at any stage without having to inform the investigators of your reasons for doing so.

Contacts

Please feel free to ask any questions, at any stage. Contact information for the staff involved in this study is as follows:

Mr Saravana Pillai Arjunan
S.P.Arjunan@lboro.ac.uk
Telephone 01509 226351

Dr David Stensel
D.J.Stensel@lboro.ac.uk
Telephone: 01509 226344

10.2 Appendix B: Informed consent form

INFORMED CONSENT FORM

(to be completed after the participant information sheet has been read)

The purpose and details of this study have been explained to me. I understand that this study is designed to further scientific knowledge and that all procedures have been approved by the Loughborough University Ethical Advisory Committee.

I have read and understood the information sheet and this consent form.

I have had an opportunity to ask questions about my participation.

I understand that I am under no obligation to take part in the study.

I understand that I have the right to withdraw from this study at any stage for any reason, and that I will not be required to explain my reasons for withdrawing.

I understand that all the information I provide will be treated in strict confidence and will be kept anonymous and confidential to the researchers unless (under the statutory obligations of the agencies which the researchers are working with), it is judged that confidentiality will have to be breached for the safety of the participant or others.

I agree to participate in this study.

Your name _____

Your signature _____

Signature of investigator _____

Date _____

10.3 Appendix C: Health screen questionnaire

Loughborough University

Name/Number .....

Health Screen Questionnaire for Study Volunteers

As a volunteer participating in a research study, it is important that you are currently in good health and have had no significant medical problems in the past. This is (i) to ensure your own continuing well-being and (ii) to avoid the possibility of individual health issues confounding study outcomes.

If you have a blood-borne virus, or think that you may have one, please do not take part in this research.

Please complete this brief questionnaire to confirm your fitness to participate:

1. **At present,** do you have any health problem for which you are:

(a)	on medication, prescribed or otherwise	Yes ☐	No ☐
(b)	attending your general practitioner	Yes ☐	No ☐
(c)	on a hospital waiting list.....	Yes ☐	No ☐

2. **In the past two years,** have you had any illness which required you to:

(a)	consult your GP.....	Yes ☐	No ☐
(b)	attend a hospital outpatient department.....	Yes ☐	No ☐
(c)	be admitted to hospital	Yes ☐	No ☐

3. **Have you ever** had any of the following:

(a)	Convulsions/epilepsy	Yes ☐	No ☐
(b)	Asthma	Yes ☐	No ☐
(c)	Eczema	Yes ☐	No ☐
(d)	Diabetes	Yes ☐	No ☐
(e)	A blood disorder	Yes ☐	No ☐
(f)	Head injury	Yes ☐	No ☐
(g)	Digestive problems	Yes ☐	No ☐
(h)	Heart problems	Yes ☐	No ☐
(i)	Problems with bones or joints	Yes ☐	No ☐
(j)	Disturbance of balance/coordination	Yes ☐	No ☐
(k)	Numbness in hands or feet	Yes ☐	No ☐
(l)	Disturbance of vision	Yes ☐	No ☐
(m)	Ear / hearing problems	Yes ☐	No ☐
(n)	Thyroid problems	Yes ☐	No ☐
(o)	Kidney or liver problems	Yes ☐	No ☐
(p)	Allergy to nuts	Yes ☐	No ☐

4. **Has any,** otherwise healthy, member of your family under the age of 35 died suddenly during or soon after exercise? ..... Yes ☐ No ☐

If YES to any question, please describe briefly if you wish (eg to confirm problem was/is short-lived, insignificant or well controlled.)

.....

.....

5. **Allergy Information**

(a) are you allergic to any food products? Yes ☐ No ☐

(b) are you allergic to any medicines? Yes ☐ No ☐

(c) are you allergic to plasters? Yes ☐ No ☐

If YES to any of the above, please provide additional information on the allergy

.....

6. **Please provide contact details of a suitable person for us to contact in the event of any incident or emergency.**

Name:

.....

Telephone Number:

.....

Work ☐ Home ☐ Mobile ☐

Relationship to Participant:.....

7. **Are you currently involved in any other research studies at the University or elsewhere?**

Yes ☐ No ☐

If yes, please provide details of the study

.....

.....

10.4 Appendix D: Physical activity questionnaire

PHYSICAL ACTIVITY QUESTIONNAIRE

During one week, how many times on average do you do the following kinds of exercise for more than 15 minutes?

(a) **Strenuous exercise** (heart beats rapidly)
For example; running, jogging, squash, hockey, football, volleyball, vigorous swimming, vigorous long distance cycling.

_____times per week.

(b) **Moderate exercise** (not exhausting)
For example; fast walking, tennis, easy cycling, badminton, easy swimming, dancing.

_____ times per week.

(c) **Mild exercise** (minimal effort)
For example; yoga, archery, fishing, bowling, golf, easy walking.

_____ times per week.

10.5 Appendix E: Physical activity questionnaire (GPAQ)

PHYSICAL ACTIVITY QUESTIONNAIRE

Please place a check mark in the boxes that reflects your current level of physical activity and **be frank** in answering the questions. Your responses will greatly help us in our research area.

ACTIVITY AT WORK

P1. Does your work involve vigorous intensity activity that causes large increases in breathing or heart rate, like carrying or lifting heavy loads, digging or construction work, for at least 10 minutes continuously?

Yes ☐ No ☐ Please go to Qu 4 I don't work ☐ Please go to Qu 7

P2. In a typical week, on how many days do you do vigorous-intensity activities as part of your work?

1☐ 2 ☐ 3 ☐ 4☐ 5☐ 6☐ 7☐

P3. How much time do you spend doing vigorous-intensity activities at work on a typical day?

Hours_____Minutes_____

P4. Does your work involve moderate-intensity activity that causes small increases in breathing or heart rate such as brisk walking or carrying light loads for at least 10 minutes continuously?

Yes ☐ No ☐ Please go to Qu 7

P5. In a typical week, on how many days do you do moderate-intensity activities as part of your work?

1☐ 2 ☐ 3 ☐ 4☐ 5☐ 6☐ 7☐

P6. How much time do you spend doing moderate-intensity activities at work on a typical day?

Hours_____Minutes_____

TRAVEL TO AND FROM PLACES

The next questions exclude the physical activities at work that you have already mentioned.

P7. Do you walk or use a bicycle (pedal bike) for at least 10 minutes continuously to get to and from places?

Yes ☐ No ☐ Please go to Qu 10

P8. In a typical week, on how many days do you walk or bicycle for at least 10 minutes continuously to get to and from places?

1☐ 2 ☐ 3 ☐ 4☐ 5☐ 6☐ 7☐

P9. How much time do you spend walking or bicycling for travel on a typical day?

Hours_____Minutes_____

RECREATIONAL ACTIVITIES

The next questions exclude the work and transport activities that you have already mentioned.

P10. Do you do any vigorous-intensity sports, fitness or recreational activities that cause large increases in breathing or heart rate like running or football, for at least 10 minutes continuously?

Yes ☐ No ☐ Please go to Qu 13

P11. In a typical week, on how many days do you do vigorous-intensity sports, fitness or recreational activities?

1☐ 2 ☐ 3 ☐ 4☐ 5☐ 6☐ 7☐

P12. How much time do you spend doing vigorous-intensity sports, fitness or recreational activities on a typical day?

Hours_____Minutes_____

P13. Do you do any moderate-intensity sports, fitness or recreational activities that cause a small increase in breathing or heart rate such as brisk walking, cycling, swimming, volleyball etc. for at least 10 minutes continuously?

Yes ☐ No ☐ Please go to Qu 16

P14. In a typical week, on how many days do you do moderate-intensity sports, fitness or recreational activities?

1☐ 2 ☐ 3 ☐ 4☐ 5☐ 6☐ 7☐

P15. How much time do you spend doing moderate-intensity sports, fitness or recreational activities on a typical day?

Hours_____Minutes_____

SEDENTARY BEHAVIOUR

The following section is about sitting or reclining at work, at home, getting to and from places, or with friends including time spent sitting at a desk, sitting with friends, travelling in a car, bus, train, reading, playing cards or watching television, but do not include time spent sleeping.

P16. How much time do you usually spend sitting or reclining on a typical day?

Hours_____Minutes_____

Your time and effort is greatly appreciated

10.6 Appendix F: South Asian verification form

South Asian Verification Data

1. First Name : _____
2. Family Name : _____
3. Place of Birth : _____
4. Country of birth : _____
5. Language : _____
6. Religion : _____
7. Race : _____
8. Parental country of birth : _____
9. History of Migration (if applicable) :