The physique associated with coronary artery disease

Thesis

THE PHYSIQUE ASSOCIATED WITH CORONARY ARTERY DISEASE

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List of Abbreviations

AHR	abdomen-to-hip ratio
apo A1	apolipoprotein A1
apo B	apolipoprotein B
apo B-100	apolipoprotein B-100
aop E	apolipoprotein E
ASD	abdominal sagittal diameter
ASD/Ht	abdominal sagittal diameter / height
ASD/Th	abdominal sagittal diameter / thigh
AT	adipose tissue
BMI	body mass index
BRFSS	Behavioural Risk Factor Surveillance System
CETP	cholesteryl-ester transfer protein
CVD	cardiovascular disease
CAD	coronary artery disease
CHD	coronary heart disease
CI	confidence interval
CT	computed tomography
DEXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
FCW	fat cell weight
FEV_1	forced-expiratory volume in 1 second
FFM	fat free mass
HDL-C	high-density lipoprotein-cholesterol
IAF	intra-abdominal fat
IDL	intermediate-density lipoprotein
IHD	ischaemic heart disease
I : S ratio	intra-abdominal-to-subcutaneous abdominal fat ratio
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein-cholesterol
LPL	lipoprotein lipase
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NEFA's	non-esterified fatty acids
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung and Blood Institute
NIH	National Institute of Health
OGTT	oral glucose tolerance test
ROC	receiver operating characteristic
SD	standard deviation
SEE	standard error of estimation
SEM	standard error of measurement
SOS	Swedish Obese Subjects
STR	subscapular-to-triceps skinfold ratio
TC	total cholesterol
TG	triglyceride
TLR	the ratio of the sum of 4 torso skinfolds-to-the sum of 4 limb skinfolds

VLDL	very low-density lipoprotein
VLDL-C	very low-density lipoprotein-cholesterol
VLDL-TG	very low-density lipoprotein-triglyceride
W/H	weight/height
WHO	World Health Organisation
WHR	waist-to-hip circumference ratio
WhtR	waist girth-to-height ratio
WTR	waist-to-thigh circumference ratio

Abstract

Studies within this thesis have investigated various aspects of the relationship between physique, coronary artery disease (CAD) and certain CAD risk factors. Data presented was collected on two separate occasions. Firstly, in a hospital setting on men undergoing investigative coronary angiography (CAD men), and secondly during a university health-screening programme (healthy men). Physique has been described using body mass and height, somatotype, skinfolds, girth measurements and various skinfold and girth ratios. CAD risk factors were related to 'metabolic fitness' : fasting serum glucose, total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and the LDL-C ; HDL-C ratio. A unique aspect of certain studies is that a proportionality technique was used to adjust the anthropometric measurements for variation in body mass and stature. Also, an angiographic scoring system was used to describe the severity of atherosclerosis as a continuous rather than dichotomous variable. Anthropometric measurements were not related to the severity of atherosclerosis and there was no discernible pattern of subcutaneous adiposity (skinfolds) in the CAD or healthy men. However, in relation to age-matched healthy men, the CAD men were heavier ($P < 0.01$), had a greater BMI ($P < 0.01$), biceps skinfold ($P < 0.05$) and subscapular skinfold ($P < 0.001$). The CAD men also had significantly greater waist and abdominal girths, abdominal sagittal diameter (ASD), waist-to-hip ratio (WHR), abdomen-to-hip ratio (AHR), waist-to-thigh ratio (WTR), waist-to-height ratio (WHtR) and ASD-to-height ratio (ASD/Ht) (all $P < 0.001$). When the skinfolds and girths were adjusted for variation in stature the differences in biceps and subscpaular skinfolds, and waist and abdominal girths remained. However, when adjusted for

body mass variation the differences were no longer apparent. Abdomen and waist girths exhibited a closer association with TC, TG, HDL-C, LDL-C and the LDL-C : HDL-C ratio than skinfolds. A higher waist or abdominal girth was positively correlated with TG ($P < 0.01$), and the LDL-C : HDL-C ratio ($P < 0.01$) but negatively with HDL-C ($P < 0.01$). Adjusting for stature had no effect on these relationships, but adjusting for body mass reduced them considerably. In studies focusing on somatotype, both the CAD and healthy men were characterised by high ratings for endomorphy and mesomorphy but low ratings for ectomorphy. The CAD men had a small but significantly greater endomorphy rating ($P = 0.038$) and the healthy men had a small but significantly greater ectomorphy rating ($P = 0.006$). Somatotype was not related to the angiographic findings but a somatotype of low endomorphy and high ectomorphy was associated with a better metabolic profile in terms of cardiovascular disease risk. In conclusion, CAD men appear to have a physique characterised by abdominal obesity, a higher rating of endomorphy and a low rating for ectomorphy. However, a distinctive skinfold pattern is not apparent. Normalising anthropometric measurements for stature does not affect the relationship between elevated serum lipids and abdominal obesity but adjusting for body mass does.

CHAPTER 1

INTRODUCTION

The association between human physique and susceptibility to a wide variety of morbid conditions, including atherosclerotic coronary artery disease (CAD), has intrigued scientists for many years. There are references to ill-health accompanying excess body fat (obesity) from Hippocrates and an awareness of differences in anatomical fat patterning that date back about 30,000 years (see Kissebah and Krakower, 1994 for further details). In more recent times, Kretschmer (1926) noted differences in the prevalence of stroke and gout according to variation in body habitus. With regard to health status, there is no doubt that most attention has focused on the important issue of obesity. However, there are other aspects of human physique, such as muscularity, linearity and proportionality, that have received much less attention. Since the discoveries of Vague were reported in 1947 (Vague, 1947), many investigators have concentrated their efforts on clarifying the apparent importance of adipose tissue distribution - particularly with regard to CAD and diabetes.

As outlined in Section 1.3, diseases of the cardiovascular system, of which atherosclerotic CAD is the most prevalent, are the major cause of premature mortality in the 'modernised' world. Atherosclerosis is a condition in which fatty substances, especially cholesterol, are deposited within the wall of small and medium-sized arteries. This deposition is accompanied by damage to endothelial cells lining the arterial wall, the adhesion of circulating monocytes to the site of injury and proliferation of smooth muscle cells. The monocytes subsequently develop into lipid-laden macrophages. As these processes continue and arterial occlusion increases, a significant reduction in blood flow distal to the site of injury occurs. If coronary vessels are affected, and blood flow is sufficiently reduced, myocardial ischaemia results. In some instances, the atherosclerotic plaque may rupture leading to the

release of large particles into the bloodstream. These particles can result in the almost total blockage of smaller coronary vessels leading to a myocardial infarction - more commonly referred to as a 'heart attack'.

1.1 DEFINITIONS AND CLASSIFICATION OF OVERWEIGHT AND OBESITY

The medical, scientific and popular literature is replete with references to the terms overweight and obesity. In the majority of studies, and for most individuals, overweight refers to a condition in which an excess of body fat is present and is thought to be associated with deterioration in health. In the 'general public' it has been estimated that about 1 in 10 will be described as overweight when, in fact, their body fat is not elevated excessively. In athletically trained populations, this proportion will be much higher because of the increased muscle mass. This problem of misclassification is due to the application of relatively crude indices of body fatness, most noticeably body mass index (BMI). A detailed description of BMI is given in Section 1.1.1. In large-scale epidemiological surveys, therefore, when simple and inexpensive measures are needed these indices suffice. In smaller, heterogeneous populations, however, they may be inappropriate.

Based on the BMI system presented in Section 1.1.1, obesity represents a continuation of the overweight condition to a higher level of body fat. Again, when body mass-for-stature is used, no indication of actual body fat is given. Thus, there is a need for some clarification of these terms so that they become meaningful in the context of either representing some level of body fat or, they are associated with co-morbid conditions. The aim of the following section is to provide this clarification by outlining currently used methods for assessing overweight and obesity. The focus has

been restricted to simple methods for two reasons. Firstly, these are the methods that have been employed by epidemiologists in their study of the relationship between obesity and disease. Second, they are the methods that the public is encouraged to recognise because they are used to direct public health policy.

Any index or measurement of overweight and obesity should meet three important conditions. If the index is going to be used to identify individuals who are more likely to experience ill-health or functional limitations, it should be closely associated with morbidity and mortality. However, it is important to note that the association with the index of overweight or obesity may vary with the health risk examined. For example, Sakurai *et al.* (1995) have shown that the waist-to-hip ratio (WHR), an index of anatomical fat distribution, is a good predictor of diabetes, probably because this index also contains information about muscle mass, whereas hypertension was more closely related to BMI than WHR. A further important issue that should be delineated clearly is the interaction of the index or measurement with age, ethnicity and gender. That is, does the association with fatness, morbidity and mortality change with variation in these population parameters. If this is the case, adjustments should be considered and a population-specific index derived.

Finally, the measurements used to construct the index should be relatively simple and reproducible. This ensures that primary health professionals are able to record them with minimal training and equipment. The measurements or index should also be related to body fatness in order that underlying mechanisms can be explored.

1.1.1 Body mass index

With the above factors in mind, several methods have been investigated and subsequently proposed for classifying and defining overweight and obesity. Body mass index is calculated from measurements of body mass and stature ($kg.m^{-2}$).

The rationale for the use of BMI as an index of fatness is that it provides a stature-independent measure of body mass. In most free-living individuals in modernised societies, an increase in body mass that is independent of stature will be due to an increase in fat mass. Therefore, on a population basis, BMI should provide a reasonable estimate of fatness. However, in the general population, the variation in body fat explained by variation in BMI is 50 to 60% (James, 1996). This suggests there is a wide variation in body fatness within any BMI category. Bouchard (1990), who suggests that the common variance between BMI and relative fat derived from underwater weighing is only about 40%, supports this. Furthermore, misclassification will occur when BMI is applied to lean individuals who have a large muscle mass. The use of stature squared is also questionable and is used by most researchers without proper consideration. Ideally, this power-function should be determined for each population on the basis that it provides the minimal correlation between BMI and stature i.e. a mass-for-stature index that is truly independent of stature

Body proportions also effect BMI. Very tall individuals with legs that are relatively long for stature have spuriously low BMI scores in comparison to shorter individuals of similar body fat. Shorter individuals, with relatively short muscular legs and a thick trunk will have a high BMI and may, therefore, be classified as obese even though they may be lean (James, 1996).

Despite these limitations, BMI remains a useful index of overweight and obesity for the following reasons. It is determined from body mass and stature, measurements

that are in widespread use throughout the world. Body mass and stature are simple measurements that can be made in the health-care facility, research centre or in the field. The simplicity and robustness of the measurements mean that normative values exist for many populations. Finally, it shows a statistical relationship with morbidity and mortality from many causes - including cardiovascular disease (CVD). This relationship will be examined in detail in Chapter 2.

The most recent classification scheme based on BMI values is given below [Table I (1.1)]. These values, proposed by the World Health Organisation (WHO, 1998) and the National Institutes of Health and National Heart, Lung, and Blood Institute (NIH & NHLBI, 1998) are appropriate for use with adults. The table also presents the health risk associated with the respective level of BMI.

Table I (1.1). World Health Organisation Classification of Body Mass Index

Classification	BMI ($kg.m^{-2}$)	Associated health risks
Underweight	< 18.5	Low (but risk of other clinical problems increased).
Normal range	18.5-24.9	Average
Overweight	25.0 or higher	
Pre-obese	25.0-29.9	Increased
Obese class I	30.0-34.9	Moderately increased
Obese class II	35.0-39.9	Severely increased
Obese class III	40 or higher	Very severely increased

1.1.2 Skinfolds and Relative Body Fat

Anthropometric skinfold measurements have been used to estimate body fatness for many years and in many different populations. Initially, it was thought that the

proportion of stored subcutaneous fat is relatively constant. Lohman (1981) suggested that approximately 50 to 70% of body fat is stored subcutaneously. Thus, there appeared to be some logic behind the use of skinfolds as a measure of body fatness. However, subsequent studies discussed later in this section have cast doubt on this assumption (Martin *et al.*, 1985, 1992, 1994; Clarys *et al.*, 1987). The skinfold method requires a double thickness of skin and underlying adipose tissue (AT) to be measured with callipers that exert a constant pressure over the range of skinfold thickness encountered.

As a close inverse relationship exists between whole-body density and relative body fat (Durnin and Womersley, 1974), it is possible to predict fatness from whole-body density. The estimation of body fat (relative and absolute) from skinfolds is, therefore, based upon the regression of the logarithmic transformation of skinfolds against whole-body density. The procedure of underwater weighing usually provides the criterion method for measuring body density. Thus, body fat derived from skinfold measurements is regarded as being 'doubly-indirect' i.e. one indirect method is validated against another indirect method. As whole-body density determined from underwater weighing is dependent on the densities of all of the body's component parts, the relationship between skinfolds and body density varies across populations. For the same amount of body fat, individuals who differ in the density of their fat-free mass (FFM) will have different whole-body densities. Thus, the literature contains many linear and quadratic regression equations for the estimation of body density (or body fat) from skinfolds. The linear equations of Durnin and Womersley (1974), and the quadratic equations of Jackson and Pollock (1978) and Jackson, Pollock and Ward (1980) are probably the most frequently used equations for predicting fatness in the general population. Each equation is specific to the population on which it was

validated and the application to other populations is likely to result in unacceptable estimation error.

Despite their widespread use, the use of skinfold regression equations to predict body fatness has been severely criticised recently. Much of this criticism emanates from the findings of the Brussels Cadaver Analysis Study (Martin *et al.*, 1985, 1992, 1994; Clarys *et al.*, 1987).

When skinfolds are used to predict body fat, several assumptions have to be made (Martin *et al.*, 1985; Heyward and Stolarczyk, 1996; Hawes and Martin, 2001). These are outlined below but are not presented in order of importance. Firstly, one has to assume that the skinfold is closely related to subcutaneous fat at that particular site. As outlined previously, a skinfold consists of a double layer of skin and the underlying AT. This assumption has two potential problems, both of which relate to factors that are unknown to the anthropometrist. The thickness of skin is an unknown quantity and the composition of the AT within the skinfold is also unknown. The second assumption is that there is a constant distribution of internal and subcutaneous fat for all individuals. Third, the compressibility of skin is assumed to be either constant or represents a negligible fraction of the skinfold thickness. The fourth assumption is that a limited number of skinfolds can be used to estimate total body fat. For this assumption to be valid, there would need to be consistency in subcutaneous fat pattern between all individuals.

The Brussels Cadaver Analysis Study (Martin *et al.*, 1985, 1992, 1994; Clarys *et al.*, 1987) consisted of two separate cadaver dissection studies of men (n = 12) and women (n = 13) ranging in age from 55- to 94-years. Cadavers were extensively measured and dissected into skin, AT, skeletal muscle, bone, organs and visceral tissues. The study aimed to extend the existing quantitative data on tissues and organs

in humans, and obtain data to validate existing *in vivo* body composition methods and develop new anthropometric models of body composition. This study has, in recent years, provided the most precise data so far with respect to the mechanical and morphological characteristics of the skinfold (although the small sample of cadavers from an elderly and in some cases diseased group raises a question about the external validity of these findings). It has also questioned the validity of the method of predicting relative body fat from skinfolds by refuting the assumptions outlined above. For example, the constancy of skinfold thickness and compressibility was shown to be fallacious. Skin thickness clearly comprises a greater fraction of a thin skinfold in comparison to a thick skinfold. Skin thickness has been shown to vary between individuals and from site to site (Martin *et al.*, 1992). Furthermore, AT compressibility varies with factors such as age, gender, tissue hydration, anatomical site and cell size (Martin *et al.*, 1992). The lipid fraction of AT may also be highly variable. Martin *et al.* (1994) suggested a range of 60-85% although an earlier investigation found a much greater variation of 5.2 to 94.1% (Orpin and Scott, 1964). The final assumptions relating to the distribution of body fat are also questionable. Whilst several phenotypes for classifying regional fat distribution have been described, the distribution of fat internally (intra-abdominal, inter-muscular, intra-muscular, intra-pelvic and essential lipids) and externally (subcutaneous) is, in fact, highly variable. Fat distribution is affected by factors such as age, gender, energy balance and the level of total body fat, and local AT biology (Bouchard *et al.*, 1993). In general, for any sum of skinfolds, total body fat is likely to be higher in older individuals because of greater fat internalisation with age (Lemieux *et al.* 1995).

Given the apparent limitations associated with predicting total body fat from skinfolds, some now advocate using the sum of skinfolds as an index of body fatness

(Hawes and Martin, 2001). There are further advantages of using skinfolds in this way. When multiple skinfolds are selected from the torso and limbs, they are also useful for identifying variation in AT patterning. Furthermore, skinfold measurements are highly reproducible in the hands of trained and experienced investigators and can be compared to normative values where they exist. Finally, they represent an indicator of energy balance over the long-term and may, therefore, be related to diseases associated with lifestyle and nutritional status.

Two methods can be used to determine obesity from skinfolds. A population-specific regression equation could be used to provide an estimation of relative body fat. There are an abundance of such equations available in the literature. As well as being limited by the assumptions outlined earlier, this method is also subject to the inherent error of applying a regression formula to a sample that is different from the original validation sample. Apparently, this error can reach 200% (Katch and Katch, 1980). The second approach is to compare skinfolds against age, gender and ethnicity specific normative values. Percentile rankings can then be used to form an opinion on individuals body fatness.

One further important point is worthy of mention with regard to the use of skinfolds. High-quality skinfold callipers such as the Harpenden and Lange instruments, are calibrated within the range of 0 to 60 mm and have a precision of 0.2 and 1.0 mm respectively (Heyward and Stolarczyk, 1996). They are not accurate, therefore, when measuring the extremely obese who have skinfolds outside of this range. Furthermore, even when the skinfolds are within this range, measurement error is likely to be greater when dealing with larger skinfolds. The identification of bony, anatomical landmarks is also more difficult in the obese (Bray and Gray, 1988). For these reasons, alternative anthropometric methods that rely on circumference

measurements (Weltman *et al.*, 1987; Weltman *et al.*, 1988) have been recommended for estimating body composition in the obese (Heyward and Stolarcyzk, 1996).

If relative body fat is predicted from skinfolds or estimated by some other method, at what level of body fatness does obesity begin? Unlike BMI, there are few prospective epidemiological investigations that have used a 'direct' measure of relative body fat as the main predictor variable (Keys *et al.*, 1971; Weinsier *et al.*, 1976). It is not possible, therefore, to ascribe an obesity level commensurate with increased morbidity or mortality. An alternative approach is to assess body fatness in relation to the average for the population (McArdle *et al.*, 2001). This value should be considered in relation to the variation that is observed in populations who differ with regard to age, gender and ethnicity. However, this technique is also subject to a major limitation. Whilst the body composition of many different groups has been evaluated, no large-scale studies of the general population exist. McArdle *et al.* (2001) suggested that the average body fat of younger men is approximately 15%. For older men they suggest a value of about 25%, and for younger and older women, 25% and 32% respectively. The standard deviation (SD) of these mean values is about 5% body fat. Thus, an extremely rigorous way of defining where the lower boundary of obesity begins is to consider the average value and its variation. Obesity then begins at the average body fat plus 5%, i.e. 20% for younger men, 30% for older men and younger women, and 37% for older women. Although no clear rationale is provided for using one SD, with respect to the number of people classified as obese in the USA, this approach apparently corresponds closely to the method of using a BMI value >25 $kg.m^{-2}$ (McArdle *et al.*, 2001).

1.1.3 Anthropometric girth measurements

One of the most significant advancements to the understanding of the association between obesity and cardio-metabolic disease came with the publication of two papers (Larsson *et al.*, 1984; Lapidus *et al.*, 1984) that supported an earlier observation made by Vague (1947). It appears from these studies that an obesity phenotype characterised by an accumulation of fat in the abdominal region carries the greatest risk of CAD. The reasons for this phenomenon, that has been shown in many studies subsequently, are explored in greater detail in Chapter 2. Briefly, disturbances in carbohydrate and lipid metabolism, elevated blood pressure, increased plasma viscosity, and a greater susceptibility to inflammation and thrombogenesis have all been implicated.

Fat deposition differences between males and females begin in childhood and become progressively established after maturation (Malina and Bouchard, 1988). Males tend to accumulate more truncal fat, whereas fat deposition in females tends to be at the same rate on the trunk and limbs (Malina and Bouchard, 1988). The study of a large number of obese men and women highlighted the sexual dimorphism that exists with regard to AT distribution in the mature individual (Krotkiewski *et al.*, 1983). When matched for body fat mass, females had a greater fat cell size and number in the gluteal and femoral regions and males a greater fat cell size and number in the abdominal region. Consequently, men had a greater AT thickness in the abdominal region and females a greater thickness in the gluteo-femoral region. Men also tend to have more visceral or intra-abdominal fat (IAF) for any given total body fat, although it increases with age in both genders and in the non-obese as well as the obese (Bouchard *et al.*, 1993; Lemieux *et al.*, 1993). Abdominal obesity, despite being primarily a male characteristic, is also observed in a sub-group of obese women.

As IAF is thought to be the principal fat depot responsible for the atherogenic metabolic profile in abdominal obesity (Bjorntorp 1990), its valid determination is of great importance. The most frequently used anthropometric indicators of abdominal obesity have been the WHR and the waist and abdominal girths (see Williams *et al.*, 1997 for a review). The underlying theory of the WHR, is that it discriminates between fat deposited in the upper (waist and abdomen areas) and lower trunk (hips and buttocks). As a predominance of fat in the upper trunk is primarily a masculine characteristic, and predominance in the lower trunk feminine, the terms android and gynoid obesity (Vague, 1947) are used to characterise these types of fat distribution. Previous studies have shown that the waist circumference, measured at the level of natural narrowing between the lower rib and superior iliac crest, is the best anthropometric correlate of computed tomography (CT) measured IAF mass (Pouliot *et al.*, 1994). This finding has received some support from a recent cadaver dissection of 100 men which found that the waist circumference, measured at a level within 1 cm of the umbilicus, is the best predictor of IAF (Pounder *et al.*, 1997).

Several cut-off or threshold points of abdominal obesity have been suggested for WHR and waist circumference measurements [Table II (1.1)]. Based on the incidence of CVD morbidity and mortality in the prospective study of 792 Gothenburg men, Bjorntorp (1985) suggested a WHR cut-off point of 1.00 for men. The same value was also later proposed by Bray (1987). Using the absolute level of visceral fat as the criteria defining increased CVD risk, Lemieux *et al.* (1996) proposed a WHR cut-off point of 0.94 and waist circumferences of 100 cm and 90 cm for men aged 40-years or less and greater than 40 respectively. Following analysis based on Receiver Operating Characteristic (ROC) Curves, Lean *et al.* (1995) proposed two waist circumference "action levels" that could be used to identify

individuals at increased CVD risk from being both overweight (BMI ≥ 25 $kg.m^{-2}$) and/or abdominally obese (WHR ≥ 0.95). This approach utilises the concepts of sensitivity (the proportion of people with a disease who are correctly identified by a positive test) and specificity (the proportion of people without the disease who are correctly identified by a negative test) (Fletcher *et al.*, 1996). The waist circumference "action 1" level for men (94 cm) identified such subjects with a sensitivity of > 96% and a specificity of > 97.5%. The "action 2" level (102 cm) identified men with a BMI ≥ 30 $kg.m^{-2}$ and/or abdominal obesity with a sensitivity of > 96% and a specificity of > 98%. The same researchers later applied these "action levels" to a group of 2183 men in order to evaluate the sensitivity and specificity of identifying individuals with a total cholesterol (TC) ≥ 6.5 $mmol.L^{-1}$, a high-density lipoprotein-cholesterol (HDL-C) < 0.9 $mmol.L^{-1}$, hypertension (treated and/or systolic pressure ≥ 160 mmHg and/or diastolic pressure ≥ 95 mmHg) or a combination of these risk factors (Han *et al.*, 1996a). At "action level 1", sensitivity ranged from 56.8 to 71.2% and specificity from 63.1 to 72.1%. The point at which sensitivity equalled specificity provided a waist circumference that was within 2 cm of "action level 1". This study found that using waist circumference as a tool to screen for individuals at risk of CVD because of hypercholesterolaemia, low HDL-C and/or hypertension would misclassify about 35% of subjects.

Table II (1.1). Guidelines for classifying abdominal obesity in men[a].

Measurement	*Cut-off point*	*Reference*
WAIST GIRTH	≥ 94.0 cm[b]	Lean *et al.* (1995)
WAIST GIRTH	≥ 102 cm[c]	Lean *et al.* (1995)
WAIST GIRTH	≥ 100 cm	Lemieux *et al.* (1996)
WHR	≥ 1.0	Bjorntorp (1985) Bray (1987)
WHR	≥ 0.94	Lemieux *et al.* (1996)

[a]Molarius, A. and Seidell, JC. (1998). Selection of anthropometric indicators for classification of abdominal fatness - a critical review. *International Journal of Obesity*, 22, 719.
[b]Represents a threshold above which risk of cardiovascular disease is slightly increased. Further weight gain should be avoided.
[c] Represents a threshold above which risk of cardiovascular disease is increased further. Weight loss should be an aim.

1.2 THE CURRENT EPIDEMICS OF OBESITY AND TYPE 2 DIABETES

One of the major concerns for health professionals today is the alarming increase in obesity and the associated increase in type 2 diabetes. This is a feature of most modern westernised countries and *also* developing countries from the third-world (WHO, 1998). Perhaps more worrying is the sharp increase in obesity prevalence in children. This is also a global phenomenon (Lehingue, 1999; Reilly *et al.*, 1999; Rasmussen and Johansson, 2000; Dwyer *et al.*, 2000; Chinn and Rona, 2001; Rudolf *et al.*, 2001; Magarey *et al.*, 2001; Styne, 2001). In the majority of developed countries, obesity prevalence tends to increase with age up to about 60- to 70-years, and is more frequent in those of relatively low socio-economic status (Seidell and Flegal, 1997; Evans *et al.*, 2000). Increasing economic prosperity in certain population groups may limit, but not stop, the increase in obesity prevalence (Maillard *et al.*, 1999).

Type 2 diabetes is a condition of hyperglycaemia caused by marked skeletal muscle and hepatic insulin resistance. Skeletal muscle is the major site of post-prandial glucose disposal, and the liver is responsible for glucose production by the process of gluconeogenesis. As both of these processes are mediated by insulin, any defect in the normal action of this hormone on these tissues will lead to hyperglycaemia. In skeletal muscle the defect is reduced glucose uptake. In the liver, the defect is a lack of suppression of gluconeogenesis. Diabetes is diagnosed by reference to the plasma glucose concentration either in the fasting state (> 7.0 $mmol.L^{-1}$) or 2-hours after an oral glucose challenge (> 11.1 $mmol.L^{-1}$) (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1999).

Obesity prevalence has increased during a time when caloric intake, *per capita*, has decreased or remained stable (Abraham *et al.*, 1995; Iwane, 1996; James, 1995; Kromhout *et al.*, 1990), and the proportion of calories derived from dietary fat has declined (Ernst *et al.*, 1997; Stephen and Sieber, 1994). Thus, other mechanisms have to be sought to explain this global occurrence. For example, Astrup (1998) reports that in Denmark, the prevalence of obesity has continued to increase despite a 10% reduction in dietary fat intake. In America, this phenomenon has been termed the 'American paradox' and has been attributed to the increased consumption of high energy, low fat foods (Astrup, 1998).

As body mass is affected by energy intake as well as energy expenditure, it is not surprising several studies have reported an inverse relationship between habitual physical activity and weight gain (French *et al.*, 1994; Schulz and Schoeller, 1994; Klesges *et al.*, 1992; Rissanen *et al.*, 1991; King *et al.*, 2001). Further support for the role of physical activity as an important determinant of body weight regulation comes from a unique, forty-year study of UK citizens (Prentice and Jebb, 1995) and

investigations of traditional rural communities who have become progressively urbanised (Orr *et al.*, 1998). Thus, whilst many individuals still, undoubtedly, consume a diet containing a high proportion of fat, and are at risk of significant weight gain, the development of obesity is extremely complex and is determined by factors affecting both sides of the energy balance equation. The rapid increase in the prevalence of obesity suggests that the epidemic cannot be explained by changes in genotype. Instead, alterations in lifestyle, particularly reductions in habitual physical activity, offer the best possible explanation of the increased obesity prevalence. Foreyt and Goodrick (1995) have suggested that the increased annual incidence of obesity is "unstoppable" in the face of modernisation and mechanisation. Adopting the term "the ultimate triumph of obesity", they further suggest that at the current rate of increase, 100% of US adults will be obese by the year 2230. The problem of the increasing incidence of obesity is not confined to modern, developed nations. In densely populated countries such as China and India, a 1% increase in obesity prevalence results in about 20 million new cases of obesity (Visscher and Seidell, 2001). The health consequences of this obesity 'explosion', especially in children and adolescents, will lead to unprecedented cases of type 2 diabetes, CVD, hypertension, gallbladder disease, postmenopausal breast cancers, osteoarthritis of the knees, back pain and mental disabilities (Bouchard, 2000).

In recognition of this increased prevalence, several of the world's major health organisations have convened expert panels to produce strategies aimed at confronting this problem. Reports from the WHO and the NIH & NHLBI in the USA summarise the findings of these panels (WHO, 1998; NIH & NHLBI, 1998).

Estimates of obesity prevalence by global region are shown below [Table I (1.2)].

Table I (1.2). Estimated World Prevalence of Obesity.

Region	Population aged over 15 years (millions)	Prevalence of obesity (%)	Approximate estimate of number of obese subjects in millions (midpoint)	
Established market economies	640	15-20	96-128	(112)
Former socialist economies	330	20-25	66-83	(75)
India	535	0.5-1.0	3-7	(5)
China	825	0.5-1.0	4-8	(6)
Other Asia and islands	430	1-3	4-12	(8)
Sub-Saharan Africa	276	0.5-1.0	1-3	(2)
Latin America and Caribbean	280	5-10	14-28	(21)
Middle Eastern Crescent	300	5-10	15-30	(22)
World	3616			(251)

Information taken from Seidell (2000) and the population sizes and regions from Murray and Lopez, (1996).

Best estimates suggest that there are approximately 250 million obese adults worldwide - this is about 7% of the global population (Seidell, 2000). The global prevalence of overweight, defined as a BMI between 25 and 30 $kg.m^{-2}$, is two or three times greater than the prevalence of obesity (Seidell, 2000).

In the UK, the prevalence of obesity (BMI $\geq$ 30.0 $kg.m^{-2}$) has also increased dramatically. From 1980 to 1996, the proportion of obese women increased from 8 to 18%. During the same period, the proportion of men who were classified as obese rose from 6 to 16% (Fehily, 2000).

The WHO MONICA project has recently provided data on global obesity prevalence using waist girth cut-off points (Molarius *et al.*, 1999). This study has shown a marked variation in the prevalence of obesity in different regions. For example, using a waist girth of 102 cm as the cut-off point for the classification of obesity, the prevalence of obese men in Beijing, China was only about 4%. In rural

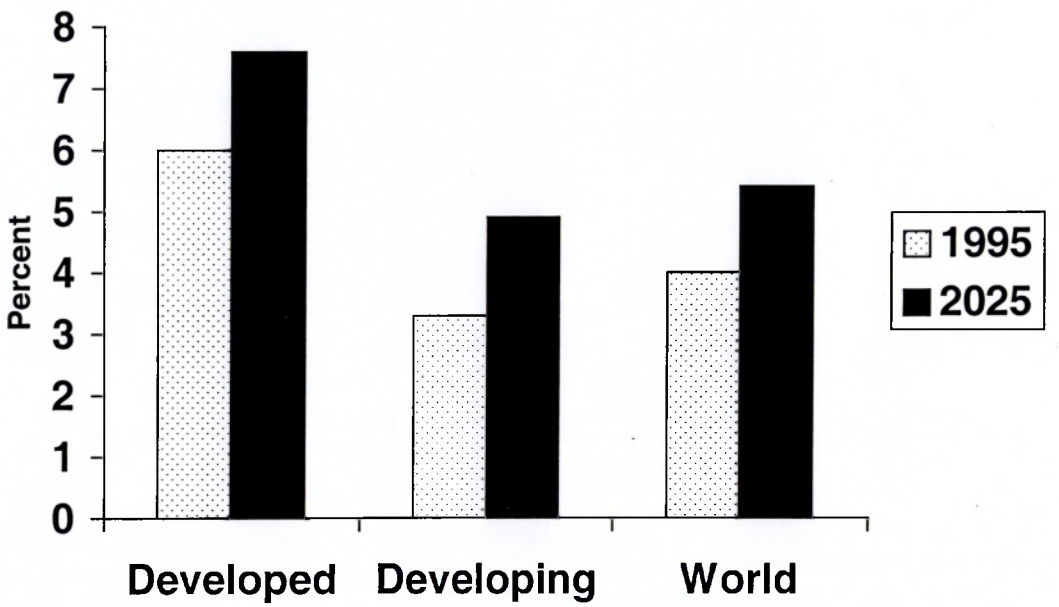
Czech Republic this value is about 32% and Glasgow, Scotland about 22%. This waist girth criteria also results in a higher obesity prevalence than using BMI $\geq$ 30.0 $kg.m^{-2}$, because it also includes some men in the overweight category (Seidell, 2000). In women, the prevalence of abdominal obesity (waist girth $\geq$ 88 cm) in the USA has recently been reported to be about 43%, 56% and 55% in White, Black and Hispanic groups respectively (Okosun *et al.*, 1999). For men, corresponding figures using a waist girth cut-off point of $\geq$ 102 cm were approximately 27%, 20% and 21%.

Whilst the aetiology of type 2 diabetes as it relates to obesity and fat distribution will be reviewed in Chapter 2, an outline of its frequency is appropriate at this point, because the increased prevalence of this disease closely resembles the increase in obesity prevalence.

Data from the Behavioural Risk Factor Surveillance System (BRFSS) have recently shown that the prevalence of diabetes in the USA increased from 4.9 to 6.5% between 1990 and 1998 (Mokdad *et al.*, 2000). This increase in diabetes frequency appears to be a characteristic of all age, sex and ethnic groups (Mokdad *et al.*, 2000; Burke *et al.*, 1999).

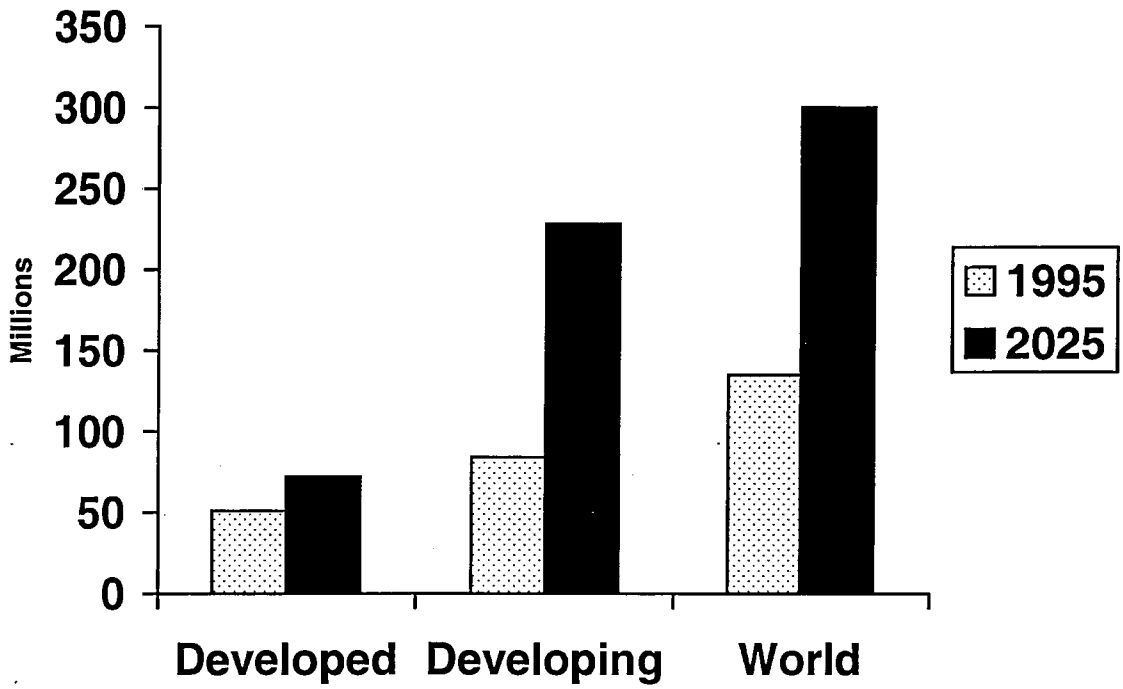
Figure 1 (1.2), shows the global prevalence of diabetes in 1995 and projected estimates for the year 2025 in adults aged $\geq$ 20 years (King *et al.*, 1998). These projections are based on the expected expansion of the world's population in developed and developing economies. Developed economies include all European and North American Nations, Australia, New Zealand and Japan. Developing economies represents all other countries. Between 1995 and 2025, it is estimated that there will be an increased global prevalence of diabetes of 35%. In developed countries the increased prevalence will be 27% and in developing countries the increase will be 48%.

Figure 1 (1.2). Global prevalence of diabetes by world region in 1995 and projected estimates in 2025. (Adapted from King et al. 1998).



The number of people diagnosed with diabetes in 1995 and the projected estimate in 2025 is shown in Figure 2 (1.2). The number of adults with diabetes in the world is estimated to increase by 122%, from 135 million in 1995 to 300 million in 2025. In the developed countries, there will be a 42% increase - from 51 to 72 million. In the developing countries, the increase will be 170%. An increase from 84 to 228 million (King *et al.*, 1998).

Figure 2 (1.2). Number of people with diabetes by world region in 1995 and projected estimates in 2025. (Adapted from King et al., 1998).



These trends for obesity and type 2 diabetes are of obvious personal and economic concern. Type 2 diabetes is the sixth leading cause of death, and accounts for nearly 95% of all diabetes in the USA (Kriska *et al.*, 1993). With treatment costs exceeding $1 billion each year, the increasing prevalence of type 2 diabetes is one of the major health issues of current times. Data from the first National Health and Nutrition Examination Survey (NHANES I) and the NHANES I Epidemiologic Follow-up Survey have recently shown that, since 1970, coronary heart disease (CHD) mortality has fallen by 36% and 27% in non-diabetic males and females respectively. However, for diabetic males there has been a decline of only 13%, and for diabetic females, there has actually been an increase in CHD mortality of 23% (Gu *et al.*, 1999).

In the USA in 1995, obesity-related medical complications were estimated to have cost approximately $52 billion. Approximately $32 billion was attributable to diabetes (Wolf and Colditz, 1998). The estimated annual number of deaths in the USA attributed to obesity is about 300,000 (Allison *et al.*, 1999; Calle *et al.*, 1999).

1.3 RECENT AND FUTURE TRENDS IN CARDIOVASCULAR DISEASE

Despite continuing to be the leading cause of morbidity and mortality in modern industrialised nations, CVD death rates have declined over the past 30 years in many developed countries (Ounpuu *et al.*, 2001). In developing countries, the opposite has been the case, where CVD mortality rates have increased (Ounpuu *et al.*, 2001). The incidence of coronary artery disease (CAD), the most prevalent cardiovascular disease has also declined during recent decades since its peak in the 1960's (Rosamund *et al.*, 1998; Goldberg *et al.* 1999). Globally, however, it is anticipated that between the years 1990 and 2020 morbidity and mortality rates from CAD will more than double (Ounpuu *et al.*, 2001). About 82% of the increase in mortality and 89% of the anticipated increase in morbidity will be seen in developing countries (Murray and Lopez, 1996).

The close association between diabetes and CVD suggests that current predictions of a large increase in the prevalence of type 2 diabetes may well precede a large increase in CVD (James, 2001). Some evidence for this is already available. Hu *et al.* (2000) have recently reported that an increase in BMI among 85,941 females explained an 8% increase in CHD, whilst decreases in cigarette smoking, an improvement in diet and an increase in postmenopausal hormone use explained decreases in CHD of 13%, 16% and 9% respectively. Table I (1.3) below, adapted

from Ounpuu *et al.* (2001) gives the estimated rates of global CAD based on demographic changes and the future effects of current cigarette smoking patterns. In the established market economies of Europe, North America, Japan and Australasia this increase in CAD mortality is equal to a 46% increase in men and a 32% increase in women from 1990 to 2020.

Table I (1.3). Regional differences in the burden of CAD by sex and projected estimates for the future.

Region	Population estimates			
	Total number of men 1990/2020 (millions)	Total number of women 1990/2020 (millions)	CAD prevalence in men 1990/2020 (x 100,000)	CAD prevalence in women 1990/2020 (x 100, 000)
Established market economies	390/434	407/455	8.3/12.1	8.4/11.1
Former socialist economies	165/170	181/191	4.7/7.1	5.6/7.0
India	439/608	410/589	6.2/14.1	5.6/12.0
China	585/727	548/721	3.9/8.1	3.8/6.8
Other Asia and islands	343/497	340/505	2.3/5.8	2.3/5.5
Sub-Saharan Africa	252/555	258/565	0.9/2.2	1.2/2.6
Latin America and Caribbean	222/331	223/336	1.8/4.4	1.7/4.1
Middle Eastern Crescent	256/496	247/487	3.2/8.7	2.9/7.2
World	2654/3819	2614/3848	31.3/62.6	31.3/56.3

From Ounpuu *et al.* (2001)

1.4 PHYSIQUE AND CORONARY ARTERY DISEASE

1.4.1 Obesity and fat distribution

The association between physique and CAD morbidity and mortality has been studied extensively over several decades. Many of these studies have been reviewed recently (Williams *et al.*, 1997). Methods employed in these studies to characterise physique

include body weight and height, weight-for-height, relative weight, body composition, adipose tissue distribution and somatotype. Vague (1947) was the first to suggest that an obesity phenotype characterised by an accumulation of fat in the abdominal region confers the greatest risk of CAD. Several prospective and case-control studies, using the WHR or some other simple anthropometric indicator of AT distribution, have since confirmed this finding (Larsson *et al.*, 1984; Casassus *et al.*, 1992; Hauner *et al.*, 1990; Kahn *et al.*, 1996; Thompson *et al.*, 1991), although there are studies reporting contrary results (Hodgson *et al.*, 1994; Flynn *et al.*, 1993; Hartz *et al.*, 1990).

The distribution of subcutaneous AT, and torso skinfold thickness, have also been shown to be predictors of CAD (Ducimetiere *et al.*, 1986; Donahue *et al.*, 1987; Hargreaves *et al.*, 1992; Stokes *et al.*, 1985; Freedman *et al.*, 1995). However, only one study has previously examined skinfold thickness in relation to angiographically-determined CAD (Hodgson *et al.*, 1994).

Data from large-scale studies of British and Japanese adults suggest that the ratio of waist circumference-to-height is the most powerful anthropometric predictor of mortality (Cox *et al.*, 1996) and CAD risk factors (Hsieh and Yoshinaga, 1995). Although Ashwell *et al.* (1996a) have supported these claims, and suggested that this ratio is a better predictor of IAF than waist circumference alone (Ashwell *et al.*, 1996b), others have disagreed (Han *et al.*, 1996b; Han *et al.*, 1997).

Most ratios aim to control for the confounding influence of the denominator. In the case of the waist-to-height ratio the aim is to control for differences in stature. This ratio has been used to address the question of whether it is the absolute waist girth, or the relative size of the waist girth to height, that is the best predictor of cardiovascular morbidity and mortality. As discussed recently, however, ratios present problems with regard to their interpretation (Molarius and Seidell, 1998) and also in

their use in statistical analyses (Allison *et al.*, 1995). For example, a large waist-to-height ratio, may result from a large waist circumference or alternatively to short stature. As height is inversely related to the risk of CAD (Hebert *et al.*, 1993) this makes it difficult to separate risk associated with increased waist girth from risk associated with shorter stature.

Proportionality refers to the relationship of body parts to one another or to the whole body (Ross and Marfell-Jones, 1991) and provides an alternative approach to the study of fat distribution in CAD that avoids the use of ratios. This approach was devised by Ross and Wilson (1974) and is based on the concept of a theoretical unisex, bilateral reference human (a Phantom) which can be used to proportionally adjust anthropometric measurements to a given body size. The Phantom is not a normative system but a calculation device based on the geometrically-adjusted means (adjusted to the Phantom stature, 170.18 cm) and standard deviations of large samples. Any anthropometric measurement can be geometrically-scaled and expressed as a *z*-value (interpreted as a SD) or proportionality score.

No study has previously used this approach to consider the proportional size of skinfolds and girth measurements in patients with CAD, although several investigators have considered this issue in relation to athletic performance (Ross and Ward, 1984; Soval *et al.*, 1992; DeRose *et al.*, 1989). Furthermore, the proportional size of skinfolds and abdominal girth measurements has not been examined in relation to the metabolic component of health-related fitness. This component, termed "metabolic fitness" by Bouchard and Shephard (1993) includes factors such as fasting and postprandial glucose and lipids.

1.4.2 Somatotype

The somatotype is a classification of human physique based on the concept of body shape independent of size (Carter and Heath, 1990). In the somatotype, body-shape is expressed as a series of three numbers each representing a particular component. These are always recorded together and in the same order. The first figure represents a rating of endomorphy, the second mesomorphy, and the third ectomorphy (Carter and Heath ,1990). Dominant in the early development of somatotype methodology was the work of Sheldon *et al.* (1940), in which ratings began at zero and had a fixed upper point of seven. More recently, the method developed originally by Heath and Carter (1967) has predominated. This method uses much of Sheldon's original vocabulary, although some of the fundamental ideas have been revised. A detailed description of this method has been provided recently (Carter and Heath, 1990). Briefly, Heath-Carter somatotype classifications can be obtained either by inspection of a standard somatotype photograph, from a series of anthropometric measurements, or preferably, from a combination of photographic inspection and anthropometric measurements (Carter and Heath, 1990). A physique attributed a high endomorphy rating is characterised by a large subcutaneous fat deposit, or noticeable relative fatness. High ratings in mesomorphy signify a large musculature and bone mass relative to stature. High ratings in ectomorphy describe a physique with little mass relative to stature and relatively elongated limb segments (Carter and Heath, 1990). Component ratings still begin theoretically at zero but have no fixed upper-end points. In general, component ratings of 0.5 to 2.5 are regarded as low, 3 to 5 as midrange, 5.5 to 7 as high and greater than 7 extremely high. Thus, the classification 7 - 1 - 1 represents an extreme endomorph, 1 - 7 - 1 represents an extreme mesomorph and 1 - 1 - 7 an extreme ectomorph. A 3 - 3 - 3 or 4 - 4 - 4 classification represents a central or balanced

somatotype, 4 - 5 - 1 an endomorphic-mesomorph and 2 - 3 - 5 a mesomorphic-ectomorph. Extreme examples for each of these components would be an obese individual (endomorphy), a body-builder (mesomorphy) and the Nilote people of Sudan who exhibit extreme ectomorphy (Carter and Heath, 1990).

The association between somatotype and CHD received some attention several decades ago but has not been studied extensively (Gertler *et al.*, 1950, 1951, 1967; Spain *et al.*, 1953, 1955, 1963; Paul *et al.*, 1963; Damon 1965; Damon *et al.*, 1969). The majority of these studies have indicated that most of the cardiac cases examined have been dominant in mesomorphy with endomorphy the secondary characteristic. However, these studies as well as now being somewhat dated, were limited by a number of features including the subjectivity of the somatotype method (Sheldon *et al.*, 1940), the failure to account for confounding variables and consideration of the somatotype as a Gestalt. The recent developments in somatotype methodology by Carter and Heath (1990) and somatotype data analysis (Carter *et al.*, 1983; Cressie *et al.*, 1986), together with a greater knowledge and understanding of CHD risk factors should enable these limitations to be overcome. The only researchers to have studied CHD in relation to Heath-Carter anthropometric somatotypes are Smit *et al.* (1979). To date, no data have been available on the somatotypes of men with angiographically-determined atherosclerotic CAD. Also, no mention has been given to the relationship between somatotype and fat distribution in men with CHD, although men with an android fat distribution have been found to be more mesomorphic and less endomorphic than men with a gynoid fat distribution (Mueller and Joos, 1985).

The most likely explanation of a link between somatotype and CAD will be provided by an examination of cardiovascular risk factors. In adults, Gertler *et al.*

(1950), Tanner (1951), Gordon *et al.* (1987) and Malina *et al.* (1997) have previously examined the association between somatotype and blood lipids and lipoproteins. Fredman (1972) studied somatotype and glycaemic status in a group of Tamil diabetics and Malina *et al.* (1997) also examined glucose and blood pressure in healthy adults. Only the studies by Gordon *et al.* (1987) and Malina *et al.* (1997) used the somatotype methodology of Carter and Heath (1990). This technique predominates today and is generally preferred because of the objectiveness provided by the anthropometric measurements on which it is based. Katzmarzyk *et al.* (1998) used this method in a study of somatotype and metabolic fitness in boys and girls aged 9-18 years from the Quebec Family Study. Results suggested that a physique characterised by high endomorphy and mesomorphy ratings is associated with a metabolic fitness profile that predisposes to increased CAD risk. The study of Malina *et al.* (1997) was exclusive to adults of French-Canadian ancestry and suggested that somatotype was only weakly associated with metabolic risk-factors. However, it was clear that a poor risk-factor profile was more likely in individuals who had higher ratings of endomorphy and mesomorphy and a low ectomorphy rating. Therefore, additional studies are required to further elucidate the significance of somatotype in relation to both CAD and metabolic fitness.

1.5 INVESTIGATIVE AIMS, RESEARCH QUESTIONS AND ORGANISATION OF THE THESIS

Data presented in this thesis were gathered on two occasions between the months of May and August. On the first occasion, men undergoing coronary angiography in the Department of Cardiology, University Hospital of Wales were examined over a three-

month period. Approximately one-year later, a control group of apparently healthy, male, university employees were examined over a period of several weeks. The data collected allowed the research questions outlined in Sections 1.5.1 and 1.5.2 to be addressed. These studies form the general theme of this thesis, which is an exploration of the relationship between physique, CAD and CAD risk-factors in men. They have been grouped into two main categories, one focusing on the significance of obesity and AT distribution, the other on somatotype. The numerical order in which these studies are presented is a logical sequence beginning with a description of the anthropometric characteristics of men with CAD, and culminating with an examination of risk-factor associations with the anthropometric measurements.

In Chapter 4 of this thesis, the results and discussions of the studies focusing on obesity and AT distribution are presented in the order of the research questions that follow. Chapter 5 performs the same function for studies focusing on somatotype. These chapters are preceded by a Review of Literature (Chapter 2) and Methodology (Chapter 3). The Review of Literature has been sub-divided into three distinct sub-sections. The first of these sub-sections (Section 2.1) reviews the relationship between "body habitus" and CAD in men. The term "body habitus"' has been used to describe physique in terms of its size, shape and composition. Section 2.2 examines the validity of assessing abdominal obesity using anthropometric measurements. Section 2.3 examines the relationship between obesity, AT distribution and several established risk factors for CAD. As the literature in this area is very extensive, where possible the review has been restricted to studies of men. However, where a study has been performed using female subjects or animals, and it has made a significant contribution to our understanding of this area, it has been included.

The methods outlined in Chapter 3 are common for all studies presented in this thesis. Within the statistical analysis sub-section (3.7), reference is given to the study where these procedures were applied.

Chapter 6 - the concluding chapter - presents a summary of the findings of all of the studies contained within this thesis, conclusions and recommendations for further investigations.

Finally, even though it results in the duplication of some references, a bibliography of the literature cited in each chapter is given at the end of that chapter.

1.5.1 Research Questions: Studies Focusing on Obesity and Adipose Tissue Distribution

Study 1. Are simple anthropometric measures of obesity and adipose tissue distribution related to left ventricular function and the severity of atherosclerotic CAD determined using coronary angiography?

Study 2. Are men with CAD characterised by a specific subcutaneous adipose tissue pattern that can be identified with principal component analysis?

Study 3. Are there differences in anthropometric indices of obesity and adipose tissue distribution between men with CAD and healthy age-matched controls and what is the effect of adjusting for body size differences?

Study 4. Are anthropometric indices of obesity and adipose tissue distribution related to fasting serum glucose and lipids? Which anthropometric measurement is the best discriminator of differences in glucose and lipids? Does adjusting for body size

variation, modify the relationship between obesity, adipose tissue distribution, glucose and lipids?

Results of these studies are presented in Chapter 4, sections 4.1, 4.2, 4.3 and 4.4 respectively.

1.5.2 Research Questions: Studies Focusing on Somatotype

Study 1. What is the somatotype of men with angiographically-determined CAD? Is somatotype related to CAD severity and left ventricular function? Is somatotype related to adipose tissue distribution in men with CAD?

Study 2. Is there a difference in the somatotype of men with CAD and healthy, age-matched controls?

Study 3. Is there an association between somatotype and fasting serum glucose and lipid concentrations?

Results of these studies are presented in Chapter 5, sections 5.1, 5.2 and 5.3 respectively.

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CHAPTER 2

REVIEW OF LITERATURE

2.1 BODY HABITUS AND CORONARY ARTERY DISEASE IN MEN

2.1 BODY HABITUS AND CORONARY ARTERY DISEASE IN MEN

During the last several decades, a great deal of attention has been focused on the identification of potentially modifiable biological, physiological and biochemical risk factors (Leon, 1987) that place the individual at an increased risk of developing atheromatous lesions in the coronary blood vessels. The degree of overweight and obesity are two possible risk factors that have attracted a great deal of research attention in men. Height has also been studied as a potential marker for ischaemic CAD. Despite this abundance of information, contrasting findings suggest that the exact position of overweight or obesity in the aetiology of CAD remains unclear. One possible explanation for this disparity is that the measurement techniques employed do not satisfactorily estimate body fatness. More recent evidence suggests that these inconsistencies can also be partly explained by the distribution of body fat. As the metabolic complications associated with excess body fat may require a prolonged period of time before their effect on cardiovascular disease mortality is observable, the duration of the obese state may also be an important factor in explaining these inconsistencies (Bjorntorp, 1985).

The focus of this part of the Review of Literature is the association between human body habitus and atherosclerotic CAD. The terms cardiovascular disease (CVD), coronary heart disease (CHD), coronary artery disease (CAD) and ischaemic heart disease (IHD) are not used interchangeably, rather, no attempt has been made to alter the terminology adopted by the original research. Commentary is made on the wide variety of both simple and more complex methods that have been used to assess body habitus. The term body habitus has been chosen to incorporate a number of distinct physical bodily characteristics. These include body weight and height, weight-for-height, relative weight, total body fat, fat distribution, subcutaneous fat pattern and

somatotype. Body weight and height are the simplest, most accessible measurements of body size and are generally reliable with small technical errors of measurement (Micozzi *et al.* 1986). Thus, they have become important and extensively used epidemiological research tools. However, it is clear they cannot provide information on body composition. To overcome this limitation, there has been continued interest in the development of valid and reliable body composition estimators such as relative weight scores or weight-for-height indices. These have been the most extensively used indicators of overweight. CAD mortality and morbidity rates have also been examined in a variety of ways, including the analysis of hospital and physicians records, self-reporting of coronary events, information from the next of kin, post-mortem findings, death certificates and recently coronary angiography. These factors, coupled with varying lengths of subject follow-up, contrasting statistical analysis and socio-economic, ethnic and risk factor variation between subjects from different studies, make interpretation of the vast amount of available literature difficult.

2.1.1 Body weight and height

(a) prospective studies

Amongst the earliest investigations of an association between CHD, body weight and height are the classic studies of Harvard and Pennsylvania University students (Paffenbarger *et al.*, 1966a, 1966b). They found that for later coronary decedents, body weight at initial examination was greater than controls. This study also found that compared to controls, a greater percentage of coronary decedents were less than 68 inches tall (32 v 22 %, $P < 0.001$).

An increased incidence of IHD was reported for shorter London transport workers (height range 151 to 167 cm) compared to their taller counterparts ($P < 0.1$)

(Morris *et al.*, 1966). A study of 17530 London office workers reported an inverse relationship between height and IHD after 7.5- and 10-years follow-up following multivariate adjustment for age and grade of employment (Marmot *et al.*, 1978; 1984). Further research of nearly 18000 civil servants discovered the highest IHD incidence rate was for subjects shorter than 5 feet 5 inches (165.1 cm) (Morris *et al.*, 1980).

A 16-year prospective study of almost 1.8 million Norwegians (approximately 900,000 men) found CVD mortality was clearly reduced for those who were taller (Waaler, 1984). For males shorter than 160 cm, CVD mortality was 50 to 100% greater than the total. For those between 185 and 189 cm, however, CVD mortality was only 70 to 80% of the total mortality.

The British Regional Heart Study of 7735 middle-aged men demonstrated a similar finding (Walker *et al.*, 1989). The mean height of subjects who suffered an IHD event (n = 443) was significantly lower than the height of the remaining subjects (171.7 v 173.3 cm, $P < 0.001$). Adjustment for age, social class, serum TC, HDL-C, systolic blood pressure and cigarette smoking weakened the association by over 50%. As height and lung function (forced expiratory volume in one second, FEV_1) were closely correlated ($r = 0.44$, $P < 0.002$), and lung function is associated with IHD (Cook and Shaper, 1988), FEV_1 was added to the multivariate model. The addition of lung function alone ($P = 0.25$) or in combination with other confounding variables ($P = 0.70$) further weakened the relationship.

The height and IHD relationship has been reported for 2512 South Wales men (Caerphilly cohort) and 2348 men from the West of England (Speedwell cohort) (Yarnell *et al.*, 1992). After just 61- and 38-months follow-up respectively, significant inverse trends were found between height and the number of IHD events (both fatal

and non-fatal) in the Caerphilly ($P < 0.001$) and Speedwell ($P < 0.05$) cohorts. In comparison to men in the tallest 20% of the height distribution, men in the shortest 20% suffered more than double the IHD events. Adjustment for age, social class, smoking habit and FEV_1 in the Caerphilly cohort, weakened the relationship ($P < 0.05$).

After 26-years follow-up of a select cohort of almost 4000 North American male airline pilots, body weight was significantly greater (76.5 ± 0.5 v 74.2 ± 0.2 kg, $P < 0.01$) and height shorter (175.8 ± 0.3 v 176.9 ± 0.1 cm, $P < 0.01$) in subjects who developed CHD (Rabkin *et al.*, 1977).

Hebert *et al.* (1993) found that among a population of 22,071 US male physicians, the relative risk of myocardial infarction was 35% lower in the tallest men (> 73 inches or 185.4 cm) compared to the shortest men (< 67 inches or 170.2 cm). Although the inverse relationship between height and myocardial infarction risk was not strictly linear, for every inch of added height, there was an approximate 2 to 3 % reduction in risk.

In a more recent but short-term study (3-year follow-up) of almost 30,000 US men, Rimm *et al.* (1995) found that, in comparison to men whose height was < 68.0 inches (173 cm), the multivariate relative risk of CHD decreased steadily with increasing stature. The relative risk in the highest quintile for height (> 73.0 inches or 186.0 cm) was 0.67 (95% confidence intervals (CI) 0.48-0.93).

In a study that adjusted for age, obesity, smoking status, HDL-C, TC, hypertension, diabetes and education, Parker *et al.* (1998) have recently reported a strong inverse association between height, CHD and stroke. In this study, men taller than 69.75 inches had an 83% lower risk of CHD compared to men shorter than 65 inches.

Post-mortem findings of 71 decedents from the Framingham Study revealed that body weight 1- and 9-years before death independently predicted left ventricular thickness (Feinleib *et al.*, 1979). Height and body weight measured 5-years before death had inverse and positive associations with heart weight respectively.

(b) case-control studies

Gertler and co-workers (1951) found that men hospitalised with myocardial infarction were approximately 5.0 cm shorter and 3 kg heavier than control subjects. Later analysis found height to be second only to TC as a predictor of CHD although cigarette smoking was not considered (Gertler *et al.*, 1959).

(c) angiography studies

The use of coronary angiography to group subjects into those with significant (> 50% stenosis in one, two or three coronary vessels) or insignificant arterial disease (a normal angiogram or < 50% stenosis), has recently shown a non-significant association ($P > 0.05$) between body weight and disease status (Flynn *et al.*, 1993). Height and CAD exhibited a significant inverse relationship following univariate ($P < 0.01$) and multivariate analysis ($P < 0.05$).

Hauner *et al.* (1990) found that height was significantly shorter ($P < 0.01$) and weight greater ($P < 0.05$) in subjects with CAD and a history of myocardial infarction compared to men free of CAD. In a further angiography study, there was no difference in height and weight between normal men and men with CAD (Ley *et al.*, 1994).

(d) evaluation of body weight and height as predictors of CHD

A number of possible explanations have been proposed to give the inverse relationship between height and CHD a biological basis. As suggested, multicollinearity with lung function as a confounding variable may be one explanation. Inadequate pre-natal, infant and childhood nutrition and the occurrence of illness during the growing years may partly account for some cases of shorter attained adult stature. It is plausible that these factors may also directly affect pulmonary development and, therefore, explain the association between height and lung function. Based on findings from a large number of studies, Barker has suggested that undernutrition of the foetus can lead to permanent changes in structure, physiology and metabolism that predispose to elevated fibrinogen and factor VII, non-insulin dependent diabetes, hypertension, hyperlipidaemia and, therefore, to an increased risk of CVD (Barker, 1994). Stern (1996) has supported this hypothesis by suggesting that non-insulin dependent diabetes mellitus and CVD share common genetic and environmental antecedents, including foetal and early life nutritional deficiencies. Inverse relationships between height and TC, HDL-C, systolic blood pressure and smoking duration have also been reported (Walker *et al.*, 1989). Correlation coefficients are weak, however ($r = -0.04$ to -0.11, $P < 0.002$), and are significant due to the large sample size.

A further possible biological mechanism is that taller individuals have larger coronary arteries than shorter individuals and, therefore, have a lessened risk of occlusion (Palmer *et al.*, 1990). Support for this mechanism can be derived from studies that have found a higher rate of post coronary by-pass surgery mortality in shorter individuals compared to taller individuals (Loop *et al.*, 1983; Fisher *et al.*, 1982).

Results from studies examining the CHD relationship with body weight are inconclusive. In the Manitoba study (Rabkin *et al.*, 1977), the mean body weight of the CHD subjects (76.5 ± 0.5 kg) was only moderate, and although significant, differed from the body weight of subjects free of CHD by only about 2.0 kg. The striking similarity in the body weight of subjects with significant (77.4 ± 9.6 kg) and insignificant (77.8 ± 11.3 kg) arterial disease (Flynn *et al.*, 1993) may be partly accounted for by the insensitivity of the disease classification criteria used. Of interest would be a comparison of the mean body weight of asymptomatic subjects and those with evidence of extreme arterial disease. Contrary to this theory, however, no difference was found in the height and weight of men free from CAD when compared to men with angina and an angiogram showing greater than 50 % luminal narrowing (Ley *et al.*, 1994).

From the limited amount of research, it appears that body weight, *per se*, is not as strong a predictor of CVD as height, although the underlying biological mechanism linking height and CVD remains to be firmly established.

2.1.2 Weight-for-height ratios

Complex laboratory methods for estimating body composition are inappropriate for large-scale surveys. The simplicity of measurement and availability of normative data have, therefore, contributed to the widespread use of weight-for-height ratios (W/H^p). The power function (p) should be calculated so that the index is highly correlated with body weight and fatness but be independent of height. The most widely used weight-for-height ratio is BMI. Other ratios that have been applied in epidemiological studies include W/H (Carlson *et al.*, 1972) and Sheldon's (1940) ponderal index ($H/W^{-0.33}$) (Paffenbarger *et al.*, 1966a, 1966b; Weinsier *et al.*, 1976).

(a) prospective studies

A number of large-scale population studies examining the association between BMI and CHD have been performed in both North America and Europe. Jooste and co-workers (1988) have examined this relationship in 7188 white South Africans. Data gathered in these studies have produced inconsistent findings.

Dyer *et al.* (1975) found that a U-shaped curve described the relationship between BMI and CHD mortality in 1233 white middle-aged North American men followed for 14-years. Rhoads and Kagan (1983) reported this phenomenon in 8006 men aged 45- to 68-years who were subsequently followed for 10-years as part of the Honolulu Heart Program. In this latter study, excess deaths amongst those in the lower BMI category were due primarily to cancer and in the upper BMI groups to CHD. In South Africa, the incidence of CHD in relation to BMI was greater in both the lowest (BMI < 20 kg.m^{-2}) ($P > 0.05$) and highest (BMI 30-35 and > 35 kg.m^{-2}) ($P < 0.01$) BMI categories (Jooste *et al.*, 1988).

Conversely, a number of studies with varying lengths of follow-up (5-26 years) have shown little or no association between BMI and CHD. Keys *et al.* (1971) reported no association between CHD and a variety of physical measurements (including BMI) in their 23-year study of Minnesota Executives. Similar findings were observed after a 5-year investigation of 11400 men from Northern and Southern Europe and North America (Minnesota Railroad Workers) (Keys *et al.*, 1972). Despite an excessive incidence of CHD in overweight subjects, after the confounding effects of age, blood pressure, TC and smoking were removed, the contribution of BMI to this trend was not significant ($P > 0.05$). After 15-years follow-up there was still no relationship (Keys *et al.*, 1984).

In a further multivariate model, with age, TC, triglyceride (TG), systolic blood pressure, cigarette smoking, presence of diabetes and a fat distribution index entered as covariates, BMI was not a predictor of CHD ($P > 0.05$) (Ducimetiere *et al.*, 1986). The Stockholm prospective study of 3168 men identified smoking and elevated levels of plasma TC and TG as independent risk factors for IHD but not the index W/H (Carlson and Bottiger, 1972). Further Scandinavian research found no association ($P > 0.05$) between BMI and the 13-year incidence of IHD, stroke and death (Larsson *et al.*, 1984).

After adjustment for subscapular skinfold thickness, the independent effect of BMI on either non-fatal myocardial infarction or death from CHD was not significant ($P > 0.05$) after 12-years follow-up in the Honolulu Heart Program (Donahue *et al.*, 1987).

Hargreaves *et al.* (1992) reported that, of an original random sample of 107 Edinburgh men, 11 developed clinical CHD over the subsequent 12-year period. Examination of baseline data revealed the BMI of CHD men (26.7 ± 0.8 kg.m^{-2}) was greater ($P < 0.05$) than the men who remained free of the disease (24.9 ± 0.3 kg.m^{-2}) (values are means $\pm$ SEM.). Other risk factors (TC, TG, diastolic blood pressure and indices of glucose-insulin homeostasis) were not significantly different ($P > 0.05$). However, following adjustment for HDL-C, which was lower in CHD patients ($P < 0.05$), BMI was no longer a significant risk factor ($P > 0.05$).

Recently, researchers from the Paris Prospective Study found increasing BMI was modestly associated with CVD in subjects with a mean blood pressure less than 96 mmHg, but had no effect in men with higher blood pressure ($\geq$ 96 mmHg) (Filipovsky *et al.*, 1993).

In a few instances, large-scale prospective studies have reported a significant independent relationship between BMI and CHD. After adjustment for age and blood pressure, BMI was found to be a significant independent predictor of sudden death ($P < 0.01$), coronary insufficiency or suspected myocardial infarction ($P < 0.05$) and myocardial infarction ($P < 0.05$) (Rabkin *et al.*, 1977).

A 7-year follow-up of 3786 men in eastern Finland found men with a BMI of 28.5 $kg.m^{-2}$ or more, experienced a significantly greater incidence of acute myocardial infarction ($P < 0.05$) (Tuomilehto *et al.*, 1987). This effect was independent of age and smoking but not other major coronary risk factors (TC and blood pressure).

In the Framingham cohort, standardised logistic regression analysis controlling the effects of age, serum TC, cigarette smoking, systolic blood pressure, blood glucose and ECG evidence of left ventricular hypertrophy demonstrated a significant ($P < 0.05$) positive influence of BMI on the 22-year incidence of CHD (Stokes III *et al.*, 1985).

Galanis *et al.* (1998) examined the 17-year incidence of CHD events in relation to BMI at 25-years of age after adjusting for the effects of age, smoking and weight change. The relative risk between the lowest and highest categories of BMI was 2.44 (95% CI 1.6 - 3.69). In comparison to men who gained less than 2.5 kg, men who gained between 2.6 kg and 5 kg, between 5.1 kg and 10 kg, or more than 10 kg had relative risks of CHD of 1.41 (95% CI 1.00-1.97), 1.60 (95% CI 1.22-2.11) and 1.75 (95% CI 1.32-2.33) respectively. After adjusting for Vitamin E, age, smoking, calories consumed, alcohol intake, family history and occupation, Rimm *et al.* (1995) reported a similar finding in men less than 65-years of age in the US Health Professionals Study. In older men (> 65-years) the association was much weaker. This study was also notable for showing that moderate levels of overweight (BMI between

25.0 and 28.9 $kg.m^{-2}$) resulted in a 72% increased risk of CHD after only 3-years of follow-up. In one of the longest follow-up studies of its kind (27-years), Lee *et al.* (1993) also found a significant positive trend (P = 0.0003) between the relative risk of CVD mortality and BMI. The lowest relative risk was for men in the BMI category < 22.5 $kg.m^{-2}$. In the next quintile (BMI 22.5 - 23.5 $kg.m^{-2}$) the relative risk increased to 2.02, and in the highest quintile (BMI > 26.0 $kg.m^{-2}$) to 2.54. This study suggested that the lowest mortality risk is observed among men weighing, on average, 20% less than the US average. In the UK (Shaper *et al.*, 1997) and California (Lindsted and Singh, 1998) similar findings have been reported. Shaper *et al.* (1997) suggested that risk of cardiovascular death, heart attack and diabetes increases progressively from a BMI of < 20.0 $kg.m^{-2}$, even after adjusting for age, smoking, social class, alcohol consumption and physical activity. Lindsted and Singh (1998) studied 5062 Seventh-day Adventists who had never smoked. The lowest risk of cardiovascular mortality was for men with a BMI in the range 14.3 to 22.5 $kg.m^{-2}$.

The validity of these findings, however, has been recently questioned by a study of 21,856 men who also underwent a treadmill exercise test to evaluate cardiorespiratory fitness (Lee *et al.*, 1998). In each BMI category, unfit men had a significantly higher relative risk of cardiovascular and all-cause mortality than fit men. This suggests that fitness offers some protection against the health impairment(s) of overweight, and that weight guidelines based on BMI may be misleading unless fitness is also considered.

(b) angiography studies

Recent results from the Honolulu Heart Program have shown BMI to be a significant predictor of both arteriographically-diagnosed severe coronary stenosis and incident

myocardial infarction after 20-years follow-up of 357 men (Reed and Yano, 1991). However, further recent angiography studies that provided similar results, conflict with these later findings from the Honolulu Program. BMI was not related ($P = 0.197$) to CAD in 286 men following stepwise logistic regression analysis (Hauner *et al.*, 1990). Chi-square analysis also revealed no difference ($P > 0.05$) in the BMI of men with CAD (> 30% stenosis), men with CAD plus a history of myocardial infarction, and men without CAD.

Flynn and her colleagues (1993) found no relationship ($P > 0.05$) between CAD and BMI. Other weight-for height indices, including the risk index of body build [W (kg)/H $(m)^{2.2}$], adipose tissue index [0.75 $(W/H^{0.35})$-21.4] and body fat index [0.72 $(W/H^{0.40})$-23.5] also showed no correlation with CAD ($P > 0.05$) (Sjostrom, 1987). Hodgson and co-workers (1994) applied different scoring systems to quantify an extent score (proportion of coronary endothelial surface area affected by atheroma) (Sullivan *et al.*, 1990) and a myocardial score (degree of stenosis of any number of arterial branches) (Brandt *et al.*, 1977) in 160 men and 66 women undergoing cardiac catheterisation. Spearman's rank correlation coefficients between BMI, extent score and myocardial score were not significant ($P > 0.05$) for men or women.

Ley *et al.* (1994) reported non-significant differences ($P > 0.05$) for the BMI of middle-aged men free of CAD (24.5 ± 0.3 $kg.m^{-2}$), men with angina but a normal angiogram (25.1 ± 0.4 $kg.m^{-2}$) and men with angina and an abnormal angiogram (25.1 ± 0.3 $kg.m^{-2}$).

Thompson and co-workers (1991) found no difference in the BMI of patients with coronary atherosclerosis (27.0 ± 3.5 $kg.m^{-2}$), hospitalised controls (27.0 ± 3.7 $kg.m^{-2}$) and neighbourhood controls (26.4 ± 3.5 $kg.m^{-2}$) ($P > 0.05$).

(c) evaluation of weight-for-height ratios as predictors of CHD

The variation in the relationship between weight-for-height indices and CHD may be due partly to the inaccuracy of these indices in estimating body fat. The numerator, body weight, is composed of lean as well as fat tissue. Body mass indices are, therefore, as much estimations of musculoskeletal mass as fat mass. An individual with a considerable muscle, bone and organ mass relative to height may be classified as obese even though they may not have a large fat mass. Similarly, in individuals with small muscle and bone masses relative to height, body fat will be underestimated (Lohman, 1992). In a population sense, this may be unimportant as the main cause of excessive weight-for-height is an increased fat mass (Shephard, 1994). However, using simple weight-for-height ratios to compare different populations is particularly unreliable if they differ in ethnicity and socio-economic status (Shephard, 1994). For instance, high BMI's found amongst the Canadian Inuit were explained by short stature and well-developed musculature rather than excessive body fat (Shephard, 1980). The genetically homogeneous Pima Indians, on the other hand, exhibit a high prevalence of obesity (Knowler *et al.*, 1981).

The correlation between BMI and body fat derived from underwater weighing has been reported to be 0.55 for men (Womersley and Durnin, 1977). This leaves 70% of the variation in fatness unexplained. Correlations between densitometrically assessed body fat and other weight-for-height indices (W/H, W/H^{-3}, $W^{-0.33}/H$, $H/W^{-0.33}$ and percentage overweight based on age, sex and height) were of a similar magnitude (Womersley and Durnin, 1977). Smalley *et al.* (1990) found a slightly stronger relationship ($r = 0.70$) between BMI and relative body fat estimated from densitometry in 150 men. In their study of United States Air Force personnel, Weinsier *et al.* (1976) found a correlation of 0.74 between BMI and relative body fat

estimated using tritium dilution. Another study reported a common variance of 41% between BMI and relative body fat in 342 males (Bouchard, 1992). Micozzi *et al.* (1986) reported a correlation of 0.77 between BMI and subscapular skinfold thickness in men in NHANES I. Even though these correlations indicate a stronger relationship, with respect to body fat estimation BMI still has little predictive power. Garn *et al.* (1986) found a significant correlation (r = 0.65) between BMI and lean body mass in their analysis of data from the Tecumseh Community Health Survey. BMI was also related to radiogrammetrically-determined bony chest breadth in men aged 50 to 60-years (r = 0.67) (Garn *et al.*, 1986). This supports the notion that BMI is as much a reflection of lean body mass as it is fat mass.

Weight-for-height indices are also supposed to dissociate height. Data from NHANES I show a non-significant association between height and BMI in men (Micozzi *et al.*, 1986). Garn *et al.* (1986), however, have shown a relationship between relative sitting height (sitting height/stature) and BMI in men aged 20 to 35 and 36 to 50-years (r = 0.21). This suggests BMI is also influenced by body proportions and means that shorter-legged individuals can have higher BMI values by as much as 5 units (Garn *et al.*, 1986).

The consequence of these limitations is that to describe individuals as obese on the basis of a W:H index is unfounded and potentially misleading. The term obesity refers to excess body fat and should, therefore, be applied when more precise measurements of body fat are used. As weight-for-height indices simply describe body weight in relation to height, the term overweight is preferable as their validity as an indicator of fatness is questionable.

2.1.3 Relative Weight

Relative weight is obtained by expressing the individuals bodyweight as a percentage of some reference weight. This reference data, usually based on a large, random, cross-sectional sample can be obtained from a regression equation or chart (Lieberman and Probart, 1992) or more frequently a set of height-weight tables. Although relative weight implies no value judgement (Harrison, 1985), correlations with mortality has led to the application of the concept of "desirable" or "ideal" weight. These terms are used to describe individuals at lowest-risk of premature mortality and as the standard for weight reduction targets.

(a) prospective studies

The relationship of Framingham Relative Weight (deviation of body weight from the median weight of the population distribution) to the 12-year incidence of CHD suggested an excess risk of angina and sudden death in "obese" men (Kannel *et al.*, 1967). This excess risk existed in the absence of elevated blood pressure and serum TC. After 18-years follow-up, a positive linear association was observable in the male population (Kannel and Gordon, 1974). An autopsy study of 127 Framingham decedents found relative weight 9-years prior to death was an independent predictor of heart weight but not left ventricular muscle thickness, percentage luminal involvement or percentage luminal insufficiency (Feinleib *et al.*, 1979). Hubert and her colleagues (1983) later gathered data on 2252 Framingham men. Metropolitan Relative Weight (ratio of actual to desirable weight) independently predicted the 26-year incidence of angina, coronary disease other than angina, coronary death and congestive heart failure. Desirable weight was derived from Metropolitan Life Insurance Company height-weight tables (Metropolitan Life Insurance Company,

1959) by taking the midpoint of the weight range for a medium build at a specified height. Metropolitan height-weight tables were also used to calculate excess weight in a group of 200 "morbidly obese men" (mean excess bodyweight = 130%) aged 23- to 70-years (Drenick *et al.*, 1980). After 7.6-years follow-up, the total number of deaths was 50. CVD was the most common cause in the study subjects (54.0%) and the U.S. male population (40.3%). Compared to the general population, life-table techniques demonstrated a 12-fold excess mortality in subjects aged 25- to 34-years and a six-fold excess in subjects aged 35- to 44-years. This ratio continued to diminish with advancing age.

The final report of the Pooling Project Research Group (1978) suggested relative weight was associated with an increased risk of a first coronary event only in younger men aged 40- to 44-years ($P < 0.01$) and 45- to 49-years ($P < 0.05$).

Keys *et al.* (1971) found no association between CHD and relative weight in 279 men after 20-years follow-up. Later multivariate analysis also found no association between relative weight and CHD in larger male cohorts from the United States, southern Europe and northern Europe after 5- and 15-years follow-up (Keys *et al.*, 1972, 1984).

(b) evaluation of relative weight as a predictor of CHD

As with weight-for-height ratios, one unequivocal limitation of the relative weight concept is its inability to differentiate fat and lean tissues and, therefore, satisfactorily predict adiposity. The 1959 Metropolitan height-weight tables (Metropolitan Life Insurance Company, 1959) were first to consider the significance of skeletal mass by introducing the 'frame-size' concept. Later, anthropometric measurements were introduced to give this concept some objectivity. The frequently used biepicondylar

elbow breadth, however, which is used to categorise frame-size in the 1983 Metropolitan tables (Metropolitan Life Insurance Company, 1984) has a poor correlation with other measures of skeletal size, bone density and, thus, bone mass (Lieberman and Probart, 1992). Furthermore, considerable inter-individual variation in bone mineral density means that even if bone size is controlled, bone mass may still differ markedly. Anthropometric bone diameters are also influenced by subcutaneous adipose tissue and skin thickness. This means that frame size tends to be overestimated in fatter subjects and underestimated in lean subjects.

Further limitations of the relative weight concept are discussed in-depth by Harrison (1985) based on Knapp's earlier discourse (Knapp, 1983). First, the quality of data used to construct height-weight tables is in some instances questionable. For example, about 10% of weights and heights used to construct the 1983 Metropolitan tables were self-reported. In addition, the clothing of those who were measured in this study (Build Study, 1980) was not standardised. Second, few studies, including the Build Study (1980) have adequately controlled variables known to have a confounding influence on the weight and mortality relationship, most noticeably cigarette smoking (Garrison *et al.*, 1983). Third, describing weight as a percentage of a reference value does not represent a constant degree of overweight. For example, 40% overweight could describe both a person weighing 84 kg whose 'desirable' weight is 60 kg, or a person weighing 140 kg whose 'desirable' weight is 100 kg. Finally, even some of the largest data sets may not be representative of populations as a whole. This means that for some under-represented sections of the population (e.g. lower socio-economic groups, non-caucasians and those older than 60-years) the tables may not be a valid indicator of the weight-to-height relationship with mortality.

2.1.4 The two-component model

(a) evaluation of absolute and relative fat mass

The lack of validity of weight-for-height ratios and relative weight as body fat surrogates is a possible explanation for the variation in the relationship between obesity and CHD (Despres, 1991). A more precise measurement of body composition should, therefore, yield a stronger correlation between body fatness and CHD. Several studies have used more valid body composition measurement methods and adopted a two-component model that includes fat and fat-free masses. In this respect, skinfold thickness measurement, which has been used in both cross-sectional (Flynn *et al.*, 1993) and prospective studies (Keys *et al.*, 1971, 1972, 1984; Larsson *et al.*, 1984), has predominated. Others have used more sophisticated methods including underwater weighing (Keys *et al.*, 1971), tritium dilution (Weinsier *et al.*, 1976) and dual energy X-ray absorptiometry (Ley *et al.*, 1994).

The underpinning theory for the use of skinfolds and underwater weighing was outlined in the Chapter 1.0. There follows a brief explanation of tritium dilution and dual energy X-ray absorptiometry (DEXA). Tritium dilution allows measurement of total body water from which fat-free mass can be estimated (assuming a fixed hydration of this tissue component, usually 73 %) i.e. fat-free mass = total body water / 0.73. The method is based on the assumption that the radio-isotope tritium (^3H), which is measured with liquid scintillation counting, has the same distribution volume as water. The subject is given an accurately measured oral or intravenous dose of labelled water, followed by an equilibration period of at least 2-hours before sampling a body fluid, either saliva, blood or urine (Westerterp, 1994). The accuracy of both isotope dilution and underwater weighing is in the range of 1-2 % (Westerterp, 1994).

Dual energy x-ray absorptiometry allows the precise measurement of total and regional body composition with a very low radiation exposure. As the dual energy radiation source scans soft tissue, the relative attenuation of the photons changes in proportion to the fat content (Lohman, 1992). The short-term precision of DEXA for measuring the relative fat in soft tissue has been reported as 1-2 % (Mazess *et al.*, 1990).

(b) prospective studies

Recognising that neither relative weight nor BMI provide satisfactory estimates of body fat, Keys *et al.* (1971, 1972) examined the CHD relationship with the sum of triceps and subscapular skinfolds and whole-body density derived from underwater weighing. Neither exhibited a significant relationship with CHD incidence ($P > 0.05$). The sum of triceps, subscapular and parathoracic skinfolds were found to be unrelated to CVD in Gothenburg men (Larsson *et al.*, 1984). Weinsier *et al.* (1976) estimated relative body fat using the tritium dilution technique and found no difference ($P > 0.05$) between those with CHD (23%) and those without (21.1%).

(c) angiography studies

Flynn *et al.* (1993) estimated relative body fat from the sum of biceps, triceps, subscapular and suprailiac skinfolds using the regression equation of Durnin and Womersley (1974). They found a significant difference ($P < 0.05$) between men with insignificant disease (27.7 ± 6.0 %) and men with significant disease (29.3 ± 5.2 %). In a multivariate model, however, relative body fat was not an independent predictor of CVD.

More recently, no differences ($P > 0.05$) in absolute fat mass measured by DEXA were found between normal healthy men (17.1 ± 0.6 kg), men with angina and a normal angiogram (18.6 ± 0.9 kg) and men with angina and an abnormal angiogram (17.0 ± 0.6 kg) (Ley *et al.*, 1994).

(d) evaluation of fat mass as a predictor of CHD

If total body fat is important in the pathogenesis of atherosclerotic CVD the results from these studies (Flynn *et al.*, 1993; Keys *et al.*, 1971, 1972, 1984; Larsson *et al.*, 1984; Weinsier *et al.*, 1976; Ley *et al.*, 1994) are perhaps somewhat surprising. Neither long-term prospective nor case-control designs, including angiography, have shown a relationship between CVD and body fat.

The estimation of relative body fat from body density relies on several questionable assumptions (Novak, 1974). Perhaps the most notable being that the fat-free mass has a chemical composition resulting in a density of 1.10 $g.ml^{-1}$. For this reason, the calculation of relative body fat from body density has been criticised and the use of density in its own right advocated (Clarys *et al.*, 1984). As Keys *et al.* (1971) used body density rather than relative body fat in their analysis, the inaccurate estimation of body fat cannot be a contributory factor in the explanation of these findings.

As outlined in Chapter 1.0, the validity for the prediction of relative body fat from skinfold thickness is based on the inverse relationship with body density and several assumptions about the morphology and mechanical properties of the skinfold. Cadaver dissections suggest that, in the elderly at least, these assumptions should be rejected (Clarys *et al.*, 1984, 1987; Martin *et al.*, 1985, 1992, 1994). Evidence to date suggests that a limited number of skinfolds, used either to estimate relative body fat or

in their own right to avoid some of the assumptions of predicting body fat, are poor predictors of CVD.

2.1.5 Body fat distribution

(a) evaluation of fat distribution

Since the results of two large prospective studies in Scandinavia (Larsson *et al.*, 1984; Lapidus *et al.*, 1984) confirmed the findings originally reported by Vague *et al.* (1947, 1956), the focus of research in the area of obesity and CVD has shifted. Evidence is accumulating in support of the hypothesis suggesting the anatomical distribution of body fat is a stronger predictor of susceptibility to CHD mortality and morbidity, than measures of overweight or obesity, *per se*.

A variety of anthropometric indices have been used to describe the distribution of fat in relation to CVD. Major prospective studies such as the Paris Prospective Study (Ducimetiere *et al.*, 1986), Honolulu Heart Program (Donahue *et al.*, 1987), and Framingham Study (Stokes III *et al.*, 1985) used skinfolds on the trunk and limbs to assess subcutaneous fat pattern. Others, including the Scandinavian studies (Larsson *et al.*, 1984; Lapidus *et al.*, 1984), and recent work embracing coronary angiography (Flynn *et al.*, 1993; Hauner *et al.*, 1990; Hartz et al., 1990; Hodgson *et al.*, 1994; Thompson *et al.*, 1991) have relied on circumference measurements of the waist and hips to distinguish upper- and lower-trunk fatness. Later analysis of the Paris cohort also included the ratio of iliac-to-left thigh circumference, termed the circumference index, as an indicator of abdominal obesity (Filipovsky *et al.*, 1993).

(b) CHD in relation to subcutaneous fat pattern: prospective studies

Extending the period of follow-up to 30-years, Stokes *et al.* (1985) published further data from the Framingham Study. They claimed the results not only reconfirmed earlier findings (Hubert *et al.*, 1983), but indicated that upper-trunk (subscapular) and arm (triceps) skinfolds were better CHD predictors than skinfolds measured at the waist (abdominal) or front-thigh.

In the Paris Prospective Study, 6718 men aged 42- to 53-years were followed for an average of 6.6-years (Ducimetiere *et al.*, 1986). CHD was classified as angina pectoris, non-fatal myocardial infarction or sudden death due to CHD. Trunk skinfolds (subscapular, axillary and subumbilicus) were the strongest predictors of CHD ($P < 0.05$), whereas thigh skinfolds (anterior, posterior, internal and external) were not associated with CHD ($P > 0.05$). The trunk-to-thigh skinfolds ratio was a highly significant predictor of angina pectoris ($P < 0.0001$) and, to a lesser extent, sudden death and myocardial infarction ($P < 0.01$). The association between the skinfold ratio and total incidence of CHD was also highly significant ($P < 0.00001$). In multivariate analysis, with TC, cigarette habit, blood pressure, diabetes, age, BMI and TG as co-variables, the skinfold ratio remained a significant predictor ($P < 0.025$).

A third large-scale prospective study, examined the relationship between definite CHD (non-fatal myocardial infarction and death from CHD) and subscapular skinfold thickness in 7692 men from the Honolulu Heart Program (Donahue *et al.*, 1987). For a given BMI, subscapular skinfold remained a significant predictor of CHD after adjustment for several established risk factors ($P < 0.05$ for the highest versus lowest tertile of subscapular skinfold and $P < 0.01$ for the middle versus lowest tertiles).

The study of Edinburgh men found baseline abdominal skinfold thickness was significantly greater ($P < 0.05$) in the 11 men who developed CHD than the 96 men who remained free of the disease (Hargreaves *et al.*, 1992). There was no difference in triceps and subscapular skinfold thickness ($P > 0.05$). After adjustment for HDL-C, abdominal skinfold thickness remained an independent predictor of CHD ($P < 0.05$).

(c) evaluation of subcutaneous fat pattern as a predictor of CHD

Whilst the findings from these studies (Ducimetiere *et al.*, 1986; Donahue *et al.*, 1987; Hargreaves *et al.*, 1992; Stokes III *et al.*, 1985) exhibit some commonality, there are distinctive differences. Excluding the Edinburgh men, subscapular skinfold consistently appears as a stronger predictor of CHD than any other skinfold. However, it only accounted for approximately 10% (R^2) of the total variance across the entire age spectrum (Stokes III *et al.*, 1985). Examined in relation to specific age groups, subscapular skinfold presents as the strongest predictor in subjects less than 50- and 50- to 59-years of age (R^2 = 15 % and 16 % respectively) but the weakest predictor in subjects older than 60-years (R^2 = 5 %) (Stokes III *et al.*, 1985). In these older subjects, thigh skinfold showed the strongest association with the 22-year incidence of CHD (R^2 = 15 %). This contradicts the results of the Paris cohort for whom thigh skinfolds clearly exhibited the weakest relationship with CHD incidence (Ducimetiere *et al.*, 1986). The claim that triceps skinfold is generally a stronger CHD predictor than abdominal or thigh skinfolds (Stokes III *et al.*, 1985) appears to be exaggerated. The results show that for each age stratum, coefficients of multiple logistic regression between triceps skinfold and CHD incidence are lower than for both abdominal and thigh skinfolds. This may be suggestive of an alternative phenomenon. That is, it is

truncal deposition of subcutaneous fat that is associated with increased CHD risk. This appears particularly apparent for younger subjects.

(d) CHD in relation to gynoid or android obesity: prospective studies

In Sweden, 13-years follow-up in men revealed significant associations between the WHR and the occurrence of stroke ($P = 0.002$) and IHD ($P = 0.04$) but not death ($P = 0.053$) (Larsson *et al.*, 1984). After the confounding effects of BMI and the sum of three skinfolds were removed, WHR remained a long-term predictor of stroke and myocardial infarction and also correlated with death ($P < 0.001$). Following adjustment for other major risk factors (smoking, systolic blood pressure and TC), WHR was not a predictor of any of the end-points. Extension of the follow-up period by 5-years revealed that only 1.7% of men in the lowest 10% of the WHR distribution suffered cerebral infarction compared with 18.9% in the upper 10% (Larsson, 1987). Whilst WHR was no longer an independent predictor of myocardial infarction, either in univariate or multivariate analysis, the risk of myocardial infarction was greater in the upper 10% compared to the lowest 10% of the WHR distribution. This difference, however, was markedly reduced at 72-years of age (after 18-years follow-up) compared to the maximal risk difference observed after 13-years.

Rimm *et al.* (1995) reported that after controlling for height and BMI, the relative risk of CHD in men in the highest WHR quintile was 1.42 (95% CI 0.99 - 2.04) in comparison to men in the lowest quintile. When separated according to age, WHR was a stronger predictor of CHD in men > 65-years than their younger counterparts. Further analysis of waist circumference data showed men in the upper quintile (> 40 inches or 102 cm), had a relative risk of 1.44 (95% CI 0.95 - 2.17) in comparison to men in the lowest quintile (< 35 inches or 89 cm). When variation in

height was controlled statistically, the relative risk of men in the upper quintile of waist circumference increased to 1.86 (95% CI 1.17 - 2.95). As with WHR, the association between CHD and waist circumference was stronger among older men. However, not all studies have agreed with this finding. In the Baltimore Aging Study, abdominal sagittal diameter (ASD) was a predictor of CHD mortality (Seidell *et al.*, 1994). This association was independent of age, height and BMI, and was more pronounce in younger men with lower TC, TG, glucose and diastolic blood pressure. BMI, WHR and skinfolds were not related to CHD mortality.

Megnien *et al.* (1999) has recently reported on the 10-year incidence of cardiovascular events in relation to WHR in 552 men. A high WHR (> 0.98) was a strong predictor of CAD, and the number of subjects in this group who exceeded a 15% risk of developing a coronary event was more than twice the number in the lowest WHR group (< 0.88).

After 11-years follow-up in the Paris Prospective Study, iliac-to-thigh ratio appeared as an independent predictor of the 129 CHD deaths that occurred in this period (Casassus *et al.*, 1992). Later analysis found this ratio was a weak predictor of CVD mortality in men with a lower mean blood pressure (< 96 mm Hg) but a stronger predictor in men with a higher mean blood pressure (≥ 96 mm Hg) (Filipovsky *et al.*, 1993).

Two recent notable studies have reported that WHR is significantly related to cardiovascular mortality in Mediterranean populations. In an Italian population characterised by low TC levels and a low incidence of early CHD (Barbagallo *et al.*, 2001). Although there were only a small number of cardiovascular deaths recorded over an 8-year follow-up period, the relative risk for those with a WHR greater than the median was 5.49 (95% CI 1.12 - 18.40) in comparison to those with a WHR below

the median. Azevedo *et al.* (1999) also found that WHR rather than BMI was associated with a higher risk of a first myocardial infarction. In comparison to men in the first tertile of WHR, the odds ratio of a heart attack in the second and third tertiles were 2.5 (95% CI 1.3 - 4.9) and 11.1 (95% CI 6.0 - 20.6) respectively.

The increased risk of CVD in men with a greater WHR is also apparent among subjects of African-American origin. The Atherosclerosis Risk in Communities Study has reported similar positive trends (P = 0.06) between WHR and CHD in both black and white men (Folsom *et al.*, 1998).

(e) angiography studies

Hauner *et al.* (1990) examined the degree of coronary stenosis and several established risk factors in 286 men aged 30- to 74-years. Coronary stenosis (> 30%) or occlusion of one or more of the coronary arteries was present in 207 men. Those remaining were free of CHD and served as controls. There were no significant differences (P > 0.05) between control and CHD subjects with respect to circumference measurements at the waist (midway between xiphoid process and umbilicus), umbilicus, or hips (level of greater trochanter). WHR was also not significantly different (P > 0.05). Stepwise logistic regression analysis revealed that in addition to low-density lipoprotein-cholesterol (LDL-C) (P = 0.0001) and age (P = 0.0005), an abdominal type fat distribution was a significant predictor (P = 0.0129) of CHD. This association was independent of TC, HDL-C, TG, fasting insulin and systolic and diastolic blood pressures. A similar study found WHR was related (Spearman's rank correlation) to both an extent (r_s = 0.18, P < 0.05) and myocardial score (r_s = 0.17, P < 0.05) (Hodgson *et al.*, 1994). After adjusting for several covariables (age, BMI, smoking habit, TC, LDL-C, HDL-C, apolipoprotein A1 (apo A1), apolipoprotein B (apo B) and

TG) these relationships lost their significance (r_s = 0.17 and 0.05 respectively, P > 0.05). Hartz *et al.* (1990) also failed to show a relationship between WHR and CAD (> 50 % stenosis) in men after adjusting for age.

Ley and co-workers (1994) used DEXA and the procedures outlined by Mazess *et al.* (1990) to evaluate android and gynoid fat in 77 men aged 31- to 60-years who presented with chest pain typical of angina pectoris. Android fat was measured by selecting a region from the superior iliac crest upward to include all abdominal and thoracic soft tissue laterally. Gynoid fat was measured as a region of the same length as the android fat region, from the lower sacral border downward to include all soft tissue laterally. Angiography revealed 39 men had greater than 50% luminal stenosis in one or more epicardial coronary arteries. The remainder had no detectable abnormality on their angiogram (< 50% stenosis of any epicardial coronary artery). A further 40 men of similar age and weight and who were apparently asymptomatic were studied as a control group. Compared to men without angina, men with angina had a greater proportion of android fat (P < 0.05). Consequently, there was a trend towards a greater proportion of gynoid fat in asymptomatic men compared to men with angina but a normal angiogram (P > 0.05), and men with angina and an abnormal angiogram (P < 0.05).

Thompson *et al.* (1991) found the WHR of patients with atherosclerosis was significantly greater than the WHR of subjects recruited from the same neighbourhood and matched for age, sex and race (0.96 ± 0.05 v 0.92 ± 0.06, P < 0.025). In a similar study, Kahn *et al.* (1996) reported that the ratio of supine ASD-to-mid-thigh girth was the AT index that best discriminated patients with IHD compared to matched controls (P < 0.0001).

Flynn *et al.* (1993) reported that both waist-to-thigh circumference ratio (WTR) ($P < 0.005$) and WHR ($P < 0.05$) were independently associated with CAD. Whilst WTR was positively associated with CAD, in contrast to other prospective (Larsson *et al.*, 1984) and angiography studies (Hauner *et al.*, 1990; Hodgson *et al.*, 1994; Thompson *et al.*, 1991) WHR was inversely related to CAD.

All of the studies reviewed in this section have relied on anthropometric girth measurements as a marker of intra-abdominal fat. To date, only one study has attempted to measure intra-abdominal fat 'directly'. Nakamura *et al.* (1994) compared CT-determined intra-abdominal fat in non-obese men with CAD and a group of men free of CAD and matched for age, sex and BMI. The men with CAD had significantly greater intra-abdominal fat ($P < 0.05$) but not subcutaneous abdominal fat ($P > 0.05$). Thus, this study not only supported the view that intra-abdominal fat was important with regard to predicting CAD risk (Bjorntorp, 1990b) but also partly explains the sometimes weak association between CAD and BMI (Garrison *et al.*, 1996).

(f) evaluation of anthropometric circumference measurements as predictors of CHD

Individuals characterised by an android fat distribution appear to represent a sub-group of obese individuals at increased risk of CVD. This may partly explain the somewhat weak associations between CVD and obesity *per se* (Bjorntorp, 1985). Consequently, it has been suggested that as android obese individuals appear to be those at increased risk, the gynoid obese, whose risk of CVD is elevated only slightly, should be considered to have a cosmetic rather than clinical problem (Bjorntorp, 1990a). Evidence from two prospective studies suggests anthropometric indicators of abdominal obesity are stronger predictors of CHD than BMI (Larsson *et al.*, 1984; Filipovsky *et al.*, 1993). After adjustment for three risk factors however, WHR lost its

predictive power (Larsson *et al.*, 1984). Furthermore, results from case-control studies with angiographically-diagnosed CAD are not convincingly supportive of the ability of WHR to predict CHD (Flynn *et al.*, 1993; Hauner *et al.*, 1990; Hodgson *et al.*, 1994). Indeed, some evidence is entirely conflicting (Flynn *et al.*, 1993). This highlights the complex nature of the fat distribution relationship with CAD and supports the conclusion that more than one measure of obesity and fat distribution should be included in future research designs (Despres *et al.*, 1990).

2.1.6 Somatotype

(a) CHD in relation to somatotype

The relationship between somatotype and CHD attracted attention in the United States in the 1950's and 1960's (Gertler *et al.*, 1951, 1959; Spain *et al.*, 1953, 1955, 1963; Paul *et al.*, 1963) and later in South Africa (Smit *et al.*, 1979). Of 97 men and 3 women who experienced a non-fatal myocardial infarction before 40-years of age, 42 % were found to be dominant mesomorphs, 26 % dominant endomorphs, 25 % were in the mid-range (no dominant component) and only 7 % were dominant ectomorphs (Gertler *et al.*, 1951, 1959).

In 1953, the first of three papers examining the somatotype-CHD relationship was published (Spain *et al.*, 1953). This reported the autopsy findings on 111 consecutive white males under 46-years of age. Of these, 38 had suffered death secondary to CAD and 73 had died suddenly and unexpectedly by violent means (suicide, homicide, accident) or some other non-cardiac condition. Of the 38 who died from CAD, 24 were classified as being dominant mesomorphs, 3 endomorphs, 3 ectomorphs and 8 were in the mid-range. In the 73 apparently healthy males, the degree of atherosclerosis was found to be distinctly more pronounced in mesomorphic

individuals compared to those of ectomorphic dominance. A second post-mortem study also revealed that the extent of coronary atherosclerosis was markedly greater in mesomorphic compared to ectomorphic individuals (Spain *et al.*, 1955). Of 64 consecutive autopsy examinations involving sudden death from coronary occlusion, 44 cases were classified as dominant mesomorphs. In a third study, the incidence of CHD amongst 5000 males aged 36- to 50-years was three times greater for endomorphic-mesomorphs (9.2%) compared to dominant ectomorphs (3.0%) (Spain *et al.*, 1963). This further evidence led to the conclusion that individuals characterised by mesomorphic dominance, were at greater risk of CHD than their ectomorphic counterparts (Spain *et al.*, 1963). This was attributed to the mesomorphs large relative muscle mass, which was hypothesised to have a more direct association with atherosclerotic CHD than adipose tissue (Spain *et al.*, 1963).

The examination of 87 men aged 40- to 55-years, failed to support these earlier findings (Paul *et al.*, 1963). It was reported that endomorphic dominance was important since there was an excess of coronary cases in the group characterised by endomorphy ($P < 0.01$). Further examination, however, showed that whilst the difference between observed to expected coronary cases (myocardial infarction, angina pectoris, death from CHD) was greatest in the endomorphic sub-sample (19 observed / 13 expected), the total number of cases was greatest in the mesomorphic group. In these individuals, for whom mesomorphy was dominant and endomorphy greater than ectomorphy, 37 confirmed cases were found, one more than may have been expected. There was also a significant number of cases in the group for whom mesomorphy and endomorphy were approximately equal (15 observed / 11 expected). Of further interest is the lower than expected number of cases in the ectomorphic dominant and mesomorphic-ectomorphic individuals.

(b) evaluation of somatotype classification as a predictor of CHD

These early studies (Gertler *et al.*, 1951, 1959; Spain *et al.*, 1953, 1955, 1963; Paul *et al.*, 1963) can be criticised on several grounds. Most notably, the subjectivity of the photoscopic somatotype technique (Sheldon *et al.*, 1940), the lack of statistical analysis or control of covariables and failure to recognise the somatotype as a Gestalt. Despite these limitations, the findings were later confirmed in a study of 146 cardiac rehabilitation patients (mean age = 52.7-years) (Smit et al., 1979). Using Heath and Carter's technique (Heath and Carter, 1967) a mean somatotype of 4 - 5.5 - 1 was reported, the majority of patients being endomorphic-mesomorphs.

The overwhelming number of cardiac cases amongst mesomorphic individuals necessitates further explanation. Predominant mesomorphs show considerable variation in body density, hence mesomorphy is only modestly associated with measures of pure muscularity (Bailey, 1985). An equally plausible interpretation is that many large-framed and muscular older males also have enlarged fat stores (Bailey, 1985).

As body fat distribution appears to be particularly important in the relationship between body habitus and CVD, the association between somatotype and fat distribution is of great interest and may help explain the abundance of CHD amongst mesomorphic individuals. Among 824 men, those classified as android obese (mean somatotype 4.67 - 4.21 - 1.89) were reported to be significantly more mesomorphic and less endomorphic than those with gynoid obesity (mean somatotype 5.91 - 2.16 - 1.84) ($P < 0.01$) (Mueller and Joos, 1985). Mesomorphy is also a masculine characteristic, and as reported for non-insulin-dependent diabetes mellitus, there appears to be an assemblage of male differentiation factors amongst individuals at increased risk of CHD (Mueller and Joos, 1985).

2.1.7 Synopsis

Whilst some studies have used quite sophisticated laboratory procedures to quantify body fat (Keys *et al.*, 1971; Ley *et al.*, 1994; Weinsier *et al.*, 1976), most have relied upon anthropometric measurements to determine some component of body habitus. Of these, body weight and height are the simplest measurements and are, therefore, well suited to large-scale prospective studies. Height and weight are highly reproducible measurements, although in the short term, weight can have considerable physiological variation associated with gastric emptying and state of hydration (Mueller and Martorell, 1988). Less reliable measurements than height and weight are skinfolds and body circumferences, both of which have been used extensively in cross-sectional and prospective analyses. For skinfolds, both the inter and intra-observer variability is affected by the measurement technique, location of the skinfold site, the skinfold calliper used and skinfold compressibility (Lohman, 1992). As measurement error has been shown to be a function of skinfold thickness (Pollock *et al.*, 1986), accurate and repeatable skinfold measurements are particularly difficult to make in the obese. In these subjects, it is not always possible to locate a specific anatomical bony landmark or to pull a parallel skinfold away from the underlying tissue. Furthermore, in the extremely obese it is sometimes possible for a skinfold to be thicker than the jaws of the currently available commercial callipers (Bray and Gray, 1988). Alternately, body circumferences are obtainable in all subjects and have greater reproducibility than skinfolds (Bray and Gray, 1988). They are, therefore, the preferred method in obese subjects (Bray and Gray, 1988). However, there is considerable work to be done to establish their association with body fatness.

The evidence examined in this section suggests that body weight is a poor predictor of CHD. Some studies have reported no difference in the body weight of

CHD patients compared to subjects free of the disease (Flynn *et al.*, 1993; Ley *et al.*, 1994; Paul *et al.*, 1963), others found the body weight of subjects with CHD to be slightly greater (Gertler *et al.*, 1951; Paffenbarger *et al.*, 1966a, 1966b; Rabkin *et al.*, 1977; Feinleib *et al.*, 1979), and one found the body weight of cardiac patients to be less than controls (Hauner *et al.*, 1990). Height, however, is negatively associated with CHD in prospective studies with long-term (Paffenbarger *et al.*, 1966a, 1966b; Morris *et al.*, 1966; Marmot *et al.*, 1978, 1984; Morris *et al.*, 1980; Waaler *et al.*, 1984; Walker *et al.*, 1989) and shorter-term (Yarnell *et al.*, 1992) follow-up periods and case-control designs (Gertler *et al.*, 1951, 1959; Flynn *et al.*, 1993; Hauner *et al.*, 1990). Foetal, infant and childhood undernutrition may link shorter adult height and susceptibility to CVD (Barker, 1994).

Many researchers have studied the relationship between overweight and CHD by using a surrogate measurement of body fatness such as relative weight or a weight-for-height index. In general, results produced by these studies suggest weight-for-height indices, particularly the often-used BMI, are not strong predictors of CHD once the confounding influence of other risk factors has been considered. Indeed case-control designs have consistently failed to show a relationship between BMI and CHD. Inconsistent results from prospective studies however, are difficult to interpret. To further confuse the situation, BMI has been examined in relation to different CHD end-points and adjusted for different confounding variables. Explaining the inconsistent results on the basis of length of follow-up is also not simple. When follow-up periods exceed 20-years (Rabkin *et al.*, 1977; Stokes III *et al.*, 1985; Lee *et al.*, 1993), and sample size is large, BMI exhibits a stronger relationship with CHD. When sample size is small however, this closer association has not been found, even with a long follow-up period (Keys *et al.*, 1971). Whilst some studies have found no

association after 15, 13 and 12 years (Keys *et al.*, 1984; Larsson *et al.*, 1984; Donahue *et al.*, 1987) others have reported a relationship after 3-, 8.5-, 10-, 12-, 10- and 7-years (Rimm *et al.*, 1995; Morris *et al.*, 1980; Rhoads and Kagan, 1983; Hargreaves *et al.*, 1992; Jooste *et al.*, 1988; Toumilehto *et al.*, 1987). Some of the best evidence of a strong, graded association between BMI and CAD is provided by the 22-year follow-up data from the Framingham Study (Stokes III *et al.*, 1985), the 15-year follow-up data from the British Regional Heart Study (Shaper et al., 1997) and the 27-year follow-up of Harvard Alumni (Lee et al., 1993). Despite adjusting for several established risk factors (age, TC, systolic blood pressure, cigarette smoking, blood glucose and ECG evidence of left ventricular hypertrophy), the 'true' relationship between BMI and CAD awaits more extensive adjustment for factors associated with the overweight state (for example, small dense LDL, endothelial dysfunction and plasminogen activator inhibitor I).

As BMI has been shown to have only a moderate correlation with body fatness (Weinsier *et al.*, 1976; Micozzi *et al.*, 1986; Womersley and Durnin, 1977; Smalley *et al.*, 1990; Bouchard, 1992), future research should establish whether BMI is a valid predictor of body fat in that particular population before the term obesity is adopted. Ideally, the power function of height should be calculated so that the index exhibits the strongest possible relationship to body fatness and is independent of height.

Relative weight, a further simple index of overweight based on height and weight alone, has been used less extensively than BMI. Data from the Framingham Study suggests relative weight can predict CHD in the short (Kannel *et al.*, 1967; Kannel and Gordon, 1974) and long term (Hubert *et al.*, 1983). However, there is contradictory evidence from studies with follow-up periods ranging from 5- to 20-years (Keys *et al.*, 1971, 1972, 1984). The principal limiting feature underpinning

measures of relative weight is the same as for BMI, i.e. an inability to reflect adiposity.

It has been suggested that the failure of weight-for-height indices and relative weight to reflect adiposity may partly account for the inconsistency in the relationship between 'obesity' and CVD (Despres, 1991). If this is so, then the more 'direct' measurement of body fat should theoretically produce a closer association between obesity and CVD. However, studies reviewed here suggest that this is not the case. Neither prospective (Keys *et al.*, 1971, 1972, 1984; Larsson *et al.*, 1984) nor case-control (Flynn *et al.*, 1993; Ley *et al.*, 1994; Weinsier *et al.*, 1976) studies that assessed body fat by more direct methods have shown a relationship between the level of fatness and CVD. This is not to say that obesity is unimportant in the pathogenesis of CVD. Studies of obese and overweight men have shown a relationship between fat loss and weight reduction and improvements in blood pressure and blood lipids (Wood *et al.*, 1988; Sopko *et al.*, 1985; Berchtold *et al.*, 1982; Reisin *et al.*, 1978; Schotte and Stunkard, 1990; Dustan, 1985). However, recent data from the Swedish Obese Subjects (SOS) study suggests that longer-term weight loss may not have an effect on the incidence of hypertension (Sjostrom *et al.*, 2000). Thus, despite the lack of an independent statistical association between obesity and CVD, the avoidance of obesity or the loss of excess fat with subsequent maintenance of the lower level should be an important aspect of CVD risk reduction (Leon, 1995).

As the combination of various skinfolds seem unrelated to CHD when summed (Keys *et al.*, 1971, 1972, 1984; Larsson *et al.*, 1984) or used to estimate relative body fat (Flynn *et al.*, 1993), it is perhaps surprising that several studies have found that individual skinfolds treated as discrete variables independently predict CHD. It appears that central or truncal skinfolds are stronger predictors than limb or

peripheral skinfolds. However, which trunk skinfold is the strongest predictor remains unclear. For instance, one study found subscapular skinfold to be a better predictor than abdominal skinfold (Stokes III *et al.*, 1985). The study of Edinburgh men however, found that baseline abdominal skinfold was significantly greater in men who developed CHD compared to those who did not (Hargreaves *et al.*, 1992). There was no difference in subscapular skinfold thickness.

Results from two prospective studies (Larsson *et al.*, 1984; Lapidus *et al.*, 1984) suggest that abdominal obesity, as measured by the WHR and ratio of iliac-to-left thigh circumference respectively, is important in the evaluation of CVD risk. However, more recent findings from case-control studies (Flynn *et al.*, 1993; Hauner *et al.*, 1990; Hodgson *et al.*, 1994) indicate that WHR is not closely associated with CAD. This may well be due to the fact that WHR exhibits only a moderate relationship with intra-abdominal fat. It is this fat compartment, particularly the metabolically-unique omental and mesenteric adipose tissues that drain into the portal circulation (Bjorntorp, 1990b), that have been linked with the metabolic complications associated with CVD (Despres, 1993). When evaluating CVD risk, therefore, considerable emphasis should be attached to measuring this depot. Comprehensive examinations of the assessment of intra-abdominal fat and its metabolic complications are presented in Sections 2.2 and 2.3 of the literature review.

The studies that examined CHD in relation to somatotype revealed very consistent findings. Men with an endomorphic-mesomorphic physique appear to experience a far greater incidence of coronary events than other somatotypes. Ectomorphic dominance appears to be the somatotype least associated with CHD. Although somatotyping does not allow the quantitative assessment of body composition compartments, it could be used to complement indices such as BMI and

waist girth, for the early identification of the individual at risk of CHD. The somatotype could be particularly useful when used in conjunction with other well-established risk factors. Advances in methodology, allows somatotype classification to be made objectively and relatively easily. Reliability of the classification depends entirely on the reliability with which several anthropometric measurements can be made (Carter and Heath, 1990).

It is clear from the literature examined in this review that a wide variety of aspects of body habitus have been studied in relation to the incidence of CHD. These characteristics have ranged from the most basic and easily quantified to the profoundly more complex. Results suggest that it is not necessarily the more complex that are most closely associated with CHD. The variability in findings indicate that future research in this area should include a wide variety of measurements in order to identify the strongest predictor for a given population.

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REVIEW OF LITERATURE

2.2 DETERMINATION OF ABDOMINAL OBESITY: THE EFFECTS OF GENDER, AGE AND DEGREE OF OBESITY

2.2 DETERMINATION OF ABDOMINAL OBESITY: THE EFFECTS OF GENDER, AGE AND DEGREE OF OBESITY

2.2.1 Anthropometric circumference measurements, computed tomography and magnetic resonance imaging

In 1956, Vague reported how simple girth measurements and skinfolds could delineate the importance of fat distribution in relation to various diseases, including diabetes and atherosclerosis (Vague, 1956). Since this original study, numerous investigators have outlined alternative methods for the evaluation of fat distribution using simple anthropometric measurements and these are reviewed below.

In recent years, the introduction and development of CT and magnetic resonance imaging (MRI) have also enabled researchers to determine IAF accumulation. This facilitates the differentiation of the 'deep' fat depot from the more superficial subcutaneous abdominal adipose mass. The expense of these techniques, together with the significant radiation exposure with CT, inhibits their use in extensive epidemiological surveys, but has permitted the validation of anthropometric indicators of IAF.

Following the initial study by Vague (1956) and maintaining the same terminology, Ashwell *et al.* (1978) described a method of classifying women according to their fat distribution using a side-view somatotype photograph to determine waist and thigh diameters. These investigators later suggested an alternative approach to the assessment of female fat distribution using anthropometric circumference measurements (Ashwell *et al.*, 1982). Also in the early 1980's, Krotkiewski *et al.* (1983) and Hartz *et al.* (1983) became the first groups to use the WHR as an indicator of fat distribution. It was claimed that this ratio was equal to the

WTR proposed by Ashwell *et al.* (1978) for distinguishing between android and gynoid obesity.

An important landmark in the search for methods that could classify fat distribution, and facilitate the investigation of hypotheses with respect to fat distribution and metabolic disease risk, came in 1982 (Borkan *et al.*, 1982). This was the first publication to recognise that a single CT scan could be used to measure abdominal fat content and, therefore, be used to differentiate between intra-abdominal and subcutaneous fat. In the subsequent decade, there were many further studies of fat distribution using CT methodology (Tokunaga *et al.*, 1983; Grauer *et al.*, 1984; Ashwell *et al.*, 1985; Enzi *et al.*, 1986; Kvist *et al.*, 1986; Seidell *et al.*, 1987; Seidell *et al.*, 1988; Kvist *et al.*, 1988a, 1988b; Baumgartner *et al.*, 1988; Weits *et al.*, 1988; Ferland *et al.*, 1989; Rossner *et al.*, 1990; Despres *et al.*, 1991; Zamboni *et al.*, 1992; Koester *et al.*, 1992), most of which were reviewed by van der Kooy and Seidell (1993). Since 1993, the use of CT technology has been further evaluated (Armellini *et al.*, 1993; Zamboni *et al.*, 1993; Pouliot *et al.*, 1994; Thaete *et al.*, 1995; Jensen *et al.*, 1995; Lemieux *et al.*, 1996a; Vehmas *et al.*, 1996; Armellini *et al.*, 1997; Schoen *et al.*, 1998; Zamboni *et al.*, 1998; Rankinen *et al.*, 1999). The measurement of AT with CT is accurate and highly reproducible (Thaete *et al.*, 1995). It is, therefore, regarded by many as the "gold-standard" for measuring IAF. However, the fact that it exposes the subject to radiation inhibits its use on ethical grounds. MRI is limited by its financial cost but does not expose the subject to radiation and, therefore, offers an attractive alternative to CT. The validity of multi-scan MRI, as a method for determining total percent lipid and total percent AT *in vivo*, has been shown using lean and obese pigs (Fowler *et al.*, 1992). Residual standard deviations were 1.9 and 2.1% respectively. Unlike CT, MRI has yet to be validated using human cadavers.

In a comparison of a multi-scan CT method and a multi-scan MRI method, Seidell *et al.* (1990) found differences of 5.4%, 10.6% and 10.1% for total, visceral and subcutaneous abdominal AT areas respectively. They concluded that whilst MRI may yield slightly different results to CT, these differences were not of sufficient magnitude to change the rank-order of individuals assessed with these methods, or to invalidate MRI as a useful tool for studying the metabolic complications of visceral obesity.

Whilst Dooms *et al.* (1986) were first to examine the effects of age, gender and obesity on the technical aspects of the MR imaging of fat, other investigators (Foster *et al.*, 1984; Fuller *et al.*, 1985; McNeil *et al.*, 1989) were first to use MRI for assessing human body composition. As with CT, many subsequent studies have evaluated MRI as a method for measuring abdominal AT distribution (Staten *et al.*, 1989; Gray *et al.*, 1991; Fowler *et al.*, 1991; Sobol *et al.*, 1991; Fowler *et al.*, 1992; Ross *et al.*, 1992; van der Kooy *et al.*, 1993a; Terry *et al.*, 1995; Sohlstrom and Forsum, 1995; Ross *et al.*, 1996).

The aim of this section is to review the CT and MRI studies of body fat distribution and to appraise the anthropometric measurements that have been validated against them. Furthermore, a discussion of how race, age, gender and degree of obesity or overweight affects the distribution of fat assessed by CT or MRI is also presented. For a technical discussion of CT and MRI, the reader is directed to the paper by van der Kooy and Seidell (1993).

Tokunaga *et al.* (1983) extended the single-slice CT method previously outlined by Borkan *et al.* (1982) with a multi-scan assessment of lean and obese individuals. This method was used to compute total body fat volume by dividing the body into 11 cylindrical shapes and measuring the height of each cylinder. However, as the CT-

scans were performed only at the middle of each segment, the determination of the cylinder volumes was limited by the assumption of a constant fat thickness along the entire length of the segment.

In a study of 25 age-matched males and females, Dixon (1983) was the first to show a difference in the distribution of abdominal fat between genders. The total cross-sectional area of the abdomen in men was approximately 100 cm^2 greater. There was no difference in the total abdominal fat content, but males had almost twice as much IAF as females ($P < 0.01$).

Grauer *et al.* (1984) also reported differences in CT-determined abdominal fat distribution between males and females. Scans performed at the L1, L3 and L5 vertebral levels revealed that females had a greater total fat volume at the L5 but not L1, and L3 levels. Relative to total fat volume, females also tended to have greater abdominal subcutaneous fat, whereas males had the greater IAF accumulation. These findings were supported by Enzi *et al.* (1986) in a study of 62 male and 68 female subjects using thoracic (heart apex level) and abdominal (upper renal pole) CT-scans. At both levels, the subcutaneous-to-visceral AT ratio was higher in non-obese women than in non-obese men, and the difference was more pronounced in obese subjects.

The suggestion that anthropometric circumference measurements are unable to differentiate visceral and subcutaneous abdominal AT was recognised by Ashwell *et al.* (1985). In a group of 28 women who exhibited a large variation in age, BMI, waist and hip circumferences, these investigators were the first to report the results of both CT-scanning of the abdomen (a single slice at the fourth lumber vertebrae) and anthropometric girth measurements (Ashwell *et al.*, 1985). After adjustment for BMI and age, the WHR, but not WTR, was significantly associated with CT-determined IAF and the intra-abdominal-to-subcutaneous fat ratio. This study did not examine the

relationship between waist girth and IAF, which has subsequently been shown to be a better predictor of IAF (Pouliot *et al.*, 1994).

Following the first attempt to determine fat volumes (Tokunaga *et al.*, 1983), Kvist, Sjostrom and Tylen (1986) analysed 22 CT-scans obtained from the foot to the hand (with arms stretched above the head) on 8 female subjects ranging in body mass from 46 to 119 kg. Subcutaneous fat volumes, determined using three different mathematical models, were greatest in the trunk (~49.0 litres), followed by the legs (~31.8 litres), arms (~7.5 litres) and head and neck (~1.7 litres). Visceral fat volume was approximately 10.0 litres. The different mathematical approaches yielded very similar results. Further analysis showed that the highest correlation between total adipose volume and one single AT area ($r = 0.99$) was found for the L4-L5 scan. However, the error in predicting total AT volume from this single scan was 4.6%. To reduce the error to approximately 1%, a minimum of 9 CT-scans had to be included.

Following the attempt by Ashwell *et al.* (1985) to predict IAF from anthropometric circumference measurements, Seidell *et al.* (1987) further investigated this possibility in a study of 71 males and 34 females subjected to a single-slice CT procedure at the L4-level. Several anthropometric measurements were performed, including circumferences at the levels of the smallest waist, umbilicus, widest hips, anterior superior iliac spine and largest thigh. Suprailiac and para-umbilical skinfolds were also measured. In men, WHR was a better correlate of IAF fat than WTR. In women, however, this situation was reversed. In stepwise multiple regression analysis, BMI, skinfolds, WHR and age explained 81.9% of the variation in IAF. In women, the best combination to predict IAF was BMI, menopausal status and WTR, explaining 79.5% of the variance.

Using the multi-scan CT technique they had reported previously (Kvist *et al.*, 1986, 1988a; Sjostrom *et al.*, 1986), Kvist *et al.* (1988b) examined the possibility of predicting total and visceral fat volumes in 17 men and 10 women from anthropometric measurements. However, only body mass and stature were true anthropometric measurements. The diameter, circumference and AT thickness measurements used to develop the predictive equations were taken from CT-images. Using approximately half of these men and women as cross-validation material, the lowest error in predicting visceral fat at the L3-L4 level was obtained using the "nonsubcutaneous ellipse", $d_3 \cdot d_4(\pi/4)$ (1). The error was only marginally (and not significantly) improved by adding W/H or the circumference at this level. The internal errors of prediction in men were 12-13% and the external errors 8-10%. In women, the internal errors were approximately 11% and the external errors 25-27%.

As Borkan *et al.* (1982) had shown that abdominal fat distribution was partly age-dependent in men, Seidell *et al.* (1988) extended this investigation in a larger group of subjects that included 66 men and 34 women. They also examined the influence of the degree of obesity on abdominal fat distribution and the association with various anthropometric measurements. IAF area and the ratio of intra-abdominal-to-subcutaneous fat (I:S ratio), measured from a single CT-scan at the L4-L5 level, was greater in the older men and women than the younger subjects. This increase was independent of BMI only in the men, as in women less than 40-years of age, IAF did not increase with obesity. Despite also showing markedly lower IAF in a group of

(1) where d_3 is the midsagittal diameter minus the sum of right and left lateral subcutaneous adipose tissue thicknesses and d_4 is sagittal diameter minus the sum of dorsal and ventral subcutaneous adipose tissue thicknesses).

7 adolescents, the cross-sectional design of this study is a limiting factor and changes in the distribution of abdominal fat remains to be shown in a prospective, longitudinal study. Intra-abdominal fat was highly correlated with waist circumference in women over the age of 40-years, and all men, but not with the sum of suprailiac and umbilical skinfolds or the WHR.

In a study of 130 patients aged 16- to 81-years, Weits *et al.* (1988) examined a single CT-scan at the umbilical level, and several anthropometric measurements. Waist circumference was again found to be a better correlate of IAF area than the WHR, and a one-year difference in age was associated with an approximately $1cm^2$ larger IAF area in men and women.

A more detailed analysis of abdominal composition was performed by Baumgartner *et al.* (1988). CT-images of the thorax, abdomen and pelvis (2) of 43 men and 53 women aged 20- to 83-years were analysed in an attempt to determine the total, subcutaneous, intra-abdominal and retroperitoneal fat areas (3). In males and

(2) The first CT-slice (xiphoid) was taken at the extreme caudal tip of the xiphoid process and the fourth (lower abdomen) at the extreme cranial edges of the iliac crests. The second (midabdomen 1) and third (midabdomen 2) slices were those approximately one-third and two-thirds of the distance (mm) between the first and fourth slices. The sixth slice was at the level of the pubic symphysis and the fifth slice was approximately midway between the fourth and sixth slices.

(3) Intra-abdominal adipose tissue was determined from an area bounded by the parietal peritoneum. The retroperitoneal adipose tissue was defined using an approach similar to that of Ashwell et al (1985b) which draws two lines diagonally from the anterior edge of the inferior vena cava tangentially across the anterior aspects of each kidney to their intersection with a line circumscribing the intra-abdominal area. Subcutaneous adipose tissue was equal to the total adipose tissue area minus the intra-abdominal adipose area.

females, IAF areas were larger for the mid-abdominal than lower or upper abdominal slices. Men had significantly greater IAF areas at the levels of the xiphoid process and mid-abdomen but not at the lower abdomen or pelvis. Retroperitoneal fat was also greater in the men, but subcutaneous fat was greater in the women at all levels. The principal difference between the sexes with respect to abdominal composition was in the proportions of intra-abdominal and subcutaneous fat. At the mid-abdominal level, IAF accounted for ~14% of the total cross-sectional area and ~50% of the total fat area in men. In women, however, the values were ~11% and ~33% respectively. Intra-abdominal, but not subcutaneous fat was positively associated with age in both sexes.

Ferland *et al.* (1989) studied 51 obese pre-menopausal women and found that the total, but not the proportion, of IAF could be reasonably well estimated from a combination of age and anthropometric measurements. This study also suggested that there was independence between total body fatness and the absolute amount of IAF in the fattest women. These authors concluded that in extremely obese women, increases in abdominal adiposity are a consequence of increasing subcutaneous fat. However, this observation was based on only four subjects. In at least two other subjects of equal total body fatness there was a linear increase in IAF.

Until the work by Rossner *et al.* (1990), the validity of CT-determinations of intra-abdominal fat was based upon information gained from phantoms. This provided the investigators with Hounsfield numbers characteristic for fat (4). Rossner *et al.* (1990) analysed 1 cm thick abdominal cross-sections from two male cadavers, aged

(4) A Hounsfield number or unit (HU) is the attenuation or absorption value for a given substance. Fat has an attenuation value in the range of approximately -190 to -30 HU (van der Kooy and Seidell 1993).

78- and 77-years. Their data indicated a close correlation between CT-measurements and these direct determinations of fat (for absolute fat at the umbilical level, r = 0.93 or 0.94 depending on the Hounsfield numbers used). However, the direct validation of CT-images in both males and females across the range of age and body fatness remains a challenge.

The difficulty predicting IAF from anthropometric measurements was further highlighted in a study of 110 men aged 18- to 42-years with BMI's ranging from 16 to 38 $kg.m^{-2}$ (Despres *et al.*, 1991). Multivariate analysis showed that most measures of total or regional fat correlated with IAF in leaner men (BMI < 28.0 $kg.m^{-2}$). This contrasted to the findings in obese men (BMI ≥ 28.0 $kg.m^{-2}$) for whom none of the measures of total fat, and only waist circumference, WHR and sagittal diameter were associated with deep abdominal fat. However, even the best combination of variables could predict IAF with only moderate accuracy. The prediction equations were more accurate in the leaner than the obese men, and accounted for approximately 70% of the variance, with standard errors of estimation in the region of 30 cm^2 or 30 %.

In studies of obese subjects, Busetto *et al.* (1992) and Zamboni *et al.* (1992) confirmed the difficulty in estimating IAF from the WHR. These investigators concluded the following: WHR is greatly influenced by the degree of obesity. The accuracy of WHR, when assessing the distribution of visceral and subcutaneous fat, decreases with increasing fatness. The use of WHR may be misleading in obese subjects, particularly females, if the aim is the assessment of visceral fat. Furthermore, in a study of 119 women whose BMI's ranged from 25 to 51 $kg.m^{-2}$, Armellini *et al.* (1993) showed that WHR and ASD were not significantly different between the women in the second and third tertiles of visceral fat.

Koester *et al.* (1992) attempted to predict IAF from extensive anthropometric measurements (nine skinfolds and thirteen circumferences), ten derived anthropometric variables and total body fat determined from hydrostatic weighing. In a cohort of 61 male subjects aged 18- to 30-years (body fat range 2 to 36%), the best prediction of IAF was from a regression model that included the product of waist and hip circumferences and percentage body fat ($R^2 = 0.73$, SEE = 30.8 cm^2). Abdominal subcutaneous fat could be predicted with slightly greater accuracy from waist circumference and percentage body fat ($R^2 = 0.81$, SEE = 29.3 cm^2). Anthropometric measurements alone were unable to provide a satisfactory prediction of the I:S ratio, but a preliminary study of the anthropometric ASD revealed high correlations with the CT-derived ASD.

In a study of men and women, Pouliot *et al.* (1994) examined the association between waist and hip girths, relative body fat and CT-determined IAF. This study is notable as it also examined the association between fat distribution and metabolic markers of CVD risk. In agreement with previous studies (Dixon 1983; Grauer *et al.*, 1984; Enzi *et al.*, 1986; Seidell *et al.*, 1987, 1988) women were found to have a greater relative body fat and total abdominal fat area than men. However, men had a greater visceral fat area, WHR and waist girth. Waist girth and sagittal diameter also exhibited higher correlations with total body fat and visceral fat than WHR. From these findings, it was suggested that waist girth and sagittal diameter were not only associated with total body fat but could discriminate between those with a predominant accumulation of fat at the abdominal level. A "threshold" waist girth value of > 100 cm was thought to be most likely associated with a metabolic profile commensurate with elevated CVD risk. As a given waist girth value indicated comparable levels of visceral fat in men and women, this threshold was reported to be

applicable to both sexes. A subsequent study (Lemieux *et al.*, 1996a), aimed to establish threshold values of waist girth and WHR that could identify individuals with a visceral fat area of ≥ 103 cm^2: a value above which substantial alterations in metabolic fitness may be found (Despres *et al.*, 1993; Hunter *et al.*, 1994). In both sexes, the "threshold" values for both parameters were age- and obesity-dependent. With regard to waist circumference, this amounted to 98.9 cm in younger men (< 40 years) and 90.9 cm in older men (≥ 40 years). For WHR, these values were 0.96 and 0.92 respectively. For men with a BMI < 25 $kg.m^{-2}$, values were 93.9 cm and 1.02. For more overweight men (BMI ≥ 27 $kg.m^{-2}$) the critical waist girth was 96.2 cm and WHR 0.93.

A further examination of the ASD was performed by Armellini *et al.* (1997) in a large group of women with a mean age of ~41 years. This study suggested that subtracting the thickness of abdominal subcutaneous fat (measured 5 cm from the umbilicus on the xiphoumbilical line) from the ASD improved the correlation with visceral fat. However, these measurements were derived from CT and ultrasound images. Whether a similar phenomenon exists with simple anthropometric measurements remains to be established. Furthermore, waist circumference remained the best predictor of fasting insulin and fasting TG concentrations. The same group of investigators provided further information on the validity and reliability of the anthropometric ASD in a study of 28 women and 23 men who ranged from lean to obese (Zamboni *et al.*, 1998). Both inter- and intra-observer reliability was extremely high. The accuracy of the ASD as a predictor of visceral fat was, however, markedly less in obese subjects ($r = 0.43$, $P < 0.05$) than in lean to moderately overweight persons ($r = 0.86$, $P < 0.001$). The ASD was not an improvement on waist girth which was also highly correlated with visceral fat in the leaner subjects ($r = 0.87$, $P < 0.001$).

Based on their findings from a study of 40 men and women characterised by a wide range of BMI, Schoen *et al.* (1998) questioned the accuracy of the CT-determined ASD as a predictor of total visceral fat. ASD was significantly correlated with total visceral fat when all subjects were analysed (R^2 = 0.50, $P < 0.001$). However, when the analysis was restricted to a more homogeneous group (those with a BMI $\geq$ 27.0 $kg.m^{-2}$), sagittal diameter was independent of total visceral fat (R^2 = 0.04, $P > 0.05$). It was suggested that within a 2 cm range of ASD, there was a nearly three-fold variability in total visceral fat.

The only cadaver study to examine directly the association between excised IAF and several anthropometric measurements was reported by Pounder *et al.* (1998). In a series of 100 male cadavers, waist girth was found to account for the largest variation (61%) in IAF. Although this association was not especially strong, there was a clear increase in IAF for a given increase in waist girth.

Table I (2.2). Weight of intra-abdominal fat in relation to waist circumference in 59 non-obese male cadavers (Pounder et al., 1998).

Waist girth (cm)	Number of subjects	Mean (g)	Median (g)	Range (g)
74-77	10	556	484	207 to 1246
78-81	14	865	761	402 to 1759
82-85	13	994	876	331 to 2170
86-89	13	1243	1250	511 to 2220
90-93	9	2057	1963	1113 to 3626

The studies reviewed so far have relied primarily on regression and multiple regression procedures to evaluate the validity of anthropometric measurements as indicators of IAF. Rankinen *et al.* (1999) have recently examined the sensitivity

(probability of correctly detecting true positives) and specificity (probability of correctly detecting true negatives) of waist circumference, WHR, BMI and relative body fat for identifying several critical visceral fat areas in men and women. This procedure relies on the construction of a ROC (receiver operating characteristic) curve, which plots sensitivity against specificity over a range of cut-off values. The cut-off value producing the best combination of sensitivity and specificity is then chosen as the optimal threshold for each predictor. The overall conclusion from this study was that waist circumference is the best overall predictor of abdominal visceral fat in younger (< 40 years) and older (> 40 years) men and women. WHR, however, was a poor predictor, especially in women. In younger men, an optimal waist girth cut-off point of 94.6 cm had a sensitivity of 90.5% and a specificity of 89.5% to detect a visceral fat area of 130 cm^2. In older men, these values were 94.5 cm, 81.0% and 85.2% respectively.

Most imaging studies of fat distribution have used CT technology. The radiation associated with this technique limits its use in otherwise healthy individuals and prevents studies being conducted that require repeat exposure. MRI, whilst being prohibitively expensive, does not have this limitation. Staten *et al.* (1989) recognised this important feature of MRI in their study of 6 subjects (3 male and 3 female) who ranged in body fat from 14 to 44%. Following MR-imaging on two occasions separated by less than 3 weeks, IAF was found to be associated with the ratio of the widest circumferences of the waist and hips ($r = 0.85$, $P < 0.05$). These circumferences were derived from the MR-images and not anthropometry. The error of IAF measurement associated with duplicate images was calculated to be approximately 10%. This was reduced to approximately 5% when the two leanest subjects were omitted from the analysis.

Following the study by Seidell *et al.* (1990) which compared the results of CT and MRI, Sobol *et al.* (1991) further explored this issue in 11 healthy subjects aged 21- to 49-years. For reasons which are not clear, fat areas measured by MRI tended to exceed those measured by CT by 8-22%. However, the correlation between MRI- and CT-determined IAF was 0.93 ($P < 0.001$). As CT is the 'gold-standard' method for determining IAF, this study suggests that MRI can be considered a valuable alternative.

In a study of diabetic (n = 24) and non-diabetic (n = 12) women, MRI-determined IAF at the umbilical level showed a low correlation ($r = 0.21$, $P > 0.05$) with the WHR (Gray *et al.*, 1991). However, when the non-diabetic women were assigned to groups of either low (< 0.80) or high (> 0.85) WHR, there was a significant difference ($P < 0.05$) in the area of IAF. Women in the low WHR category had a mean (± SD) IAF area of 79 (14) cm^2 compared to 127 (38) cm^2 in the high WHR group. Interestingly, the subcutaneous fat areas were remarkably similar ($P > 0.05$). Values of 473 (58) cm^2 and 477 (99) cm^2 were reported for the low and high WHR groups respectively.

Ross *et al.* (1992) conducted an extensive MRI and anthropometric study of 27 healthy male subjects varying in age [40.8 ± 14.5 years (mean ± SD)], BMI (28.5 ± 4.8 $kg.m^{-2}$) and WHR (0.96 ± 0.07). Total fat volume was derived from 41, 10 mm slices taken consecutively from head-to-toe at 50 mm intervals. The best anthropometric model for the prediction of IAF area at the L4-L5 level was provided by a combination of age and WHR ($P < 0.001$). This prediction equation explained 65% of the variance in IAF area, and had a SEE of 27.3cm^2. This study also showed that the anthropometric prediction equation proposed by Seidell *et al.* (1987), did not perform well under cross-validation ($R^2 = 0.58$, SEE = 40.1cm^2, actual mean ± SD

visceral fat area at the L4-L5 level = 117.9 ± 62.1cm^2, predicted mean visceral fat area at the L4-L5 level = 80.9 ± 66.2cm^2, $P < 0.001$).

A further examination of the usefulness of anthropometric measurements to predict abdominal adiposity in a sample of obese men and pre-menopausal women was undertaken by van der Kooy *et al.* (1993a). In this study of weight-loss, the correlation between MRI-determined visceral fat area and the sagittal and transverse abdominal diameters derived from either the MRI-scans or anthropometry were almost equal. In women, the correlation between visceral fat area and the MRI sagittal diameter was $r = 0.76$ ($P = 0.007$), whereas the correlation between visceral fat and the anthropometrically assessed supine diameter was $r = 0.72$ ($P = 0.01$). In men, these correlations were $r = 0.66$ ($P = 0.04$) and $r = 0.61$ ($P = 0.06$) respectively. In women, visceral fat area was most strongly associated with the WHR ($r = 0.64$, $P < 0.001$). In men, the sagittal diameter showed the highest correlation with visceral fat area ($r = 0.61$, $P < 0.001$), with waist circumference showing the strongest association with abdominal subcutaneous fat area ($r = 0.73$, $P < 0.001$). Several of the anthropometric regression equations reviewed earlier in this *critique*, were also applied to this sample. The equations of Seidell *et al.* (1987) and Despres *et al.* (1991) performed best of all, yielding correlations between measured and predicted visceral fat areas of $r = 0.66$ ($P < 0.001$) and $r = 0.75$ ($P < 0.001$) respectively. The mean differences between the measured and predicted values were not significant ($P > 0.05$). A further important finding in this study, was the lack of a strong association between changes in abdominal fat areas and changes in diameters and circumferences. The highest correlation was $r = 0.56$ ($P < 0.001$) between change in visceral fat area and change in sagittal diameter. This finding was further highlighted in a study of 40 obese women and 38 obese men (van der Kooy *et al.*, 1993b), that showed the WHR

was insensitive to changes in visceral fat area. The only significant association with a change in visceral fat area was a change in waist circumference for men ($r = 0.33$, $P < 0.05$).

In a similar study to that by Rankinen *et al.* (1999) outlined earlier, Ross *et al.* (1996) determined the associated sensitivity and specificity of a 100 cm waist circumference as a marker for a visceral fat area of 130 cm^2 or greater. Waist circumference was significantly related to visceral fat area in both men and women [$r = 0.65$ and 0.70, ($P < 0.01$) respectively]. As there was no difference ($P > 0.05$) between the regression lines describing these relationships, the male and female subjects were combined to form one sample for the following analysis. A waist circumference of 100 cm was associated with a sensitivity of 83% for identifying subjects with a visceral fat > 130 cm^2 and a specificity of 38% for identifying those with a visceral fat of < 130 cm^2. That is, 29 of 35 subjects were correctly identified (true positives) but 24 of the 64 subjects with a visceral fat <130 cm^2 also had a waist circumference > 100 cm (false positives).

2.2.2 Novel anthropometric indices of fat distribution

Since Vague (1956) first used anthropometry to describe human fat distribution, numerous investigators have proposed anthropometric alternatives. Whilst most of these studies have used the WHR, other combinations have been examined. The aim of this section is to outline these measurements and to examine their usefulness to the scientific community and general population.

In 1991, Valdez introduced a model-based index of abdominal obesity, referred to as the "conicity index" or C-index. Its aim is to standardise waist circumference for body shape. This index was based on the idea that, as people accumulate fat in the

abdominal region, "the shape of their bodies seems to change from that of a cylinder to that of a double cone (two cones with a common base)" (Valdez, 1991). The outermost circumference of such a double cone is given by the formula:

$$C = \sqrt{12}\,(\Pi / D)\,\sqrt{wt / ht}$$

where: wt = weight of the subject (kg)

ht = height of the subject (m)

D = body density (kg/m^{-3}).

If the "average human body density of 1050 kg/m^{-3} is used" the formula for the C-index becomes:

$$\text{C-index} = AG / [0.109\,(\sqrt{wt / ht})]$$

where: AG = abdominal girth (m)

0.109 is a constant that results from the conversion of units of volume and mass, to units of length.

Essentially, the C-index has no units and its predicted range is between 1.00 (perfect cylinder) and 1.73 (perfect double cone). So, if a person has a C-index of 1.25, it means that such a person has an abdominal girth which is 1.25 times larger than the circumference of a cylinder generated with the height and weight of that person (Valdez, 1991). Unfortunately, until Valdez *et al.* (1993) applied this index to CVD risk in a cohort of European and US men and women, there was no further description or justification of this method. It appears to be limited by the fact that it relies on a constant "average" body density, a value that is unknown. Furthermore, the C-index is probably too complicated to use in a public-health context and is difficult to interpret biologically (Molarius and Seidell, 1998).

As indicated previously, the close relationship between the ASD and visceral fat volume was first proposed by Kvist *et al.* (1988b). Kvist *et al.* (1988b) and later

Sjostrom (1991) suggested that in subjects in the supine position, increasing accumulation of visceral fat would maintain the depth of the abdomen in a sagittal direction while subcutaneous abdominal fat would reduce the abdominal depth due to the force of gravity. Later investigations found that anthropometrically-assessed abdominal diameters in the standing and supine positions are strongly correlated with abdominal diameters extracted from images (van der Kooy *et al.*, 1993a; Koester *et al.*, 1992).

In one study, the CT-derived ASD at the L4-L5 level, was the single best indicator of visceral fat volume ($r = 0.90$, $P < 0.05$), the error being in the region of 15% for cross-validation males and females (Sjostrom *et al.*, 1996). Ferland *et al.* (1989) and Despres *et al.* (1991), however, studied larger cohorts of men and women and found lower correlations between these parameters. All of these correlations were considerably greater than those observed between the anthropometrically-derived ASD and the visceral fat area ($r = 0.51$ and 0.61, $P < 0.05$, in men and women respectively) (van der Kooy *et al.*, 1993a). In the absence of data showing that the anthropometric ASD is a better predictor of visceral fat, there is no justification for its use in place of waist circumference. The latter of these measurements has been examined extensively in clinical and epidemiological studies and threshold values exist. Furthermore, as the public is familiar with the measurement of waist girth, and it is easily understood, it has been suggested that the focus of body-weight regulation should remain on this variable (Seidell, 1996). The limitation of using waist circumference is that it is unclear what this measurement is actually measuring, i.e. it is comprised of visceral and subcutaneous fat, muscle, internal organs and bone. Kahn (1993) has suggested several anthropometric ratios depending on the hypothesis of the investigator(s). These include waist girth/height (WhtR), ASD/height (ASD/ht),

ASD/thigh girth (ASD/Th) and the C-index. However, ratios have limitations that will be discussed in the following section.

2.2.3 Anthropometric classification of adipose tissue distribution and adjustment for body size variability.

The WhtR was initially proposed by Higgins *et al.* (1987) who explored its relationship with morbidity and mortality in Framingham participants. Data from large-scale studies of British and Japanese adults, subsequently suggested that this ratio is the most powerful anthropometric predictor of mortality (Cox *et al.*, 1996) and CAD risk factors (Hsieh and Yoshinaga, 1995). Although Ashwell *et al.* (1996a) have supported these claims and suggested that this ratio is a better predictor of IAF than waist circumference alone (Ashwell *et al.*, 1996b) others have disagreed (Han *et al.*, 1996; Han *et al.*, 1997). Kahn (1993) proposed that including height as a denominator acknowledges the larger bones and muscles that would be incorporated within either the waist girth or ASD in taller subjects.

Most ratios aim to control for the confounding influence of the denominator. In the case of the WhtR, the aim is to control for differences in stature. This ratio has been used to address the question of whether it is the absolute waist girth, or the relative size of the waist girth-to-height, that is the best predictor of cardiovascular morbidity and mortality. As discussed recently, however, ratios present problems with regard to their interpretation (Molarius and Seidell, 1998) and statistical analyses, where their use can introduce spurious correlations among the ratios and other variables (Allison *et al.*, 1995). For example, a large WhtR, may result from a large waist circumference or alternatively to short stature. As height is inversely related to

the risk of CAD (Williams *et al.*, 1997) this makes it difficult to separate risk associated with increased waist girth from risk associated with shorter stature.

2.2.4 Sensitivity of girth measurements to reflect changes in intra-abdominal fat following weight loss

If anthropometric girth measurements are valid indicators of IAF, they should also be sensitive to changes in this particular tissue mass. In comparison to the subcutaneous and femoral sites, studies have shown that the visceral fat depot exhibits a larger relative decrease with dietary-induced weight loss (van der Kooy *et al.*, 1993b; Zamboni *et al.*, 1993). Using a 13-week, 4.2 MJ/d energy-deficit diet, van der Kooy *et al.* (1993b) induced an average (± SD) weight loss of 12.9 (3.5) kg ($P < 0.001$). The proportional reduction in visceral fat was 40% in men and 33% in women. At the trochanter level, the relative reduction in subcutaneous fat was 29% in men and 26% in women. The waist and hip circumferences decreased significantly in men and women after weight loss ($P < 0.001$), as did the WHR ($P < 0.001$). In men and women, the decrease in subcutaneous fat at the abdominal and femoral areas was significantly related to the change in waist and hip circumferences ($r = 0.46$ to 0.70, $P < 0.05$). The change in visceral fat area was related to the change in waist circumference in men only ($r = 0.33$, $P < 0.05$), whilst the WHR was a poor predictor of all MRI-determined fat areas except the subcutaneous abdominal fat in men ($r = 0.37$, $P < 0.05$).

Zamboni *et al.* (1993) subjected 16 pre-menopausal women to a 2-week very-low energy diet (1286 kJ/d) and an additional 14-week low-energy diet (4200 kJ/d). After the full 16-week period, the average weight loss was 16 kg (SD not reported). Waist circumference, hip circumference, ASD, total fat, visceral fat, subcutaneous fat

and the subcutaneous-to-visceral fat ratio all exhibited significant reductions ($P < 0.05$). The WHR, however, did not change ($P > 0.05$) and was not related to visceral fat reduction ($P > 0.05$).

A combination of dietary restriction (4.18 MJ/d) and exercise (5-days per week of aerobic activity or 3-days per week resistance training) was found to reduce visceral fat area by 34.8 ± 18.2% in obese men and 25.9 ± 16.8% in obese women (Ross *et al.*, 1996). Corresponding values for subcutaneous fat loss were 32.7 ± 15.1% and 23.2 ± 11.9% respectively. Waist circumference was significantly ($P < 0.05$) reduced in men (11 ± 3.1%) and women (8.3 ± 3.4%), but the WHR was reduced in the men only (4.7 ± 3.2%, $P < 0.05$). Regression analysis revealed a significant relationship between a decrease in waist girth and a reduction in visceral fat ($r = 0.66$, $P < 0.01$). There was no sex difference in this relationship and a 1 cm decrease in waist girth corresponded to a 4% reduction in visceral fat mass or 5 cm^2 (3.5%) reduction in area. Although the WHR decreased with weight loss in the male subjects, this decrease was not related to the change in visceral fat ($r = 0.33$, $P > 0.05$).

After a 7-year period in women, Lemieux *et al.* (1996b) have shown that increases in waist girth, ASD and total fat mass were all highly correlated with an increase in visceral AT ($r = 0.81$ to 0.91, $P < 0.0001$). The relationship with WHR, however, was much weaker ($r = 0.35$, $P < 0.05$).

2.2.5 Conclusion

Epidemiological studies (Larsson *et al.*, 1984; Lapidus *et al.*, 1984) published almost two decades ago were the stimulus for a renewed interest in anatomical fat distribution. For reasons to be highlighted in the next section, the IAF depot now has

particular significance for researchers investigating the health implications of obesity. It is of high importance, therefore, that techniques exist for the accurate and reliable measurement of IAF. Studies reviewed above suggest that both CT and MRI are capable of this. Studies performed in quite recent times have shown that IAF accumulation is affected by several factors including age, gender and degree of obesity. Biologically, body fat distribution is determined by many other factors including genetics, sex and stress hormones, hormone receptor density and local lipoprotein lipase activity to name but a few (Bouchard *et al.*, 1993).

In order to facilitate larger-scale studies, it has been necessary to try and validate 'indirect' measurements of IAF. Furthermore, it is important that health professionals working in the community can make measurements that are relatively simple and inexpensive but at the same time scientifically meaningful. Thus, several anthropometric girth measurements have been evaluated. Initially the WHR was the measurement of choice. However, more recently the simple waist girth measurement has become pre-dominant. Although it only has a moderately strong correlation with IAF, it is capable of distinguishing individuals with high and low levels, it avoids the statistical pitfalls of ratios like the WHR, and threshold values have been proposed for both men and women. Furthermore, as will be highlighted in Section 2.3, it is closely associated with several risk factors for CVD.

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REVIEW OF LITERATURE

2.3 OBESITY AND FAT DISTRIBUTION: INDEPENDENT RISK FACTORS FOR CORONARY ARTERY DISEASE OR COMPONENTS OF A MULTIFACTORIAL SYNDROME?

2.3 OBESITY AND FAT DISTRIBUTION: INDEPENDENT RISK FACTORS FOR CORONARY ARTERY DISEASE OR COMPONENTS OF A MULTIFACTORIAL SYNDROME?

This section of the Literature Review aims to explain the association between obesity, fat distribution and CAD. Firstly, an examination of the relationship between glycaemia, blood lipids and lipoproteins, and CAD is presented, as disturbances in glucose and lipid metabolism are central to this discussion. A widely held belief is that insulin-resistance and compensatory hyperinsulinaemia are the key features of these metabolic disturbances. Thus, a brief description of the relationship between insulin and CAD is also given.

2.3.1 Glycaemia and CAD

In patients with type 2 diabetes, CHD is the most common cause of morbidity and mortality (Barrett-Connor, 1997). As people with type 2 diabetes have a risk of CVD that is two to four times greater than non-diabetic individuals (Coutinho *et al.*, 1999), there is overwhelming agreement that this condition is a powerful risk factor for a cardiovascular event (Stern, 1997). Until recently, the relationship between CVD and glycaemia at levels of blood glucose below the diabetic thresholds (7.0 $mmol.L^{-1}$ fasting and 11.1 $mmol.L^{-1}$ 2-hour post-load) was less clear (Barrett-Connor, 1997). Two important publications of recent times (Coutinho *et al.*, 1999; Khaw *et al.*, 2001), however, have provided the most convincing data yet that the association between blood glucose concentration and CVD occurs throughout the normal glucose range.

Coutinho *et al.* (1999) conducted a meta-regression analysis of 95,783 individuals followed for 12.4 years. In comparison to a fasting glucose level of 4.2 $mmol.L^{-1}$, fasting and 2-hour post glucose challenge levels of 6.1 $mmol.L^{-1}$ and 7.8

mmol.L^{-1} were associated with relative risks of a cardiovascular event of 1.33 (95% CI 1.06 - 1.67) and 1.58 (95% CI 1.19 - 2.10) respectively ($P < 0.02$ for the trend).

Khaw *et al.* (2001) showed that glycosylated haemoglobin was positively associated with the future risk of CHD. This is an important finding as glycosylated haemoglobin provides a reliable integrated estimate of glucose over the preceding 6 to 12 weeks. Furthermore, this association was independent of other risk factors for CHD and there was no evidence of a threshold effect.

Thus, there is now evidence that elevated levels of fasting and post-load glucose below the diabetic thresholds, represent risk factors for CVD. This continuous relationship appears to exist in all people, and is therefore, similar to the relationship between cholesterol, blood pressure and CVD (Gerstein, 1997).

Several mechanisms have been proposed to explain the relationship between blood glucose and CVD (Gerstein, 1997). These include: a direct toxic effect of glucose on cell function and structure through advanced glycation end products; indirect effects due to insufficient insulin secretion to prevent hyperglycaemia and the associated metabolic abnormalities; a long history or pre-existing insulin resistance and hyperinsulinaemia; an association with both known and unknown risk factors for CVD. Amongst other risk factors that are associated with hyperglycaemia are hypertension, hyperinsulinaemia, abdominal obesity and dyslipidaemia (Gerstein, 1997).

2.3.2 Insulin and CAD

The role of insulin as an 'independent' risk factor for CAD has been the subject of intense debate (Jarret, 1994; Reaven and Laws, 1994; Fontbonne, 1994; Stern, 1994). Several studies have reported an increased fasting plasma insulin level is associated

with an elevated risk of CAD in men (Ducimetiere *et al.*, 1980; Pyorala *et al.*, 1985; Eschwege *et al.*, 1985; Welborn and Wearne, 1979; Yarnell *et al.*, 1994; Fontbonne *et al.*, 1991). However, in all of these studies this association could be explained predominantly by the presence of other risk factors, particularly an elevated TG concentration and a low HDL-C. This observation has been reaffirmed recently (Pyorala *et al.*, 1998; Lakka *et al.*, 2000). In these studies, the increased incidence of stroke (Pyorala *et al.*, 1998) and cardiovascular mortality (Lakka *et al.*, 2000) was dependent on the co-existence of other risk factors, including upper-body fat distribution.

In some instances, no effect of insulin on CAD risk has been found (Welin *et al.*, 1992; Hargreaves *et al.* 1992; Orchard *et al.*, 1994). This is surprising given that hyperinsulinaemia frequently occurs alongside other recognised risk factors (Reaven, 1988).

In one study, the relationship between fasting plasma insulin and risk of IHD was reported to be independent of systolic blood pressure, medication use, a family history of IHD, TG, apo B, LDL-C and HDL-C (Despres et al., 1996).

The reasons for the discrepant findings are not clear, although several explanations have been proposed (Jarret, 1994; Reaven and Laws, 1994; Fontbonne, 1994; Stern, 1994). One possibility centres around the accompaniment of other risk factors with hyperinsulinaemia. As will be outlined in the sections below, whilst hyperinsulinaemia and obesity are inexorably linked, it has become apparent that not all obese individuals have the cluster of metabolic and haemostatic factors that increase the risk of CAD. This means that elevated insulin levels may well be found in large numbers of obese individuals who are not at increased risk of CAD.

2.3.3 Dyslipidaemia and CAD

With regard to CAD risk factor identification, one of the least controversial subjects concerns the role of blood lipids and lipoproteins. Evidence gathered for several decades shows unequivocally that elevated total and LDL-cholesterol and reduced HDL-cholesterol are independently associated with CAD risk (Neil, 1997). Conversely, the role of plasma TG as a risk factor for CAD has remained poorly defined. However, a recent meta-analysis of 17 population-based prospective studies that represented 2445 cardiovascular events among 46413 Caucasian men found that elevated TG was associated with a 14% increased risk of a cardiovascular event (Austin *et al.*, 1998). This association was independent of HDL-C. Subsequent studies have since confirmed this independent association (Stampfer *et al.*, 1996; Gardner *et al.*, 1996; Lamarche *et al.*, 1997). Plasma TG and LDL particle size both predicted subsequent CAD in three different Caucasian populations.

2.3.4 The Insulin Resistance Syndrome

In 1988, the clustering of several variables frequently associated with an increased incidence of CVD, namely insulin resistance and reduced glucose tolerance, increased very low-density lipoprotein (VLDL), decreased HDL-C and hypertension, was given the term 'Syndrome X' (Reaven, 1988). As this potentially atherogenic profile frequently co-exists with abdominal obesity, this latter characteristic was later added to the 'list', leading to the term "the deadly quartet" (Kaplan, 1989). Recent data from a study of men and women in Finland illustrates the importance of considering the type of obesity in this syndrome (Vanhala *et al.*, 1998). The prevalence of dyslipidaemia (increased TG and decreased HDL-C) and insulin resistance was 4% in non-obese subjects and 18% in those with a WHR >1.00 in men and >0.88 in women

with a BMI < 30 $kg.m^{-2}$. This increased to 28% in those with a BMI > 30 $kg.m^{-2}$ but WHR's lower than 1.00 and 0.88. The highest prevalence (46%) was found in those subjects who were both abdominally obese (WHR > 1.00 or 0.88) and obese (BMI > 30 $kg.m^{-2}$). A similar finding has also been reported recently in a large cohort of Canadian citizens (Connelly *et al.*, 1999). Furthermore, Lemieux *et al.* (1994) have suggested that differences in several lipid risk factors between men and premenopausal women of equal body fat, can be partly explained by gender differences in IAF accumulation. The same group also suggested that visceral fat deposition is partly responsible for the deterioration in the lipoprotein profile associated with aging in men (Lemieux *et al.*, 1995), and for the more cardio-protective lipoprotein profile found in obese black versus obese white individuals (Despres *et al.*, 2000).

Enzi *et al.* (1994) suggested extending this list of variables with a tendency to cluster to a "deadly sextet", including intra-abdominal obesity, insulin resistance, hypertriglyceridaemia, hypoalphalipoproteinaemia, hyperuricaemia and hypertension. Despres (1993) proposed a syndrome that included abdominal obesity, elevated TG and reduced HDL-C, an elevated number of small, dense LDL particles and glucose intolerance. As insulin resistance and the ensuing compensatory hyperinsulinaemia is thought by many to be the cause of the many metabolic and circulatory disturbances characteristic of the syndrome, the term insulin resistance syndrome has also been proposed (Ferrannini, 1993). Irrespective of its name, it is now clear that intra-abdominal obesity is a component of a cluster of abnormalities including glucose intolerance caused by insulin resistance, compensatory hyperinsulinaemia, hypertension, hypertriglyceridaemia and a lipoprotein profile that is highly atherogenic. Furthermore, a delayed post-prandial lipid clearance (Taira *et al.*, 1999;

Couillard *et al.*, 1998), impaired vascular endothelial dysfunction (Steinberg *et al.*, 1996; Westerbacka *et al.*, 1999), elevated plasminogen activator inhibitor (Vague *et al.*, 1989) and increased C-reactive protein (Lemieux *et al.*, 2001) are also observed in subjects with abdominal obesity. Until the exact pathophysiology of this syndrome is unravelled, a discussion of the best descriptive term is likely to continue (Reaven, 1997). Presently, insulin resistance syndrome, syndrome-X, or simply 'metabolic syndrome,' are all terms that are used. As the focus of this section is the association between abdominal obesity and disturbances in carbohydrate and fat metabolism, of which insulin resistance is undoubtedly a key element, the term insulin-resistance syndrome will be adopted.

2.3.5 Obesity, Fat Distribution and Metabolic Fitness

The relationship between abdominal adiposity and risk factors for CVD, including type 2 diabetes, glucose intolerance, insulin resistance and dyslipidaemia, has now been examined extensively in studies of both obese and non-obese males and females. Most of these studies have used anthropometric indices of fat distribution, although there are now a number that have more precisely estimated IAF with CT or MRI. Some studies have reported on the association between CVD risk factors and adipocyte morphology and metabolism following AT biopsy. The following sections review these studies. As this is an area that has received considerable attention in the last two decades, studies in women have been excluded so that greater details of studies in men can be presented. The exception to this is where the studies have examined adipose tissue morphology by the biopsy technique. In this case, the data are still sparse so studies of women have been included.

(a) adipose tissue morphology, type 2 diabetes and glucose-insulin homeostasis in obese and non-obese men and women

In men, fasting insulin but not glucose has been found to be modestly associated with fat cell weight (FCW) from the gluteal, femoral and epigastric regions ($r = 0.20$, $P < 0.01$) but not hypogastric FCW (Krotkiewski *et al.*, 1983). In women, the incidence of type 2 diabetes, fasting levels of glucose and insulin, and the sum of glucose and insulin levels during an oral glucose tolerance test (OGTT), were greater in those subjects with larger epigastric fat cells compared to gluteal fat cells (Krotkiewski *et al.*, 1983). Evans *et al.* (1983) proposed that, in premenopausal women, an increase in upper-body fat, enlargement of abdominal adipocytes and the accompanying imbalance in glucose-insulin homeostasis are attributable, in part, to an elevated level of free androgens.

(b) body fat distribution, type 2 diabetes and glucose-insulin homeostasis in obese and non-obese men

A comparison of two simple anthropometric indices of fat distribution (WHR and subscapular-to-triceps skinfold ratio, STR) suggested that WHR had the stronger relationship with type 2 diabetes (Haffner *et al.*, 1987). Fasting concentrations of insulin and glucose have also been reported to be more strongly associated with the waist circumference ($r = 0.61$, $P < 0.01$) than the hip circumference ($r = 0.47$, $P < 0.01$) (Krotkiewski *et al.*, 1983). The European Fat Distribution Study (Cigolini *et al.*, 1992) reported a similar finding. After adjustment for BMI, waist circumference was more closely associated with fasting insulin than either the WHR or WTR.

A study of 126 men with a mean BMI of 40.9 ± 8.9 kg.m^{-2} found no relationship between fasting glucose and BMI, but a significant association between fasting glucose and WHR ($r = 0.347$, $P < 0.001$) (Ditschuneit *et al.*, 1994). In a study of trained and sedentary men, the abdomen-to-hip girth ratio (AHR) was related to the

insulin sensitivity index in both groups (Houmard *et al.*, 1991). However, there was a greater insulin response during an OGTT in the sedentary subjects ($P < 0.01$). This study, however, reported a closer association between insulin sensitivity and relative body fat ($r = -0.68$, $P < 0.001$) than with fat distribution.

Sparrow *et al.* (1986) randomly selected 41 men from the Normative Aging Study and found that CT-determined IAF was significantly related to the 2-hour post challenge serum glucose concentration ($r = 0.44$, $P < 0.01$). The relationship with BMI and CT-measurements of extremity fat were not significant ($P > 0.05$). In a similar study of obese men, Fujioka *et al.* (1987) found fasting plasma glucose and the glucose area following an OGTT were both significantly greater ($P < 0.05$) in subjects with visceral compared to subcutaneous-abdominal obesity. The plasma insulin area, however, was greater in subcutaneous-abdominal obese individuals ($P < 0.05$). Park *et al.* (1991) also found that insulin sensitivity was closely related to IAF ($r = -0.88$, $P < 0.01$) in a small ($n = 9$) group of healthy, young men aged 28.6 ± 0.7 years (mean $\pm$ SEM).

Pouliot and co-workers (1992) found that obese subjects had significantly greater concentrations of fasting glucose, insulin and glucagon than their lean counterparts ($P < 0.05$). In these obese men, WHR was not related to fasting insulin, glucose or glucagon ($P > 0.05$). The area of visceral AT between the fourth and fifth lumbar vertebrae (L4 - L5) however, was related to fasting insulin ($r = 0.45$, $P < 0.001$) as was the abdominal-to-femoral AT ratio ($r = 0.48$, $P < 0.001$). Following a 75-g oral glucose dose, WHR had the closest relationship with the glucose area under the curve ($r = 0.47$, $P < 0.001$) and visceral AT the strongest association with the insulin area ($r = 0.57$, $P < 0.0001$).

A study of men with a large variation in age and BMI, found a significant relationship between the area of visceral AT measured by a single CT-scan at the L4 level and the insulin response during an OGTT ($r = 0.43$, $P < 0.01$) (Zamboni *et al.*, 1994). BMI, but not visceral AT, was associated with the plasma glucose response to the OGTT. Further analysis suggested a trend toward exacerbated glucose intolerance when a larger BMI is accompanied by an increased visceral AT mass.

Given the apparent association between visceral AT and insulin sensitivity described above, it is surprising that Abate *et al.* (1996) failed to show a greater intra-peritoneal fat mass in type 2 diabetic men compared to non-diabetic men. The diabetic men did, however, have increased amounts of subcutaneous truncal AT as determined from skinfolds, and this was an important determinant of insulin sensitivity. Abate *et al.*,(1995) have also shown that after adjusting for total body fat, glucose disposal rate and residual hepatic glucose output showed the highest correlation with the sum of trunk skinfolds ($r = -0.40$, $P = 0.01$ and 0.33, $P = 0.04$ respectively). Other measures of fat distribution including the WHR and MRI-determined IAF were unrelated to these measures of insulin sensitivity. A similar finding was noted in a study of 26 healthy men who had their abdominal composition assessed by CT (Goodpaster *et al.*, 1997). Subcutaneous abdominal fat was inversely related to insulin sensitivity in a multiple regression model that included IAF while the converse was not found. A recent study has extended these findings with the suggestion that posterior abdominal subcutaneous AT, assessed by MRI, is a more important determinant of peripheral and hepatic insulin sensitivity than the anterior subcutaneous abdominal AT (Misra *et al.*, 1997)

(c) adipose tissue morphology and fasting lipid and lipoprotein levels in obese and non-obese men and women

Studies indicate that fasting TG concentration is associated with subcutaneous abdominal fat-cell size ($P < 0.01$) (Krotkiewski *et al.*, 1983; Stern *et al.*, 1973) but not gluteal or femoral fat-cell size (Krotkiewski *et al.*, 1983) or abdominal fat cell number (Stern *et al.*, 1973). Plasma TC has been reported to be unrelated to either adipocyte size or number, or total body fat (Stern *et al.*, 1973).

One study has reported a significant univariate relationship between fat-cell size, determined from a bilateral buttock biopsy, and serum TG in women ($r = 0.27$, $p < 0.05$), but found no such relationship in a smaller sample of men (Foster *et al.*, 1987). Fat cell size also related inversely to HDL-C ($r = -0.17$, $P < 0.05$) and HDL-C / TC ($r = -0.17$, $p < 0.05$) in women but not men. However, neither fat-cell size nor number was related to TG, LDL-C or HDL-C in a multiple regression model.

In 22 non-obese premenopausal women, subcutaneous abdominal FCW was found to be related to the LDL-apo B / LDL-C ratio ($R = 0.58$, $P < 0.005$), HDL-apo AI ($r = -0.51$, $P < 0.05$), HDL_2-C ($r = -0.51$, $P < 0.05$), HDL-apo AI / LDL -apo B ($r = -0.53$, $P < 0.01$) and HDL_2-C / HDL_3-C ($r = -0.52$, $P < 0.01$) (Pouliot *et al.*, 1989).

In a recent study using both CT-scanning and biopsy techniques, Imbeault *et al.* (1999) showed that visceral AT and subcutaneous abdominal FCW were both positively related to fasting plasma insulin, TG, LDL-C, apo B and the TC : HDL-C ratio in men and women ($P < 0.05$). They also found that for a given amount of visceral AT, enlarged subcutaneous abdominal fat-cells were associated with a deterioration of the metabolic risk profile. Conversely, the hypertrophy of femoral adipocytes did not appear to have this effect.

(d) body fat distribution and related dyslipidaemias in obese and non-obese men

One of the earliest investigations into the association between body composition, lipids, and lipoproteins found that BMI, skinfolds and body fat were almost equally related to TG and HDL-C (Leclerc *et al.*, 1983). Despite their statistical significance, after adjustment for several confounding variables, the size of the correlations were surprisingly low. The largest correlation with TG ($r = 0.16$) and HDL-C ($r = -0.17$) was with fat mass. A later study by the same group reported that, in comparison to women, body fatness was more closely related to serum lipids in men (Despres *et al.*, 1985). When six skinfolds were examined individually, the subscapular and abdominal sites were more powerfully related to TG and HDL-C. A similar finding was reported by Contaldo *et al.* (1986) in a study of middle-aged men in Southern Italy. Relative body fat and subscapular skinfold thickness were related to TC ($r = 0.37$ and 0.41 respectively, $P < 0.01$), but BMI and triceps skinfold were not. TG was equally related to all measures of adiposity ($P < 0.01$). Among 2110 men participating in the Northwick Park Heart Study (Haines *et al.*, 1987), there was essentially no difference in the magnitude of the partial correlations between TC and skinfolds at the forearm, subscapular and suprailiac sites ($P < 0.0001$). The partial correlation between TC and triceps skinfold, although still significant ($P < 0.0001$), was slightly lower.

It is well known that serum TG and HDL-C are inversely related (Albrink *et al.*, 1980). Thus, Despres *et al.* (1988) investigated the independence of the relationship between fat distribution and HDL-C in 429 healthy men after statistically adjusting for TG concentration. The distribution of subcutaneous fat, as reflected by the trunk-to-extremity skinfold ratio, and abdominal skinfold thickness were significantly related to TG ($r = 0.27$ and 0.35 respectively, $P < 0.0001$) and HDL-C (r -0.14, $P <$ 0.01 and -0.26, $P < 0.001$ respectively). The relationship between abdominal skinfold

and HDL-C remained significant after adjustment for TG and BMI ($r = -0.16$, $P < 0.01$) suggesting that a portion of the relationship between HDL-C and subcutaneous abdominal adiposity is independent of obesity and TG.

After the findings of the epidemiological studies in Gothenburg (Lapidus *et al.*, 1984; Larsson *et al.*, 1984), many groups of researchers were prompted to examine the relationship between lipids and body fat distribution assessed by the WHR. Some evidence suggests fasting plasma TG is unrelated to WHR in obese men after adjustment for age and relative body fat (Leenen *et al.*, 1992). Other studies have found WHR is associated with fasting TG concentration independently of BMI (Haffner *et al.*, 1987; Larsson *et al.*, 1989).

Barakat *et al.* (1988) investigated the association between WHR and plasma lipids, lipoproteins and apolipoproteins in 100 male volunteers who ranged widely in age (19- to 68-years) and WHR (0.89 to 1.09). WHR was significantly related to TC ($r = 0.21$, $P = 0.04$), LDL-C ($r = 0.22$, $P = 0.03$), TG ($r = 0.25$, $P = 0.01$) and the TC : HDL-C ratio ($r = 0.30$, P 0.002). Inverse associations were found with HDL-C ($r = -0.19$, $P = 0.05$), apo AI ($r = -0.28$, P 0.005) and apo AI : aop B ($r = -0.26$, $P = 0.01$). Further analysis showed that men with a high WHR were more likely to have a lipid profile suggestive of higher CVD risk than men with a lower WHR. This difference was regardless of age or the degree of obesity.

In a group of healthy, sedentary men, WHR had a stronger relationship with fasting TG concentration ($r = 0.43$, $P < 0.0001$) than either waist girth, STR, subscapular skinfold, relative body fat or BMI (Terry *et al.*, 1989). WHR remained a significant predictor of TG concentration after adjustment for STR and relative body fat ($r = 0.27$, $P < 0.05$). Pouliot *et al.* (1992) also found that WHR, but not relative body fat, was related to fasting TG concentration in obese men ($r = 0.28$, $P < 0.05$). In

a further study of overweight men, WHR and WTR both correlated with plasma TG concentration ($r = 0.17$ and 0.20 respectively, $P < 0.05$) (Terry *et al.*, 1991). Thigh girth was also significantly related to TG concentration but in an inverse manner ($r = -0.21$, $P < 0.05$) (Terry *et al.*, 1991). Fasting TG concentration has also been found to be higher in non-obese men with abdominal adiposity compared to non-obese men with gluteo-femoral adiposity after they were matched for age, body fat and BMI ($P < 0.05$) (Peebles *et al.*, 1989). Anderson *et al.* (1988) found that men who were in the upper tertiles of both BMI and WHR had the greatest TG concentration. WHR was related to fasting TG after adjustment for BMI, age, smoking, alcohol intake and exercise.

High-density lipoprotein in humans is composed of two principal fractions - HDL_2 and HDL_3. Of these, HDL_2 has been most consistently linked with a protection against CVD (Musliner and Krauss, 1988). Using multiple regression procedures, Ostlund *et al.* (1990) reported that 41% of the variance in HDL_2 level could be explained by the combined effect of the WHR ($P < 0.0001$), plasma insulin ($P = 0.0003$) and glucose tolerance ($P = 0.05$). BMI and relative body fat were not related to HDL_2 and subjects at the 25^{th} percentile for WHR had a HDL_2 level 153 % of that in subjects at the 75^{th} percentile.

Studies conducted over the last 20-years or so, have used a wide variety of methods to describe fat distribution. Wallace *et al.* (1994), found that 29 different anthropometric methods had been used for this purpose, and several alternatives had been used to determine the WHR. Commonly, waist girth has been measured at either the level of natural narrowing between the lower rib and the superior iliac crest, midway between these points or at the level of the umbilicus. Hip girth has been measured at the level of the greater trochanters or the widest point around the

buttocks. This can potentially lead to inconsistency when placing subjects into obese categories. In a study of 324 men, aged 36.5 ± 8.0 years and with a BMI of 27.4 ± 3.4 $kg.m^{-2}$ (means ± SD), Jakicic *et al.* (1993) examined the relationship between blood lipids and five different WHR measurements. The waist girth measured at the level of the umbilicus, and at the midpoint between the lower rib and iliac crest were equally related to all lipid parameters ($P < 0.05$). The WHR's derived from these waist measurements and hip girth measured at the greatest gluteal circumference were also related to lipids ($P < 0.05$). However, these relationships existed only in those men in the top quartile for BMI, indicating that obesity is a necessity for this association. Richelsen and Pedersen (1995) examined a small group (n = 58) of 44-year old non-obese men to investigate the association between the total body fat, BMI WHR, ASD, ASD/Ht, conicity index and blood lipids. Multiple regression analysis showed that ASD and ASD/Ht were the best predictors of the blood lipids with no significant influence of BMI. The conicity index was the weakest predictor. Thus, even a minor accumulation of abdominal AT was related to increased CVD risk in non-obese men. In a recent study of 165 men from the UK, however, no consistent relationship could be identified between blood lipids and five anthropometric measure of adiposity (BMI, WHR, WhtR, waist girth and conicity index) (Yasmin, 2000).

Han *et al.* (1996) adopted an alternative approach to regression analysis in their study of waist girth and blood lipids. Using ROC curves, they reported that with regard to identifying men with a low HDL-C, sensitivity and specificity were equal (~60%) at a waist circumference of ~94.0 cm in men.

CT-scan studies have shown a positive relationship between IAF and the level of fasting TG (Pouliot *et al.*, 1992; Zamboni *et al.*, 1994; Fujioka *et al.*, 1987,). Visceral AT area quantified by MRI was also shown to be related to fasting TG

concentration in obese men following univariate analysis ($P < 0.05$), but not after the effects of age and relative body fat were considered ($P > 0.05$) (Leenen *et al.*, 1992). A trend toward an increased TG concentration was demonstrated in men with visceral obesity compared to men with gluteo-femoral obesity, although this difference failed to reach significance ($P > 0.05$) (Fujioka *et al.*, 1987). After adjustment for total body fat, visceral AT area has been found to be related to TG concentration ($r = 0.28$, $P < 0.05$) (Pouliot *et al.*, 1992). In the same study, multiple regression analysis showed the abdominal-to-femoral AT ratio was the best independent predictor of TG concentration ($R^2 = 0.366$, $P < 0.0001$) and, in partial agreement with an earlier finding (Terry *et al.*, 1991), the femoral AT area was inversely related to TG concentration. Zamboni *et al.* (1994) found the relationship between visceral AT and fasting TG was stronger than with any other metabolic variable ($r = 0.47$, $P < 0.01$).

A number of investigators have found that the WHR is related to TC and various other lipoproteins and lipoprotein-lipids. Larsson *et al.* (1989) reported a relationship between TC and WHR independently of BMI in a large-scale population survey. Terry *et al.* (1989) found WHR, but not STR or relative body fat, was positively related to TC and a number of lipoprotein-lipids including LDL-C, very low-density lipoprotein cholesterol (VLDL-C) ($P < 0.01$), small LDL (S_f 0-7), intermediate-density lipoprotein (IDL) (S_f 12-20), smaller VLDL (S_f 20-60) ($P < 0.001$) and larger VLDL (S_f 60-100 and 100-400) ($P < 0.05$). WHR was also inversely related to HDL-C ($P < 0.01$), HDL_2 ($P < 0.0001$) and LDL peak flotation rate ($P < 0.001$). In a later study, these researchers reported similar findings in a group of moderately overweight men (Terry *et al.*, 1991). WHR and WTR were positively related to small LDL ($P < 0.01$) and inversely related to HDL_2-C, LDL peak flotation

rate ($P < 0.01$), large LDL and HDL_2 particle size ($P < 0.05$). Total VLDL was also positively related to both WHR ($P < 0.05$) and WTR ($P < 0.01$).

In a study of two groups of non-obese men matched for relative body fat ($P > 0.05$) but differing in WHR ($P < 0.001$), TC and LDL-C levels were not different ($P > 0.05$) (Peebles *et al.*, 1989). HDL-C and apo AI, however, were greater and apo B was lower in subjects with gluteo-femoral adiposity. A smaller LDL particle size was also a characteristic of subjects with abdominal adiposity ($P < 0.005$).

Walton *et al.* (1995) found that abdominal adiposity assessed by DEXA was independently associated with elevated TG and decreased HDL_2-C. Total adiposity and age were unrelated to a number of lipids and lipoproteins. However, DEXA is unable to distinguish intra-abdominal and subcutaneous AT. CT-scan studies, on the other hand, have shown that with respect to body fatness, visceral AT is the most important morphological determinant of an atherogenic lipid profile (Pouliot *et al.*, 1992; Zamboni *et al.*, 1994; Fujioka *et al.*, 1987; Tchernof *et al.*, 1996). Results from an MRI study, however, suggested that visceral fat accumulation is associated with an adverse lipid profile in obese women but not obese men (Leenen *et al.*, 1992). Visceral AT has been found to be positively associated with LDL-TG, apo B ($P < 0.05$), VLDL-C and VLDL-TG ($P < 0.01$), and inversely with the HDL-C : LDL-C ratio ($P < 0.01$) in a group of subjects with a wide range of IAF (Zamboni *et al.*, 1994). In obese men, visceral AT but not subcutaneous abdominal AT was found to be inversely related to HDL-C, HDL_2-C and the HDL_2 : HDL_3 ratio (Pouliot *et al.*, 1992). Independently of several fat distribution variables (total body fat, visceral AT area, subcutaneous abdominal AT area, femoral AT area), the abdominal-femoral AT ratio had the strongest association with HDL-C, HDL_2-C and the HDL_2 : HDL_3 ratio. The level of significance of these relationships ranged from $P < 0.05$ to $P < 0.0001$.

As indicated earlier, the lipoprotein phenotype associated with an increase in the number of small, dense LDL particles is highly prevalent amongst CHD patients (Austin *et al.*, 1988; Campos *et al.*, 1992). Tchernof *et al.* (1996) examined LDL-particle size in relation to visceral AT, other lipoproteins and hyperinsulinaemia in 79 obese and non-obese men. Subjects classified as having the small, dense LDL phenotype had higher levels of TG, HDL-C, visceral AT and fasting insulin. In multivariate analysis, visceral AT was not a significant predictor of the small, dense LDL phenotype after insulin and the other lipoproteins were considered.

In one of the largest CT studies, Boyko *et al.* (1996) found a significant, independent association between IAF and TG ($r = 0.22$, $P < 0.001$), total HDL ($r = -0.29$, $P < 0.001$), HDL_2-C ($r = -0.30$, $P < 0.001$) and HDL_3-C ($r = -0.19$, $P < 0.01$) in 290 second-generation Japanese Americans. Correlations with subcutaneous abdominal fat were low and not significant ($P > 0.05$).

Whilst visceral AT accumulation appears to be closely associated with disturbances in carbohydrate and lipoprotein metabolism that represent an increased risk of CVD, some evidence indicates that femoral AT may have a protective effect (Terry *et al.*, 1991; Pouliot *et al.*, 1992). Thigh girth adjusted for waist girth has been shown to be inversely related to TC, VLDL-C, small LDL ($P < 0.01$), IDL ($P < 0.05$), TG and total VLDL ($P < 0.001$) in overweight men (Terry *et al.*, 1991). LDL peak flotation rate was positively related to thigh girth ($P < 0.01$). CT-scan results have also shown femoral AT area to be inversely related to fasting TG ($P < 0.01$), and positively associated with HDL ($P < 0.05$) and HDL_2-C ($P < 0.01$) (Pouliot *et al.*, 1992). Young and Gelskey (1995), however, have warned against ignoring people with 'non-central' obesity. This warning is based on their findings from the Manitoba Heart Health

Study. In a sample of 2339 adults, those with non-central obesity tended to have blood pressure, lipids and glucose between those of the non-obese and centrally obese.

Whilst abdominal adiposity is closely related to elevated TG levels and other lipoprotein-lipid variables associated with elevated CVD risk, investigators studying this relationship in a mixed group of sedentary and exercise-trained men, found that aerobic fitness was a better predictor of TG and HDL than the AHR (Houmard *et al.*, 1991). Abdominal adiposity was more closely associated with LDL particle diameter and HDL_{2b}. The importance of physical activity as a lifestyle variable that attenuates the risk of CVD among the obese has received considerable support recently. This results from data suggesting a lower risk of cardiovascular and all-cause mortality in fit obese men in comparison to unfit and obese men (Lee *et al.*, 1999). This trend was apparent irrespective of whether obesity was defined by BMI, relative body fat or waist circumference.

In summary, it appears that an abdominal distribution of body fat, particularly an increased deposition of fat in the intra-abdominal cavity, is associated with hypertriglyceridaemia, an elevated number of small, dense LDL particles and apo B, and reduced HDL-C, especially HDL_2-C (Kissebah and Krakower, 1997). The traditional lipid markers of CVD risk, TC and LDL-C are not commonly found in subjects with visceral obesity (Despres and Lamarche, 2000).

2.3.6 Mechanisms Linking Obesity and Body Fat Distribution with the Metabolic Disturbances of Lipid and Carbohydrate Metabolism Associated with Coronary Artery Disease

In recent years, many review papers have proposed evidence-based mechanisms to explain the relationship between obesity, particularly obesity associated with

increased IAF, and CVD (Bjorntorp, 1993; Frayn, 1993; Frayn and Coppack, 1992; Reaven, 1995; Despres, 1991, 1993, 1998; Sniderman *et al.*, 1998; Kissebah and Krakower, 1994). Two central phenomena outlined in these papers as being of major importance for explaining the metabolic aberrations of abdominal obesity are insulin resistance and elevated non-esterified fatty-acids (NEFA's). As a potential cause of insulin resistance, elevated NEFA's in the hepatic portal circulation was first proposed by Bjorntorp (1990). Whilst it has not been possible to measure NEFA concentrations in the portal blood of humans directly, the mechanism proposed by Bjorntorp has received almost universal acceptance. Figure 1 (2.3) illustrates this proposed mechanism that links IAF and several metabolic disturbances associated with an increased risk of CVD. However, Barnard and Wen (1994), presented a compelling argument that physical inactivity, combined with a high fat and refined sugar diet, may well be the initiating factors for the insulin resistance of obesity, and that the elevated NEFA concentrations are, therefore, a consequence and not the cause of insulin resistance. In reality, it is likely that the insulin-resistance syndrome is a consequence of a sedentary, 'westernised' lifestyle that is exacerbated by intra-abdominal obesity. Although obesity plays a role in the development of insulin resistance, this condition can be found in lean individuals whilst some obese people can be relatively insulin sensitive (Reaven, 1997). Indeed, a recent study suggests that the association between hyperinsulinaemia and the cluster of metabolic abnormalities that define the insulin resistance syndrome is stronger in the lean than the obese (Nabulsi *et al.*, 1995). Bjorntorp (1993) rather aptly referred to visceral obesity as a "Civilization Syndrome". In this section, Barnard and Wen's model has been expanded by the inclusion of skeletal muscle fibre type and Bjorntorp's proposal that intra-abdominal adipocytes release a high concentration of NEFA's into the hepatic

portal vein. The combination of these three factors is likely to present the most likely explanation for the increased incidence of CAD in men with abdominal obesity.

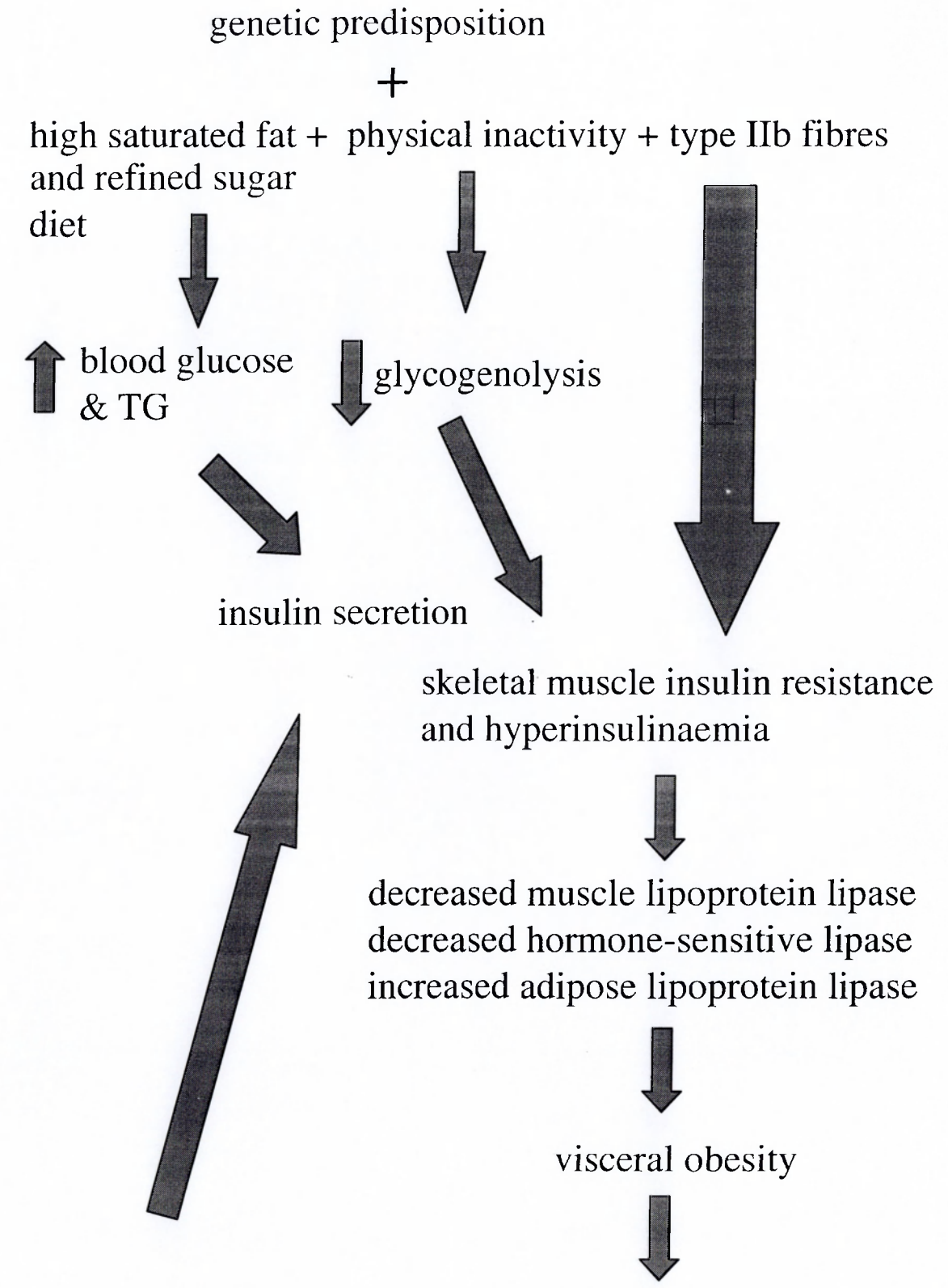

Figure 1 (2.3). The role of a high fat, refined sugar diet, physical inactivity, skeletal muscle and visceral obesity in the insulin resistance syndrome.

(a) effect of a high fat and refined sugar diet, physical inactivity and skeletal muscle morphology on insulin-mediated glucose uptake

During a euglycaemic clamp procedure, non-oxidative glucose storage i.e. glycogen synthesis, represents the major mechanism by which the increased circulating glucose is removed. Thus, skeletal muscle is the major target tissue for the restoration of insulin-mediated euglycaemia (DeFronzo *et al.*, 1979). A defect in this mechanism is, therefore, likely to result in glucose intolerance, with an excessive and prolonged rise in post-load or post-prandial glycaemia (Felber, 1992). In subjects with adequate pancreatic β-cell function, this leads to elevated fasting and post-prandial insulin levels that can be thought of as 'compensatory'. That is, the greater than normal insulin response compensates for the apparent insulin resistance. The compensatory hyperinsulinaemia results in a normal fasting glucose level.

With regard to diet, Grimditch *et al.* (1987, 1988) have shown that within 10-weeks, rats fed a high fat, high sucrose diet develop skeletal muscle insulin resistance and hyperinsulinaemia without any increase in body fat. This has since been confirmed by other researchers (Storlien *et al.*, 1993; Vrana *et al.*, 1993) and has also been shown to occur in the liver (Davidson and Garvey, 1993). Furthermore, after a 2-year intervention period, in comparison to rats fed a low-fat, high-complex-carbohydrate diet, rats fed with a high-fat and sucrose diet were significantly fatter, had a greater fasting insulin and TG concentration, greater systolic blood pressure and had an enhanced blood clotting tendency (Barnard *et al.*, 1993).

The mechanism by which a high fat and refined sugar diet promotes skeletal muscle insulin resistance is presently unclear. Steiner (1991) has argued that hypertriglyceridaemia is the cause and not a consequence of insulin resistance. However, diets that are low in fat and high in carbohydrate and lead to an elevated TG

concentration (Coulston *et al.*, 1983), have been found to have no effect (Garg *et al.*, 1992) or to increase insulin sensitivity (Kolterman *et al.*, 1979). There appears to be no change in the number of insulin receptors, GLUT-4 glucose transporters or insulin receptor tyrosine kinase (Barnard and Youngren, 1992; Fryer and Kruszynska, 1993; Boyd *et al.*, 1990). However, there is evidence to suggest a decrease in insulin receptor autophosphorylation and tyrosine kinase activity in rats fed a high-fat diet (Iwanishi and Kobayashi, 1993) and a reduced tyrosine kinase activity in skeletal muscle insulin receptors in patients with type 2 diabetes (Scheck *et al.*, 1991).

Current available evidence suggests that the amount and type of dietary fat consumed, together with physical activity, are important determinants of skeletal muscle insulin sensitivity (Vessby, 2000). Several studies have indicated that a diet high in fat is associated with insulin resistance and greater risk of developing type 2 diabetes (Marshall *et al.*, 1994; Marshall *et al.*, 1997; Mayer-Davis *et al.*, 1997). A high fat diet may be especially deleterious in sedentary individuals (Mayer-Davis *et al.*, 1997).

Systemic (Nikkari *et al.*, 1995) and skeletal muscle membrane (Ayre and Hulbert, 1996; Vessby, 2000) lipid composition are a reflection of dietary fat composition. In a study of newly diagnosed type 2 diabetic patients, Salomaa *et al.* (1990) were able to demonstrate a higher proportion of saturated fatty acids in the serum cholesterol esters in comparison to non-diabetics. A similar finding has been reported by Vessby *et al.* (1994) in a study of elderly men - insulin sensitivity was inversely related to the saturated fatty acid content of serum cholesterol esters. Laserre *et al.* (1985) found that if the dietary fat composition was changed from more saturated to more unsaturated fatty acids, the serum fatty acid profile changes to resemble one that is associated with greater insulin sensitivity.

Several studies have demonstrated a relationship between skeletal muscle phospholipid composition and insulin sensitivity. Borkman *et al.* (1993) showed that insulin sensitivity was directly related to the sum of the proportions of long-chain polyunsaturated fatty acids with 20-22 carbon atoms. The similar results reported by Pan *et al.* (1995), and the inverse relationship between the proportion of palmitic acid and insulin sensitivity reported by (Vessby *et al.*, 1994), suggest that an increased saturation of skeletal muscle membrane fatty acids adversely affects insulin sensitivity.

Physical inactivity is associated with a reduced muscle glycogen utilisation. Furthermore, some of the skeletal muscle characteristics associated with physical inactivity (reduced fibre size, capillary density, mitochondrial volume density, GLUT-4 content, insulin receptors, hexokinase isoforms) predispose this tissue to a reduced glucose uptake and insulin resistance (Simoneau, 1995). Muscle glycogen concentration is tightly regulated by two mechanisms. Glycogen synthesis is catalysed by the enzyme glycogen synthase, that is activated by glucose-6-phosphate and insulin (Nuttal *et al.*, 1974), and by dephosphorylation (Felber, 1992). Conversely, an increased glycogen concentration and dephosphorylation inhibits glycogen synthase (Danforth, 1965; Villard-Palasi, 1969) but activates glycogen phosphorylase (Hers, 1976). In figure 1 (2.3), a high dietary sugar intake leads to elevated blood glucose and, therefore, to pancreatic insulin secretion. However, glucose uptake for glycogen synthesis (the normal physiological pathway for the restoration of euglycaemia) is blocked due to inhibition of glycogen synthase by a high muscle glycogen concentration and also by the morphological characteristics of untrained skeletal muscle outlined above. This slowing of the glycogen cycle, due to a reduced emptying of the glycogen stores, leads to down-regulation of the number of insulin receptors

and, therefore, to insulin resistance, glucose intolerance, compensatory hyperinsulinaemia, and in the longer-term type 2 diabetes in genetically-prone individuals (Felber, 1992).

This model also suggests that skeletal muscle fibre type is an important factor to consider in the overall development of the insulin-resistance syndrome. There have been several studies that have examined the association between obesity, skeletal muscle characteristics and insulin-mediated glucose uptake (Lillioja *et al.*, 1987; Simoneau and Bouchard, 1993; Wade *et al.*, 1990; Richelsen *et al.*, 1993; Krotkiewski and Bjorntorp, 1986). A comprehensive review of the significance of skeletal muscle in obesity and the insulin resistance syndrome has been provided by Kelley and Simoneau, (1997).

Type II muscle fibres, particularly type IIb fibres have a lower capillary-to-fibre ratio (Bassett, 1994). In obese men, the muscle fibre capillary density has been found to be inversely related to fasting glucose and insulin (Lithel *et al.*, 1981). Furthermore, Lillioja et al. (1987) reported an inverse relationship between insulin-mediated glucose uptake and percentage of type IIb fibres in vastus lateralis muscle. This study also found a positive relationship between insulin sensitivity and capillary density. Studies of rat muscle conducted *in vitro*, have shown greater insulin binding and basal and insulin-stimulated glucose uptake in predominantly type I muscles compared to predominantly type II muscles (Bonen *et al.*, 1981; Henriksen *et al.*, 1990).

With regard to body fatness and fibre type, several studies have shown an association. Wade *et al.* (1990) reported a significant inverse relationship between body fatness and the percentage of type I fibres, whilst Lillioja *et al.* (1987) reported a similar finding with WHR. Simoneau and Bouchard (1993) found a positive relationship between body fatness and percentage type IIb fibres. Others have found

that males and females with android obesity had approximately 70% type II fibres, whereas gynoid obese females had approximately 50% type II fibres (Krotkiewski and Bjorntorp, 1986). Some of the properties of type I fibres, for example, increased GLUT-4 levels, capillary density per fibre, insulin receptors and enzyme activity, may explain the relationship between fibre type and insulin resistance. However, because of certain adaptive responses of skeletal muscle to habitual exercise training, for example an increased capillary density (Coggan *et al.*, 1992; Ingjer, 1979), it may be more desirable to have a predominance of aerobically trained type II fibres than untrained type I fibres. A single bout of moderate- to high-intensity exercise has a significant and positive effect on skeletal muscle insulin sensitivity that may persist for several days (King *et al.*, 1995; Kang *et al.*, 1999). However, a return to sedentary existence causes a decrease in insulin sensitivity (Mikines *et al.*, 1991). Likely explanations for the improved insulin sensitivity in skeletal muscle and adipose tissue associated with exercise are increased translocation and quantity of GLUT 4 transporters (Ferrara et al., 1998; Hansen et al., 1998; Hirshman *et al.*, 1993). Devlin *et al.* (1987) have also shown that exercise can positively influence splanchnic insulin sensitivity in type 2 diabetic men.

As a possible explanatory factor of the insulin resistance associated with obesity, substrate competition has received considerable attention. Some time ago, Randle and colleagues demonstrated the existence of decreased glucose oxidation and glycogenesis in skeletal muscle in the presence of elevated NEFA's (Randle *et al.*, 1963). This was attributed to increased NEFA oxidation, driven by a concentration-dependent NEFA uptake, that reduced insulin sensitivity and glucose uptake. In obesity, conditions exist that suggest the existence of this "glucose-fatty acid" cycle could explain the insulin resistance. First, total fat mass is enlarged, thereby,

providing ample substrate i.e. NEFA's. Second, as will be discussed later, intra-abdominal adipocytes have a lively basal and catecholamine-stimulated lipolysis that presents the circulation with high levels of NEFA's. However, studies indicate that insulin resistance in obesity is not caused by increased uptake and oxidation of fatty acids (Kelley and Simoneau, 1997). Rather, a decreased oxidative capacity of fat in the skeletal muscle of obese subjects leads to the accumulation of intra-muscular fat that reduces insulin sensitivity and causes a defect in glycogen synthesis (Kelley and Simoneau, 1997). This leads to the intriguing thought that, due to their morphological and metabolic characteristics, a high proportion of untrained type II skeletal muscle fibres predisposes to both obesity, insulin resistance and the CVD risk factors of these conditions (Bassett, 1994).

(b) abdominal adipose tissue fat storage and lipolysis

It is well established that a high intake of dietary fat contributes to the development of obesity (Astrup *et al.* 2000). Furthermore, obesity per se can lead to a decrease in insulin-mediated glucose uptake and hyperinsulinaemia, that can be corrected by weight loss (Olefsky *et al.*, 1974).

Figure 1 (2.3) proposes that the hyperinsulinaemia secondary to chronic insulin resistance is associated with reduced lipoprotein lipase (LPL) in skeletal muscle (Pollare *et al.*, 1991; Kiens *et al.*, 1989). Conversely, insulin within the normal physiological range has been shown to stimulate LPL and inhibit hormone sensitive lipase in adipocytes (Farese *et al.*, 1991; Ong *et al.*, 1988; Fried *et al.*, 1993; Sadur and Eckel, 1982). These changes in lipase activity favour fat storage in the AT fat cells as opposed to fat metabolism by skeletal muscle and, therefore, has a causal role in the development of obesity (Kern, 1996). Furthermore, regional LPL activity partly

explains differences in body fat distribution. In men, visceral AT-LPL activity is lowest whilst femoral and abdominal subcutaneous activities are equal. In women, femoral AT-LPL activity is greatest and subcutaneous abdominal LPL activity is higher than visceral (Poirier and Eckel, 2000).

As outlined previously, the deposition of fat varies between individuals according to genetic and local biological factors (Bouchard *et al.*, 1993). Adipocytes from the abdominal region, particularly from the intra-abdominal cavity (omental and mesenteric adipose tissues) have unique lipolytic properties related, in part, to the distribution and adrenergic receptors and sensitivity to insulin. Under normal conditions, the release of NEFA's from AT is suppressed by insulin (Frayn, 1993). However, studies have shown that intra-abdominal adipocytes have a low concentration of insulin receptors and are relatively insulin resistant in comparison to subcutaneous fat cells (Bolinder *et al.*, 1983; Mariege *et al.*, 1995). Therefore, despite the presence of hyperinsulinaemia in visceral obesity, the condition is associated with a hyperlipolytic state (Despres and Lamarche, 2000). This elevated lipolysis is compounded by the presence of the enlarged intra-abdominal adipocytes that also exhibit a high-rate of lipolysis because of their adrenoceptor characteristics. Thus, visceral obesity is characterised by elevated NEFA concentrations, because of the reduced antilipolytic effect of insulin and an increased lipolytic effect of catecholamines. This second lipolytic feature is discussed in more detail below.

The omental and mesenteric adipose tissues have a very high rate of lipolysis due to a preponderance of β-adrenergic receptors and little α-adrenergic inhibition (Rebuffe-Scrive *et al.*, 1989, 1990). These AT depots drain directly into the hepatic portal vein, thereby exposing the liver to high concentrations of NEFA's. This has two effects. Firstly, the hepatic extraction of insulin is reduced resulting in a further

increase in the hyperinsulinaemia of visceral obesity (Hennes *et al.*, 1990; Svedberg *et al.*, 1990). The mechanism here is thought to involve interference in the binding process of insulin with its receptor (Svedberg *et al.*, 1989, 1990). This is due to a decreased number of insulin receptors caused by receptor internalization followed by a parallel decrease in insulin degradation (Svedberg *et al.*, 1989, 1990. Secondly, the NEFA's are the substrate for the production of TG-rich lipoproteins (Despres, 1994, Bjorntorp, 1990). The preponderance of β-receptors compared to α-receptors means that intra-abdominal adipocytes are highly sensitive to the lipolytic effects of circulating catecholamines. Specifically, Lonnqvist *et al.* (1997) have shown with an *in vitro* preparation that this phenomenon is due to an increase in the function of β_3-adrenoceptors, a decrease in the function of α_2-adrenoceptors and an increased ability of cyclic AMP to activate hormone sensitive lipase. When combined with the insulin-resistant state, the NEFA mobilisation capacity of the portal AT of abdominally obese men and women is markedly elevated. In psychologically stressful situations, exercise and smoking this effect is even more pronounced (Bjorntorp, 1993). Therefore, figure 1 (2.3) suggests that the relative insulin resistance of intra-abdominal AT is both a cause and consequence of abdominal obesity.

(c) the effect of excess non-esterifed fatty acids in the portal circulation on lipoprotein kinetics

Exposure of the liver to elevated NEFA's has been shown to have effects on insulin extraction, gluconeogenesis and VLDL-TG secretion. The increased appearance of systemic VLDL-TG has repercussions for 'downstream' lipoprotein metabolism resulting in the formation of an atherogenic profile as described below. The, secretion

of VLDL seems to be mainly regulated by the synthesis of TG, that in turn is dependent on substrate availability, in this instance NEFA's (Kissebah *et al.*, 1974; Byrne *et al.*, 1991). Insulin inhibits the secretion of VLDL-TG from isolated liver cells and this inhibition is blunted in insulin-resistant hepatocytes (Durrington *et al.*, 1982, Bartlett and Short, 1988). Exposing the liver to elevated NEFA concentrations *in vivo*, results in hepatic insulin resistance (Wiesenthal *et al.* 1999), increased gluconeogenesis (Ferrannini *et al.*, 1983) and an overproduction of VLDL-TG (Carlson *et al.*, 1965). The increased gluconeogenesis presents a further glucose load that exacerbates the hyperinsulinaemia.. A further way in which elevated portal NEFA's influence hepatic VLDL-TG secretion appears to be the excess synthesis of apolipoprotein (apo) B-100, the protein backbone of VLDL and LDL (Bjorntorp, 1990; Kissebah and Krakower, 1997). This is partly due to an unusually long half-life of the mRNA for apo B-100 that secures translation of apo B-100 for a long time (Bjorntorp, 1990).

This production of hepatic TG in the fasting state may contribute to the impaired clearance of dietary fat (Lewis, 1997), because in addition to the increased production of VLDL-TG, obesity and other insulin resistant states are associated with a reduced responsiveness of AT-LPL to insulin (Eckel, 1987). This leads to a reduced catabolism of chylomicrons and other TG-rich lipoproteins during post-prandial lipaemia (Brunzell *et al.*, 1979; Ooi *et al.*, 1992129-132). As the retention of LDL in the circulation is dependent on both the rate of production and removal, an increased VLDL secretion lends itself to increased concentrations of VLDL, LDL and apo B-100 in the circulation (Bjorntorp, 1990; Sniderman *et al.*, 1998). Many of the LDL particles will be smaller and denser than normal due to increased exchange of core lipids (Sniderman *et al.*, 1998).

The insulin resistance, hypertriglyceridaemia of hepatic origin and reduced LPL activity may also explain the low HDL-C of subjects with visceral obesity (Despres, 1991). Through the action of the cholesteryl-ester transfer protein (CETP), the prolonged residence of TG-rich lipoproteins in the circulation leads to an increased exchange of TG from these particles to LDL and HDL at the expense of cholesterol (Despres *et al.*, 1989a, 1989b). Disturbance in this LPL-mediated mechanism may well underlie the association between hypertriglyceridaemia and low HDL-C as weight loss is associated with increased LPL activity and HDL-C and a reduced TG concentration (Frayn and Coppack, 1992). Further mechanisms that may be important factors in the association between visceral obesity and low HDL-C levels are, an elevated hepatic-TG lipase action which is related to a decreased HDL_2-C level (Despres *et al.*, 1989a), an increased catabolism of apo AI and AII (Barnard and Wen, 1994), and apolipoprotein E (apo E) polymorphisms (Kissebah and Krakower, 1997).

Insulin resistance and obesity are also related to the occurrence of small dense LDL particles in the circulation (Barakat *et al.*, 1990; Reaven *et al.*, 1993; Tchernof *et al.*, 1996). Thus, the relationship between abdominal adiposity and the atherogenic small dense LDL particle, the so-called type B phenotype (Austin *et al.*, 1990; 1992), may also be explained by the effect of hepatic insulin resistance and increased VLDL-TG secretion. Based on recent studies, Frayn (1993) has suggested a possible mechanism by which insulin resistance may affect the formation of small dense LDL particles. The presence of larger TG-rich particles in the circulation, particularly in the post-prandial period, offers a high potential for CETP-mediated neutral lipid exchange. This is shown by an increase in their cholesteryl ester content during this period (Fisher *et al.*, 1993). If this exchange occurs not just with HDL, as is normally considered, but also with LDL, then the result will be cholesteryl ester-depleted, TG-

enriched LDL particles. The TG may then be removed by the action of hepatic lipase, leading to a lipid depleted, atherogenic, small dense particle.

(d) concluding remarks

Two eminent researchers in the field of obesity have proposed that insulin resistance is an adaptive change in obesity to protect against further fat deposition (Ravussin and Swinburn, 1996). Insulin stimulates AT LPL that results in adipocyte fatty acid uptake. The elevated NEFA's seen in obesity, partly as a consequence of the diminished anti-lipolytic effect of insulin, lead to increased fat oxidation and decreased post-prandial storage of TG. Other equally eminent obesity researchers (Sims, 1996) have argued that insulin resistance is a result of our genetic inheritance and the modern environment in which we live. Obesity, argues Sims, develops as a consequence of the anti-lipolytic action of compensatory hyperinsulinaemia. Whichever comes first, one thing is now clear - individuals with abdominal obesity are at increased risk of CVD and type 2 diabetes and this risk is mediated through a cluster of metabolic, thrombotic and haemodynamic factors. Thus, features that may once have provided a survival advantage via the so-called 'thrifty gene', now may be responsible for the most prevalent morbid conditions of our time (Sims, 1996).

Barnard and Wen (1994), Basset (1994) and Bjorntorp (1990) produced papers outlining the importance of diet and physical inactivity, skeletal muscle characteristics and intra-abdominal adiposity respectively in the development of the insulin-resistance syndrome. This section of the Review of Literature has attempted to bring these areas together, and has presented a model suggesting a 'vicious circle' of events leading to insulin resistance, chronic hyperinsulinaemia, glucose intolerance, an atherogenic dyslipidaemia and obesity.

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CHAPTER 3

METHODOLOGY

3.1 SUBJECT SELECTION

3.1.1 Coronary artery disease patients

Patients for the studies outlined in this thesis were 70 men who reported consecutively for cardiac catheterisation at the Department of Cardiology, University Hospital of Wales, Cardiff. Catheterisation was undertaken as part of a series of investigations into suspected atherosclerotic CAD. Five men had angiography scores of zero for both of the scoring systems used in this study. These men were excluded from analyses involving either a comparison with control subjects or when only patients with CAD were required. They were included, however, in any regression procedures as the aim was to examine the relationship between anthropometry and CAD across the range of CAD i.e. no CAD to severe CAD. All participants gave their written informed consent and the study was approved by the South Glamorgan Local Research Ethics Committee. Other than subjects whose body mass had not been stable (± 3 kg) for six months prior to the study, no patients were excluded from participation. Anthropometry was performed on the hospital ward at the patients' bedside prior to angiography.

3.1.2 Controls

Subjects were 72 men who volunteered to participate in a university health-screening programme. Four men did not provide blood samples and were excluded from analyses when these data were required. All subjects gave their written informed consent and the study was approved by the South Glamorgan Local Research Ethics Committee. Details of medical history, past and present smoking and alcohol habit, family history of all cardiovascular diseases and diabetes, and employment and educational status were recorded by questionnaire. Any subject whose body mass had

not been stable (± 3kg) for 6 months prior to the study, who was taking lipid-lowering medication or with physician-diagnosed diabetes was excluded from any further analysis.

3.2 CORONARY ANGIOGRAPHY

In conjunction with symptoms and clinical evaluation, diagnostic coronary angiography was undertaken via the right femoral artery (Judkins, 1967) to assess the presence of CAD. A scoring system (Brandt *et al.*, 1977) was applied to each angiogram to take into account the degree of stenosis, the number of arterial branches affected, and their anatomical distribution to the myocardium as follows. Following angiography, a black and white two-dimensional image of the coronary tree was produced. Each coronary vessel was then graded according to the following guidelines. A complete blockage in a coronary artery (100% cross-sectional area loss) was graded 'a'. Cross-sectional area losses of 90-99%, 75-89%, 50-74% and <50% were graded 'b', 'c', 'd' and 'e' respectively. A myocardial value ranging from 1 to 10 was then given to each vessel depending on the proportion of myocardium being supplied by that artery. A final myocardial score that was dependent on the grade and myocardial value was then given to each vessel. Thus, this system accounts for the location of coronary atherosclerotic lesions as well as the degree of stenosis. A score of zero represented no detectable coronary atheroma in any vessel. A maximal score of 15 represented severe three-vessel disease with blockages near the top of the left anterior descending, left circumflex and right coronary arteries.

A ventricular score was also determined based on the movement of the left ventricular wall that was divided into five segments according to American Heart

Association (Brandt *et al.*, 1977). These five segments are described as the superior basal, antero-lateral, apical, diaphragmatic and inferior basal. The movement of each segment was then scored as follows: 0, normal; 1, hypokinetic; 2, akinetic and 3, dyskinetic. Thus, a ventricular score of 0 would mean normal movement of all 5 segments. A score of 15 would mean irregular movement in all segments.

3.3 ANTHROPOMETRY

Body mass and stature were measured with a beam balance (Seca 710) and stadiometer (Seca 220). Mass was measured to the nearest 0.1 kg and stature to the nearest 0.1 cm. Anthropometry was performed following standard guidelines (Lohman *et al.*, 1991). Four limb skinfolds (biceps, triceps, front mid-thigh and medial calf) and four torso skinfolds (subscapular, suprailiac, supraspinale and abdominal) were measured on the right side of the body with Harpenden skinfold callipers (Holtain Ltd, Crymych, UK). Skinfolds were recorded to the nearest 0.2 mm within 2-seconds of the full pressure of the callipers being applied. Girths (hip, abdominal, waist, contracted upper-arm, mid-thigh, medial calf) were measured with a flexible metallic tape measure (Holtain Ltd) and standing ASD with a large sliding anthropometer fitted with straight branches (Holtain Ltd). Girths and the ASD were recorded to the nearest 0.1 cm. To measure the ASD, the subject was asked to stand upright with the shoulders relaxed. One branch of the anthropometer was positioned on the skin immediately above the umbilicus. With the anthropometer held horizontally, the other branch was then pressed against the spinous process of a vertebra. The antero-posterior diameter of the abdomen at this level was then recorded at the end of a normal expiration. Supraspinale skinfold was measured as part of the

somatotyping procedure (Carter and Heath, 1990) and was used in this study as an additional torso skinfold so that there were equal numbers of torso and limb skinfolds. As there is no published Phantom value for supraspinale skinfold it was not normalised for stature or body mass.

Body mass index, WHR, AHR, WHtR, WTR, ASD/Ht and the ratio of the $\sum 4$ torso-to-$\sum 4$ limb skinfolds (TLR) were calculated from the anthropometric measurements.

Intra-observer reliability coefficients, derived from duplicate measurements of each variable on 20 subjects, were all > 0.99. Standard errors of measurement (SEM = $SD\sqrt{1-r^2}$) ranged from 0.17 mm for the triceps skinfold to 0.32 cm for the waist girth.

Biceps skinfold

This vertical skinfold was measured on the anterior aspect of the arm midway between the acromion process and the olecranon process.

Triceps skinfold

This vertical skinfold was measured on the posterior surface of the arm midway between the acromion process and the olecranon process.

Front mid-thigh skinfold

This vertical skinfold was measured in the midline of the anterior aspect of the thigh, midway between the inguinal crease and the proximal border of the patella.

Medial calf skinfold

This vertical skinfold was measured with the subject in a seated position with the right knee flexed at about 90°. The skinfold was lifted on the medial aspect of the calf at the level of maximal circumference.

Subscapular skinfold

This diagonal (~45°) skinfold was measured at a point immediately below the inferior angle of the scapula. The skinfold was lifted following the natural cleavage lines of the skin.

Suprailiac skinfold

This diagonal (~45°) skinfold was measured in the midaxillary line immediately superior to the iliac crest.

Supraspinale skinfold

This diagonal (~45°) skinfold was lifted at the intersection of the anterior-superior iliac crest and the superior iliac crest in the midaxillary line.

Abdominal skinfold

This horizontal skinfold was measured at a point 1cm below and 3cm laterally to the mid-point of the umbilicus.

Hip girth

For this measurement, the tape measure was placed over the subjects underwear at the level of maximal circumference around the buttocks.

Abdominal girth

For this measurement, the tape measure was placed in contact with the skin at the level of the umbilicus following a normal expiration.

Waist girth

For this measurement, the tape measure was placed in contact with the skin at the level of the narrowest part of the torso as viewed from the anterior aspect. In some obese subjects it was not possible to identify a waist narrowing, so the measurement was made as the smallest horizontal circumference between the iliac crest and lower ribs.

Upper-arm girth (contracted)

For this measurement the subject was asked to maximally contract the biceps muscle with the arm flexed at the elbow to approximately 45°. The tape measure was positioned around the upper-arm and the maximal circumference recorded.

Mid-thigh girth

This measurement was recorded at the level of the mid-thigh skinfold with the tape measure positioned horizontally around the thigh. The subject stood upright for this measurement with the weight equally distributed over both feet.

Medial calf girth

The tape measure was positioned horizontally around the calf at the level of maximal circumference. The subject stood with weight equally distributed over both feet.

3.4 SOMATOTYPING

Heath-Carter anthropometric somatotypes were determined following standard procedures and using the equations presented below (Carter and Heath, 1990). Intra-observer reliability coefficients (correlations), derived previously from duplicate measurements of each variable on 20 subjects, were all greater than the values recommended by Carter and Heath (1990).

Somatotype components were calculated using the following equations:

Endomorphy = $-0.7182 + 0.1451(X) - 0.00068(X^2) + 0.0000014(X^3)$
X = sum of triceps, subscapular and supraspinale skinfolds.

Mesomorphy = [(0.858 x humerus breadth) + (0.601 x femur breadth) + (0.188 x corrected arm girth) + (0.161 x corrected calf girth)] - (height x 0.131) + 4.5.

Ectomorphy = (HWR x 0.732) - 28.58.
HWR = height / cube root of weight. If HWR was less than 40.75 but more than 38.25, ectomorphy = HWR x 0.463 - 17.63. If HWR was equal to or less than 38.25 a rating of 0.1 was given.

3.5 PROPORTIONALITY

As outlined in Chapter 1, proportionality refers to the relationship of body parts to one another or to the whole body (Ross and Marfell-Jones, 1991). Proportionality scores, or z-values, for skinfold and girth measurements were calculated using the approach devised by Ross and Wilson (1974).

To adjust for differences in body size the following formula was employed (Ross and Wilson, 1974):

$$Z = 1/S\ [V\ (170.18/h)^{d} - P]$$

Where Z is the proportionality score, 1 is a constant, S is the standard deviation of the Phantom measurement, V is the variable being scaled (in this case a skinfold or girth), 170.18 is the Phantom height, h is the obtained height of the subject, ^{d} is a dimensional exponent (1) and P is the Phantom value for the variable V.

This formula geometrically scaled the skinfolds to the Phantom stature (170.18 cm), obtained the difference from the given Phantom value, and expressed this value in terms of the SD of the Phantom. A *z*-value of 0.00 indicated that the variable V was proportionally the same as the Phantom and *z*-values of <0.00 or >0.00 indicated that V was proportionally smaller or larger than the Phantom respectively.

When scaling for body mass the same procedure was used, except that the Phantom stature was replaced by the Phantom body mass (64.58 kg) and the subject's stature was replaced by their body mass.

3.6 BLOOD SAMPLING AND DETERMINATION OF SERUM GLUCOSE, LIPIDS AND LIPOPROTEINS

Following a 12-hour overnight fast, venous blood samples were drawn from an ante-cubital vein into SST Vacutainer tubes (Becton Dickinson, Oxford UK). Subjects assumed a supine position for the blood withdrawal and a tourniquet was fixed around the upper-arm. The site of venupuncture was first cleansed with a sterilised swab containing 70% v/c isopropyl alcohol (Medi Swab, Smith and Nephew, UK.). Serum

glucose, TC and TG were analysed by dry chemistry slide technology (Kodak Ektachem Clinical Chemistry Slides, Kodak Clinical Diagnostics, Rochester, USA), on an Ortho Vitros 750 analyser (Ortho Clinical Diagnostics, Amersham, UK.). The between batch coefficient of variation for TC was 2.09% at 4.25 mmol.L^{-1} and 2.64% at 6.65 mmol.L^{-1}. The corresponding figures for TG measurement were 1.25% at 1.10 mmol.L^{-1} and 1.35% at 3.09 mmol.L^{-1}. For glucose these figures were 2.05% at 6.10 mmol.L^{-1} and 1.12% at 14.7 mmol.L^{-1}. HDL-C was determined after precipitation of the non-HDL lipoproteins with 10% polyethylene glycol 6000 (Warnick et al., 1985). The between batch coefficient of variation was 4.47% at an HDL-C concentration of 1.33 mmol.L^{-1}. Concentrations of LDL-C were calculated using the Friedewald (1972) method other than where TG were found to be > 4.0 mmol.L^{-1}.

3.7 STATISTICAL ANALYSIS

3.7.1 General statistical procedures

Kolmogorov-Smirnov test's of normality revealed all variables were normally distributed. Significance of all differences and relationships was accepted at the 5% probability level ($P < 0.05$). Other than where specified, data are presented as mean ± SD. All analyses were performed using SPSS software (SPSS Inc, 1999).

3.7.2 Statistics used in Chapter 4

Pearson product-moment correlation coefficients were determined to show the relationship between the angiographic findings and age, body mass, stature, skinfolds, girths and the indices of AT distribution. This technique was also used to investigate the relationship between fasting serum glucose, lipids, lipoproteins and anthropometric measurements.

A form of factor analysis known as principal component analysis was used to explore the anatomical distribution of subcutaneous AT in the men with CAD and the healthy control men. The aim of the principal component analysis was the reduction of variables and the identification of AT distribution components.

With this method, a set of correlated variables (in this case skinfolds) is replaced by a set of uncorrelated variables (principal components), which are linear transformations of the original variables. The extent to which a single principal component can explain the bulk of the variance depends on the extent to which the original variables are correlated. From a set of n variables, there are n possible principal components. Subsequent components are uncorrelated with the first component and each explains less of the multivariate variance than the one preceding it. With regard to finding specific AT patterns, it is the components subsequent to the first that are interesting, as the first is likely to reflect variation in total adiposity (Mueller and Reid, 1979).

In the principal component analysis, the first step was to compute a simple correlation matrix between the skinfolds. Next, the suitability of the data for principal component analysis was assessed using the correlation matrix, the Kaier-Meyer-Olkin Measure of Sampling Adequacy and Bartlett's Test of Sphericity. Scree plots and eigenvalues were then computed to determine the number of identifiable principal components. Usually, only components with eigenvalues greater than 1.0 are interpreted (Tabachnick and Fidell, 1996). Finally, inspection of the loadings (correlation's) of the original variables on the principal components was performed in order for this interpretation to take place.

Differences in anthropometric measurements (raw scores and size-adjusted) between the CAD patients and the healthy men were investigated using *t*-tests for independent samples.

3.7.3 Statistics used in Chapter 5

Differences in somatotype between the CAD patients and healthy, age-matched men were investigated using the procedures outlined by Cressie *et al.* (1986). A mulitvariate analysis of variance (MANOVA) was performed on the mean somatotypes of each group using Wilk's lambda as the test statistic. A univariate F-test was then used to identify differences in the somatotype components.

Second-order partial correlation's were used to assess the strength of the relationship between each somatotype component and anthropometric measures of AT distribution. This technique examines this relationship whilst statistically controlling for the effects of the other two somatotype components.

The relationship between the individual somatotype components and the indicators of metabolic fitness were determined using third-order partial correlation's. This technique was used to adjust for the effect of the interrelationship between the somatotype components and also for differences in age.

Multivariate non-linear canonical correlation analysis was used to investigate the relationship between metabolic fitness and the somatotype treated as a gestalt. The canonical correlation is interpreted as Pearson product-moment correlation coefficient. Bartlett's (1947) test, where the canonical correlation's are evaluated as a chi-square variable, was used to test the significance of these correlation's. The aim of canonical correlation analysis is the formation of linear combinations of the variables that have maximum correlation. The combinations of the variables are known as canonical variates and the correlation between the two canonical variates is the

canonical correlation. The correlation's between the original, standardised (z-transformed) variables and the canonical variates were calculated to determine the strength of their contribution to that variate. The squared canonical correlation indicates the level of explained variance between the pairs of variates. For this analysis, the dependent variate was metabolic fitness (serum glucose, TC, LDL-C, HDL-C, TG) and the independent variate somatotype (endomorphy / mesomorphy / ectomorphy).

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CHAPTER 4

RESULTS & DISCUSSION

STUDIES FOCUSING ON OBESITY AND ADIPOSE TISSUE DISTRIBUTION

4.1 SUBCUTANEOUS ADIPOSITY AND GIRTH MEASUREMENTS IN MEN: THE ASSOCIATION WITH ANGIOGRAPHIC FINDINGS

The aim of this study was to examine the relationship between a variety of anthropometric measurements and the findings of coronary angiography. Tables I (4.1) and II (4.1) show the mean values (± SD) of the angiography procedure, age, height, body mass, BMI, skinfolds and girths. Angiography revealed a range of coronary atherosclerosis ranging from zero (no detectable atheroma in any of the major coronary arteries) to 14.1 (severe stenosis in one or more major vessel). There was a significant correlation between the myocardial score and the LV score ($r = 0.347$, $P = 0.003$).

TABLE I (4.1) Means ± standard deviations (SD) of the results from coronary angiography (N = 70).

	Mean (SD)	Range
Myocardial score	6.22 (3.86)	0.00 to 14.10
LV score	2.04 (1.99)	0.00 to 7.00

The range of BMI scores (20.0 to 41.7 $kg.m^{-2}$) shows there was a wide variation in the degree of overweight amongst these men. Forty-three (62%) were overweight (BMI > 25.0 $kg.m^{-2}$) and 15 of these (21%) were obese (BMI > 30.0 $kg.m^{-2}$). The ratio of torso-to-limb skinfolds (1.91 ± 0.50) indicates a two-fold greater subcutaneous adiposity on the torso compared to the limbs. With regard to some of the WHR and waist girth cut-off points discussed in Chapter 1 (section 1.1.3), twenty-seven men (38%) had a WHR greater than 1.00, 24 (34%) had a waist girth greater than 100 cm, 18 (26%) were greater than 102 cm and 44 (63%) were above 94 cm for waist girth.

TABLE II (4.1) Means ± standard deviations (SD) for age, height, body mass, BMI, skinfolds and girths for men undergoing coronary angiography (N = 70).

Variable	Mean ± (SD)
Age (yr)	60.5 (9.3)
Height (cm)	173.4 (6.2)
Body mass (kg)	82.0 (14.8)
BMI ($kg.m^{-2}$)	27.2 (4.3)
Skinfolds (mm)	
Triceps	15.2 (6.8)
Biceps	9.2 (4.0)
Front mid-thigh	15.2 (6.6)
Medial calf	10.2 (4.0)
Subscapular	26.7 (8.9)
Suprailiac	25.9 (8.4)
Supraspinale	16.8 (7.9)
Abdominal	25.9 (8.4)
Σ 8 skinfolds	145.1 (45.5)
Σ 4 torso skinfolds	95.3 (29.4)
Σ 4 limb skinfolds	49.8 (18.4)
Σ torso / Σ limb skinfolds	1.91 (0.50)
Girths (cm)	
ASD	26.4 (3.4)
Waist	97.4 (10.0)
Abdomen	99.8 (10.2)
Hip	99.5 (8.1)
Mid-thigh	50.7 (4.6)
ASD/Ht	0.15 (0.02)
WHtR	0.56 (0.06)
WHR	0.98 (0.06)
AHR	1.00 (0.05)
WTR	1.79 (0.13)

ASD, abdominal sagittal diameter; ASD/Ht, abdominal sagittal diameter/height; WHtR, waist-to-height ratio; WHR, waist-to-hip ratio; AHR, abdomen-to-hip ratio; WTR, waist-to-thigh ratio.

Table III (4.1) shows the relationship (using simple correlation analysis) between body mass and height, skinfolds, girth measurements and the angiographic findings.

Only the relationship between myocardial score and mid-thigh girth was significant ($r = -0.258$, $P < 0.05$).

TABLE III (4.1). Pearson product-moment correlations showing the relationship between skinfolds, girths and angiographic findings in men with CAD (N = 70).

Skinfolds	Myocardial score	Ventricular score
Body mass	-0.176	-0.067
Height	-0.125	0.089
Skinfolds		
Triceps	0.057	-0.044
Biceps	-0.119	-0.061
Front mid-thigh	-0.035	-0.082
Medial calf	-0.058	0.028
Subscapular	-0.027	-0.039
Suprailiac	0.017	-0.148
Supraspinale	-0.107	0.033
Abdominal	-0.097	-0.012
Σ 8 skinfolds	-0.050	-0.057
Σ 4 torso skinfolds	-0.059	-0.056
Σ 4 limb skinfolds	-0.030	-0.053
Σ torso / Σ limb skinfolds	-0.069	-0.074
Girths		
ASD	-0.094	-0.124
Waist	-0.125	-0.064
Abdomen	-0.119	-0.082
Hip	-0.114	-0.029
Mid-thigh	-0.258*	-0.212
ASD/Ht	-0.010	-0.041
WHtR	-0.077	-0.093
WHR	-0.056	-0.074
AHR	-0.067	-0.145
WTR	0.135	0.127

* $P < 0.05$.

Several prospective studies have shown a relationship between skinfolds, particularly torso skinfolds, and future risk of CHD (Ducimetiere *et al.*, 1986;

Donahue *et al.*, 1987; Hargreaves *et al.*, 1992; Stokes III *et al.*, 1985). However, as far as can be established, no study has ever examined the association between skinfolds and the severity of atherosclerosis determined with coronary angiography. This investigation clearly suggests that skinfolds are not related to the degree of coronary artery stenosis assessed with a relatively sensitive scoring system or to impaired left ventricular function. This may be due in part to the sample size employed in this study. However, the relationships are so weak as to suggest that even with a larger sample, significance would be attached to small correlation coefficients and would, therefore, be of questionable value.

Several investigators have in the past examined the association between anthropometric girth measurements and angiographic findings (Hauner *et al.*, 1990; Hodgson *et al.*, 1994; Ley *et al.*, 1994; Flynn *et al.*, Thompson *et al.*, 1991 Kahn *et al.*, 1996; Hartz *et al.*, 1990). These studies have provided mixed findings. This investigation has attempted to extend these studies by using an angiogram scoring system. Previously, the decision of who does, and who does not, have CAD was based on an arbitrary decision in terms of arterial occlusion i.e. > or < 50% narrowing. Thus, it was possible that subjects with small differences in arterial occlusion were allocated to either disease or control group. Furthermore, no consideration was given to the anatomical location of the occlusion within the coronary arteries. The scoring system employed in this study overcomes these limitations by treating CAD as a continuous rather than dichotomous variable. It also considers the anatomical location of the occlusion.

As for body mass, height and skinfolds, this investigation failed to show a relationship between anthropometric girth measurements used to assess body fat distribution and CAD severity. One significant relationship did appear, however,

between mid-thigh girth and myocardial score ($r = -0.258$, $P < 0.05$). There are several potential explanations for this, including the possibility of a type I statistical error. As a significant portion of the skeletal muscle is located in the thigh, another possibility is that mid-thigh girth may reflect muscle mass. Bjorntorp (1993) postulated that atrophied gluteal muscles could be responsible for high WHR's and explain some of the relationship between WHR and CVD. In the same way, a larger mid-thigh girth may be a marker of greater (or more active) muscle mass, and, therefore, a reduced susceptibility to the atherogenic consequences of insulin-resistance associated risk factors.

To summarise, this investigation found no relationship between a multitude of anthropometric measurements that provide information of adiposity, the severity of coronary atherosclerosis and left ventricular function. Mid-thigh girth showed a weak, inverse but significant association with atherosclerosis severity. Further research is required to evaluate the physiological significance of this finding. Likely explanations for the findings in this are the multi-factorial nature of CAD, and a 'mismatch' between the sensitive angiogram scoring system and the anthropometric measurements.

4.2 SUBCUTANEOUS ADIPOSE TISSUE PATTERN IN MEN WITH CAD AND HEALTHY CONTROLS: A PRINCIPAL COMPONENT ANALYSIS

The aim of this investigation was to examine subcutaneous adipose tissue distribution in men with CAD (N = 65) and also in a group of apparently healthy men (N = 72) using principal component analysis. For this analysis, five men with zero scores from angiography were excluded to produce a group with indisputable CAD. The mean values (± SD) from the angiography were 6.70 (3.58) and 2.20 (2.00) for myocardial and left ventricular scores respectively.

TABLE I (4.2). Mean values ± standard deviations for age and anthropometric characteristics of men with angiographically-documented CAD and healthy controls.

	CAD patients (N = 65)	Healthy men (N = 72)
Age (yr)	61.5 (8.7)	43.5 (9.4)
Body mass (kg)	81.0 (13.0)	75.7 (9.5)
Stature (cm)	173.1 (6.1)	174.2 (5.6)
BMI ($kg.m^{-2}$)	27.0 (4.0)	25.7 (3.1)
Skinfolds (mm)		
Triceps	15.2 (6.8)	15.6 (5.2)
Biceps	9.2 (4.0)	8.5 (4.8)
Front mid-thigh	15.2 (6.5)	20.8 (7.3)
Medial calf	10.2 (4.0)	11.1 (4.0)
Subscapular	26.7 (8.9)	21.6 (8.2)
Suprailiac	25.9 (9.8)	32.7 (9.7)
Supraspinale	16.8 (7.9)	21.6 (8.6)
Abdominal	25.8 (8.4)	27.6 (9.2)

Tables II (4.2) and III (4.2) show the inter-relationships between skinfolds in men with CAD and healthy controls respectively. The data demonstrate that significant associations exist between all of the skinfolds ($P < 0.01$). In the CAD men, the strongest relationship was between the biceps and triceps skinfolds ($r = 0.766$) and the weakest between the abdominal and triceps skinfolds ($r = 0.320$). In the healthy men, the strongest relationship was between the mid-thigh and triceps skinfolds ($r = 0.719$) and the weakest was between the mid-thigh and supraspinale skinfolds ($r = 0.300$). Examination of the correlations suggest that, in all but a few cases, linear relationships amongst skinfolds were stronger in the CAD patients.

The initial step in assessing the suitability of data for the application of principal component analysis is an inspection of the correlation matrix (Tabachnick and Fidell, 1996). Correlations greater than 0.30 suggests appropriateness, but is not indisputable proof that components exist. Bartlett's test of sphericity and the Kaier-Meyer-Olkin (KMO) measure of sampling adequacy are more robust tests of the suitability of the data for principal component analysis.

TABLE II (4.2) Correlation matrix showing the relationships between skinfolds in CAD men. Values are Pearson product-moment correlation coefficients (N = 65).

	Biceps	Subscapular	Suprailiac	Supraspinale	Abdominal	Mid-thigh	Calf
Triceps	0.766	0.652	0.707	0.723	0.320	0.711	0.572
Biceps		0.735	0.641	0.732	0.460	0.561	0.614
Subscapular			0.591	0.693	0.535	0.483	0.529
Suprailiac				0.712	0.552	0.644	0.514
Supraspinale					0.539	0.568	0.628
Abdominal						0.473	0.440
Mid-thigh							0.602

All correlation coefficients are statistically significant ($P < 0.01$).

TABLE III (4.2) Correlation matrix showing the relationships between skinfolds in healthy men. Values are Pearson product-moment correlation coefficients (N = 72).

	Biceps	Subscapular	Suprailiac	Supraspinale	Abdominal	Mid-thigh	Calf
Triceps	0.609	0.591	0.539	0.534	0.602	0.719	0.669
Biceps		0.427	0.452	0.327	0.378	0.427	0.385
Subscapular			0.522	0.515	0.541	0.422	0.426
Suprailiac				0.604	0.496	0.349	0.369
Supraspinale					0.548	0.300	0.436
Abdominal						0.490	0.497
Mid-thigh							0.664

All correlation coefficients are statistically significant ($P < 0.01$).

Table IV (4.2) presents the results of these tests. With respect to the KMO test, a critical value of 0.6 is recommended for a satisfactory principal component analysis to take place (Tabachnick and Fidell, 1996). Values of 0.872 and 0.877 for the CAD men and controls respectively, indicate a high level of correlation between the skinfolds and, therefore, the appropriateness of the data for principal component analysis. Bartlett's test of sphericity, which tests whether correlations between the skinfolds are sufficiently high to indicate the existence of factors (components), is also highly significant ($P = 0.000$) and justifies the application of this analysis.

TABLE IV (4.2). Initial results generated from the principal component analysis showing the Kaier-Meyer-Olkin Measure of Sampling Adequacy and Bartlett's Test of Sphericity.

	CAD patients (N = 65)	healthy controls (N = 72)
Kaier-Meyer-Olkin Measure of Sampling Adequacy	0.872	0.877
Bartlett's Test of Sphericity:		
Chi-square	352.3	271.3
Degrees of freedom	28	28
Significance	0.000	0.000

As only eigenvalues greater than 1 were selected for interpretation, Figures 1 (4.2) and 2 (4.2), known as scree plots in principal component analysis, together with Tables V (4.2) and VI (4.2), support the conclusion that there is only one identifiable principal component in each group of subjects. This component is interpreted as one of subcutaneous adiposity as it correlates uniformly with all of the skinfolds entered into the analysis [Table VII (4.2)]. Figures 1 (4.2) and 2 (4.2) show a clear 'flattening' of the curve subsequent to the consideration of the first principal component. In the CAD patients this component explained approximately 65% of the variance in skinfold thickness. In the healthy men, this value was approximately 56%. Table VI (4.2) shows the variable loadings (correlations) with the first component. All skinfolds loaded positively on this component. The triceps skinfold had the greatest contribution to the component in the control subjects (r = 0.889) and supraspinale skinfold the greatest contribution in the CAD patients (r = 0.874).

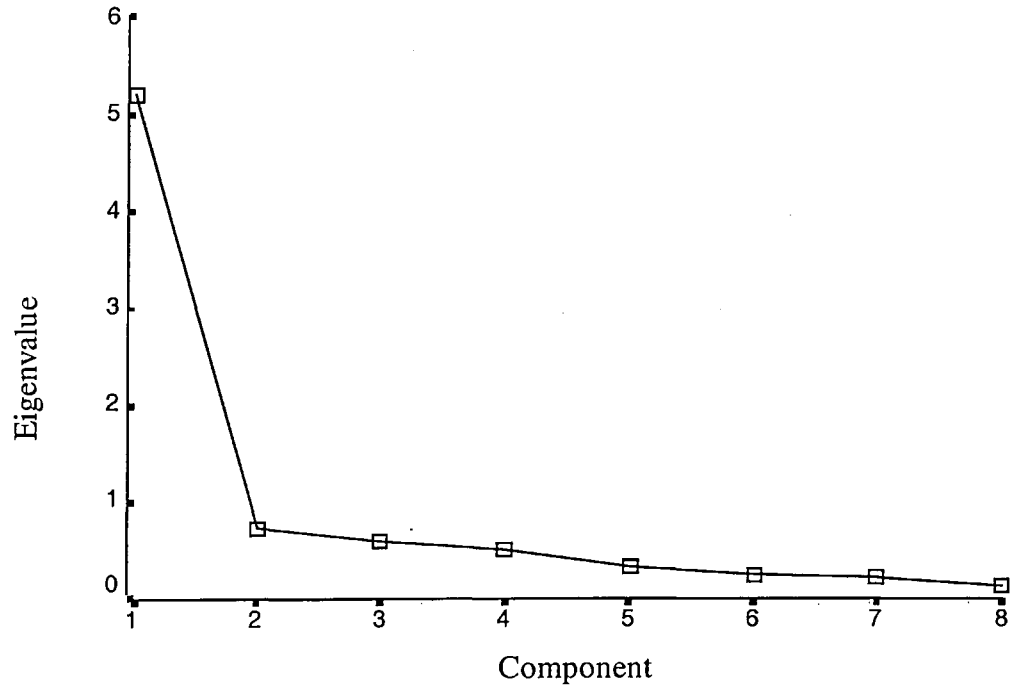

FIGURE 1 (4.2). Scree plot showing the eigenvalues associated with each component identified by the principal component analysis in CAD men (N = 65).

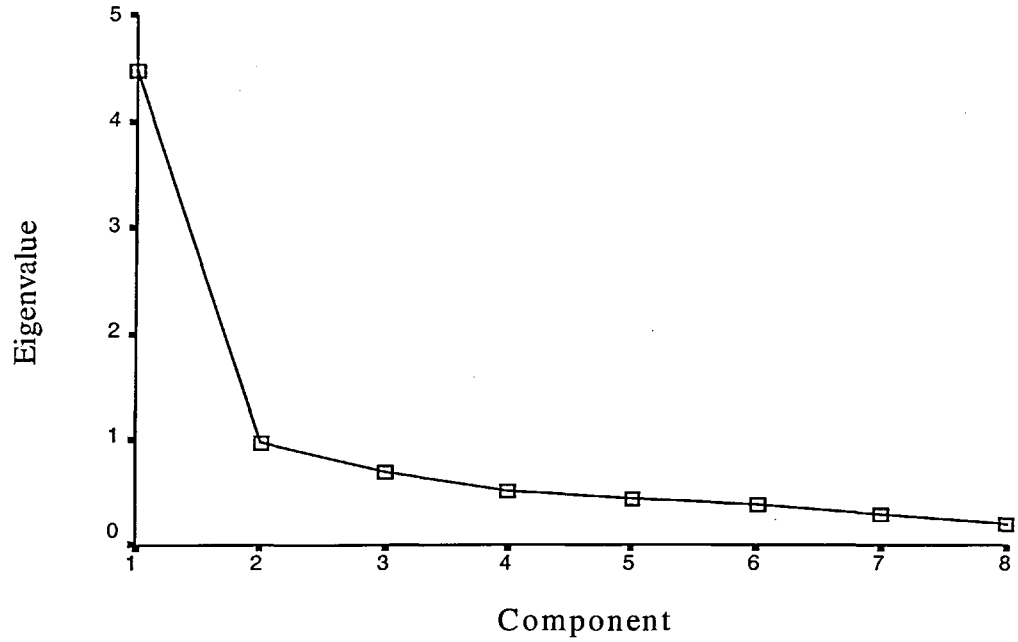

FIGURE 2 (4.2). Scree plot showing the eigenvalues associated with each component identified by the principal component analysis in healthy men (N = 72).

TABLE V (4.2). Unrotated solution from principal components analysis of skinfolds in CAD men (N = 65).

	Initial Eigenvalues		
Component	Total	% of Explained Variance	Cumulative %
1	5.208	65.103	65.103
2	0.735	9.182	74.286
3	0.606	7.571	81.857
4	0.511	6.387	88.244
5	0.340	4.255	92.499
6	0.235	2.939	95.439
7	0.228	2.855	98.293
8	0.137	1.707	100.000

TABLE VI (4.2). Unrotated solution from principal component analysis of skinfolds in healthy men (N = 72).

	Initial Eigenvalues		
Component	Total	% of Explained Variance	Cumulative %
1	4.488	56.094	56.064
2	0.976	12.201	68.295
3	0.704	8.804	77.099
4	0.506	6.321	83.419
5	0.436	5.447	88.866
6	0.391	4.892	93.759
7	0.300	3.754	97.513
8	0.199	2.487	100.000

TABLE VII (4.2). Skinfold loadings (correlations) with principal component extracted from men with CAD and healthy controls.

	CAD men (N = 65)	Healthy men (N = 72)
Triceps	0.821	0.694
Biceps	0.863	0.662
Subscapular	0.813	0.743
Suprailiac	0.835	0.719
Supraspinale	0.874	0.709
Abdominal	0.651	0.764
Mid-thigh	0.780	0.737
Calf	0.757	0.748

Principal component analysis is a form of factor analysis that has been used to describe subcutaneous AT pattern in children and adults of differing age, sex and ethnic background (Baumgartner *et al.*, 1986; Mueller and Reid, 1979; Mueller and Wohlleb, 1981; Mueller *et al.*, 1986). The aim of this analysis is the identification of

'fatness factors' (principal components) that allow the reduction of information gained from many skinfold sites to be reduced to a more manageable number of variables (the components). In general, these studies have extracted two stable principal components. The first component typically explains about 70 to 80% of the variance in subcutaneous AT and has been termed an obesity component, as all skinfolds load positively on it. The second component that explains about 15% of the variance in subcutaneous AT has been termed a trunk-to-extremity component. This component has been interpreted as a fat pattern that contrasts subcutaneous AT on the trunk with AT on the limbs. These components were stable with variations in age, sex, and ethnicity (Mueller and Wohlleb, 1981) and fatter subjects appear to be more patterned than leaner subjects (Mueller and Reid, 1979). Mueller *et al.* (1986) studied a large sample of Canadian men (N = 12,446) and women (N = 7,018) and revealed a first component that contrasted trunk skinfolds (subscapular and suprailiac) with limb skinfolds (triceps and calf). This component of "centralized fatness" was associated with less subcutaneous fat than "peripheral fatness". It was also suggested that centralized obesity was associated with enlarged intra-abdominal fat deposits.

This investigation revealed only one principal component in both the CAD men and the healthy men. This is interpreted as a subcutaneous obesity component. Thus, in contrast to other studies, principal component analysis was unable to identify any pattern of subcutaneous adiposity in either group of men.

4.3 SKINFOLDS AND ANTHROPOMETRIC GIRTH MEASUREMENTS OF MEN WITH CAD AND HEALTHY AGE-MATCHED CONTROLS: THE EFFECTS OF ADJUSTING FOR BODY SIZE VARIATION.

The aim of this study was to compare the skinfold and girth measurements of men with CAD and men who were apparently healthy and matched for age. A further investigation took place to consider the effect of differences in body size on these variables.

TABLE I (4.3). Angiographic scores, age and skinfolds of men with CAD and healthy controls. Values are means ± (standard deviations).

Variable	CAD men (n = 27)	Controls (n = 38)	significance
Age (years)	53.2 (6.5)	51.2 (4.0)	NS
Myocardial score	6.4 (3.3)		
Ventricular score	1.9 (1.7)		
Body mass (kg)	85.4 (15.7)	76.0 (8.3)	$P < 0.01$
Stature (cm)	173.1 (6.2)	173.3 (5.3)	NS
BMI ($kg.m^{-2}$)	28.4 (4.6)	25.7 (2.9)	$P < 0.01$
Skinfolds (mm)			
Triceps	18.3 (8.6)	15.1 (3.6)	NS
Biceps	11.0 (4.6)	8.5 (4.2)	$P < 0.05$
Front mid-thigh	18.2 (8.2)	20.2 (6.3)	NS
Medial calf	11.1 (3.8)	10.9 (3.4)	NS
Subscapular	30.4 (8.5)	22.2 (7.7)	$P < 0.001$
Suprailiac	30.8 (11.0)	32.3 (8.4)	NS
Supraspinale	18.9 (8.3)	22.2 (8.5)	NS
Abdominal	28.6 (8.7)	26.6 (9.0)	NS
Σ 8 skinfolds	167.5 (47.5)	157.9 (35.5)	NS
Σ 4 torso skinfolds	108.8 (27.8)	103.2 (26.1)	NS
Σ 4 limb skinfolds	58.6 (22.2)	54.6 (13.3)	NS
Σ torso / Σ limb skinfolds	1.98 (0.50)	1.94 (0.50)	NS

NS = $P > 0.05$

Table I (4.3) presents the results of a comparison of age, body mass, height, BMI and skinfolds between the CAD patients and a group of age-matched healthy men. The CAD patients were heavier and had a greater BMI ($P < 0.01$). They also had significantly greater biceps ($P < 0.05$) and subscapular ($P < 0.001$) skinfolds. There were no statistical differences for any other skinfold variables.

Table II (4.3) shows differences in torso, hip and leg girths. Differences in several ratios formed from these measurements are also shown. The CAD patients had significantly greater abdomen and waist girths, ASD, WHR, AHR, WTR, WHtR, and ASD/Ht ($P < 0.001$). Hip and mid-thigh girths were not different ($P > 0.05$).

TABLE II (4.3). Anthropometric girth measurements and ratios in men with CAD and healthy controls. Values are means ± (standard deviations).

Variable	CAD men (n =27)	Controls (n = 38)	significance
Waist	99.5 (9.6)	90.2 (8.5)	P < 0.001
Abdomen	102.6 (9.9)	93.7 (7.8)	P < 0.001
Hip	100.6 (8.6)	98.6 (4.6)	NS
Mid thigh	52.2 (4.8)	53.7 (4.5)	NS
ASD	27.1 (3.2)	24.4 (2.8)	P < 0.001
WHR	0.97 (0.08)	0.91 (0.05)	P < 0.001
AHR	1.02 (0.04)	0.94 (0.05)	P < 0.001
WTR	1.91 (0.13)	1.68 (0.13)	P < 0.001
WHtR	0.57 (0.05)	0.52 (0.04)	P < 0.001
ASD/Ht	0.16 (0.02)	0.14 (0.02)	P < 0.001

NS = $P > 0.05$. ASD, abdominal sagittal diameter; WHR, waist-to-hip ratio; AHR, abdomen-to-hip ratio; WTR, waist-to-thigh ratio; WHtR, Waist-to-height ratio; ASD/Ht, abdominal sagittal diameter/height.

In order to consider the effect of body size, many of the variables contained in Tables I (4.3) and II (4.3) were adjusted to the Phantom stature and body mass. The resultant z-values are, therefore, proportionality scores i.e. they represent the size of the variable in relation to size. Table III (4.3) contains the corrected skinfolds and girths normalised to the Phantom stature. These z-values are also presented in Figure 1 (4.3), which shows similar proportionality profiles of the patients and controls. For both groups, mean z-values for the triceps and abdominal skinfolds were close to 0.00 and, therefore, proportional to stature. The subscapular skinfold of the CAD patients had a z-value of 2.49 ± 1.64. The suprailiac skinfold of both groups had mean z-values greater than 3.00. The front mid-thigh and medial-calf skinfolds exhibited negative z-values that were close to 1.00. Compared to the controls, the patients had proportionally greater subscapular and biceps skinfolds ($P < 0.01$).

The mean z-values for stature-normalised waist and abdomen girths indicate that these parameters were proportionally large. Both girths were significantly ($P < 0.001$) larger in the CAD patients compared to the controls. The mean stature-normalised waist girth of the CAD patients was 5.28 ± 2.05 i.e. more than five standard deviations greater than the Phantom.

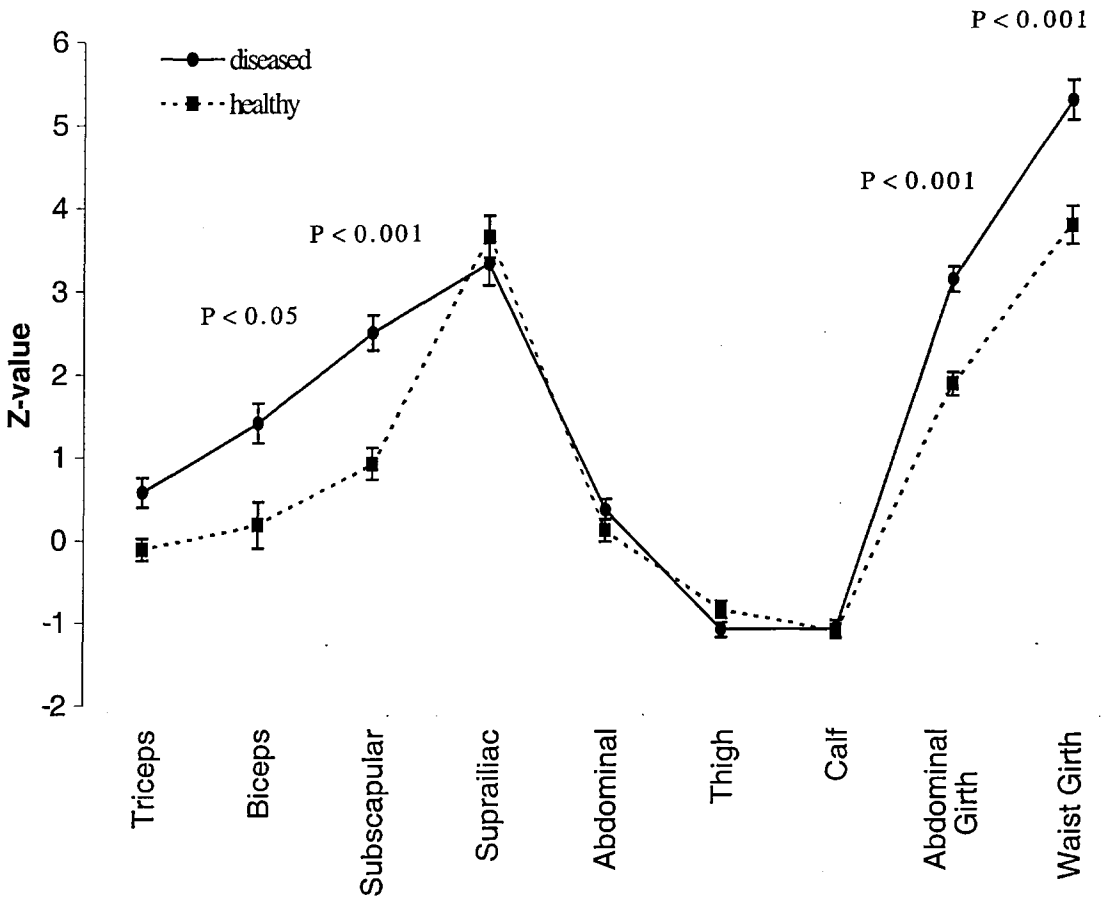

Figure 1 (4.3) Proportionality profile of skinfolds and girth measurements normalised to the phantom stature. Data are shown as means +/- SEM. (N = 27 for the patients and 38 for the controls).

TABLE III (4.3). Means ± (standard deviations) of corrected skinfolds, waist and abdominal girths (z-values) normalised to the Phantom stature (170.18 cm).

Variable	CAD patients (n = 27)	Controls (n = 38)	significance
Skinfolds			
Triceps	0.57 (1.87)	-0.12 (0.80)	NS
Biceps	1.40 (2.25)	0.17 (2.02)	$P < 0.05$
Front mid-thigh	-1.10 (0.93)	-0.86 (0.73)	NS
Medial calf	-1.09 (0.77)	-1.12 (0.72)	NS
Subscapular	2.49 (1.64)	0.91 (1.47)	$P < 0.001$
Suprailiac	3.32 (2.32)	3.64 (1.84)	NS
Abdominal	0.35 (1.08)	0.10 (1.15)	NS
Girths			
Waist	5.28 (2.05)	3.78 (1.93)	$P < 0.001$
Abdomen	3.13 (1.32)	1.87 (1.13)	$P < 0.001$

NS = $P > 0.05$

Table IV (4.3) and Figure 2 (4.3) contain skinfold and girth z-values after they were normalised to the Phantom body mass. With the exception of the subscapular and suprailiac sites, all of the mean z-values are either zero or negative. The triceps, biceps and abdominal skinfolds are all less than 1.00. The z-values for the front mid-thigh and medial-calf skinfolds, however, although negative were between 1.00 and 2.00 i.e. proportionally small for the body mass. The patients had significantly smaller body mass normalised front mid-thigh and suprailiac skinfolds ($P < 0.05$) but larger subscapular skinfold ($P < 0.01$). The body mass normalised waist girth was more than one SD greater than the Phantom in the patients and controls. The mean z-values for the abdominal girth were both close to zero. There was no significant difference between patients and controls when the body mass normalised girths were compared.

TABLE IV (4.3). Means ± (standard deviations) of corrected skinfolds (z-values) normalised to the Phantom body mass (64.58 kg).

Variable	CAD patients (n = 27)	Controls (n = 38)	significance
Skinfolds			
Triceps	-0.40 (1.05)	-0.55 (0.68)	NS
Biceps	0.00 (1.20)	-0.41 (1.54)	NS
Front mid-thigh	-1.60 (0.74)	-1.17 (0.64)	$P < 0.05$
Medial calf	-1.63 (0.52)	-1.41 (0.66)	NS
Subscapular	1.16 (1.11)	0.30 (1.16)	$P < 0.01$
Suprailiac	1.80 (1.67)	2.70 (1.55)	$P < 0.05$
Abdominal	-0.40 (1.03)	-0.35 (0.97)	NS
Girths			
Waist	1.07 (2.02)	1.19 (1.88)	NS
Abdomen	-0.01 (1.28)	0.16 (1.14)	NS

NS = $P > 0.05$

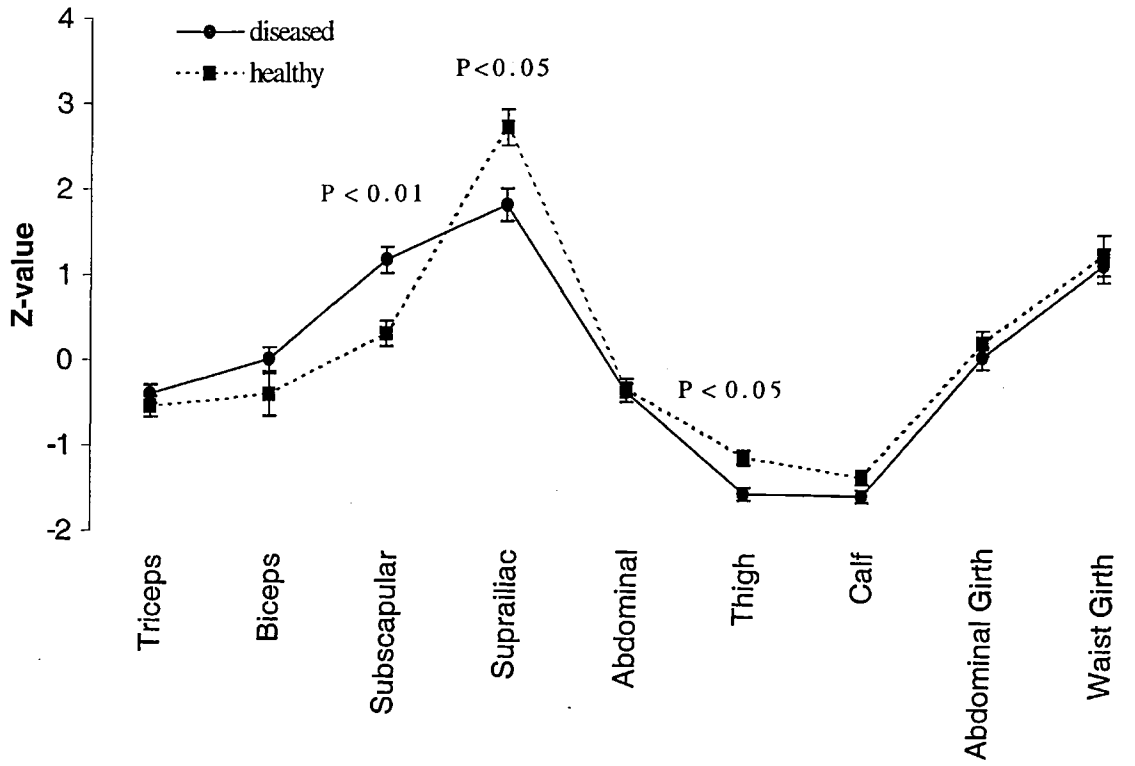

Figure 2 (4.3) Proportionality profile of skinfolds and girth measurements normalised to the Phantom body mass. Data are shown as means +/- SEM. (N = 27 for the patients and 38 for the controls).

This study examined subcutaneous fat pattern and abdominal obesity in CAD by comparing a group of men undergoing investigative coronary angiography and a group of apparently healthy controls. Anthropometric differences of men with CAD and controls have been investigated previously (Hauner *et al.*, 1990; Hodgson *et al.*, 1994; Ley *et al.*, 1994; Thompson *et al.*, 1991; Kahn *et al.*, 1996; Flynn *et al.*, 1994) The association of intra-abdominal visceral fat and CAD has also been examined using this type of study design (Nakamura *et al.*, 1994).

The present study used an approach to adjust for differences in body size that was originally devised to assess proportional growth (Ross and Wilson, 1974). The method has been subsequently revised (Ross and Ward, 1982; Ross and Marfell-

Jones, 1991), and applied to athletic performance (Ross and Ward, 1984; Sovak *et al.*, 1992; DeRose *et al.*, 1989.

The simplest procedure to account for differences in body size is to use a ratio (i.e. weight / height). However, as ratios are a function of both the denominator and numerator, their interpretation is not simple (Ross and Wilson, 1974). Furthermore, questions have been raised about their ability to detect changes in body composition (Molarius and Seidell, 1998) and their suitability for statistical analysis (Allison *et al.*, 1995). The method proposed by Ross and Wilson (1974) advocates the use of a single, unisex reference human as a calculation device for quantifying proportional differences that avoids the use of ratios. A z-value, which is interpreted as a SD, is determined for each anthropometric measurement. A z-value of 0.00 indicates that the variable in question is proportionally the same as the Phantom. Z-values of ≤ 1.00 or ≥ 1.00 indicate that the variable is proportionally smaller or greater than the Phantom respectively. Thus, this technique addresses the issue of the magnitude of anthropometric variables in relation to body size. For example, a skinfold of 20 mm in two subjects is the same in absolute terms. However, if these subjects differ in size i.e. height and weight, then this skinfold thickness is relatively smaller in the larger person.

The significance of body size as a confounding variable of the relationship between girth measurements and CAD risk has attracted some attention in the past (Cox *et al.*, 1996; Hsieh and Yoshinaga, 1995; Ashwell *et al.*, 1996a, 1996b, Han *et al.*, 1996, 1997). These studies attempted to study the influence of height in the relationship between waist circumference and CHD by using height as the denominator in a ratio with waist girth. Some of these researchers suggested that WHtR was a better predictor of mortality (Cox *et al.*, 1996) CAD risk (Hsieh and

Yoshinaga (1995) and IAF (Ashwell *et al.*, 1996b). However, Han *et al.* (1996, 1997) did not support this proposition. No study has previously used a proportionality strategy to examine this issue.

Usually all anthropometric measurements are geometrically scaled to the Phantom stature (170.18 cm). An implicit assumption with this technique is a perfect correlation between the variable being scaled and stature; although this is generally not the case the differences are seldom great enough to invalidate the technique (Ross and Wilson, 1974). In this study, only the thigh skinfold ($r = 0.266$, $P < 0.05$) was significantly related to stature. As all skinfolds (except abdominal) and girth measurements were significantly related to body mass ($r = 0.263$ to 0.781, $P < 0.05$), and body mass was significantly different between the two groups, it was also decided to geometrically scale all measurements to the Phantom body mass.

The anthropometric characteristics presented in Table I (4.3) show that the patients were heavier but not taller. Consequently, the BMI of the patients was also greater. As there was no difference in the sum of eight skinfolds, factors other than increased subcutaneous adiposity are likely to be responsible for the difference in body mass. A speculative suggestion is that an increased fat mass in another depot (i.e. the intra-abdominal depot) may well explain the difference in body mass. This is supported by the greater ASD, waist and abdominal girths in patients compared to controls, as waist girth may be the best anthropometric predictor of intra-abdominal adipose tissue (Pouliot *et al.*, 1994).

The stature-normalised skinfolds for both groups show that the triceps and abdominal skinfolds are proportionally similar. Also in both groups, the suprailiac skinfold was proportionally much greater than the Phantom and the thigh and calf skinfolds smaller. A proportionally large subscapular skinfold also appears to be a

physical characteristic of the patients. Subscapular skinfold thickness has been reported previously to be an independent predictor of CAD (Stokes III *et al.*, 1985; Ducimetiere *et al.*, 1986; Donahue *et al.*, 1987) and a correlate of low HDL-C (Despres *et al.*, 1985). Given that several investigations have pointed to an increased 'central' or abdominal fat deposition as being an important predictor of CAD, the finding of a proportionally large suprailiac skinfold in the patients is not surprising. However, this finding is confounded by the equally large suprailiac skinfold in the healthy men. Compared to the Phantom, the profile of z-values suggests a particular phenotype with regard to subcutaneous fat pattern in the patients. This phenotype is, with the exception of the abdominal site, one of proportionally large skinfolds on the torso, proportionally small skinfolds on the lower limb and proportional skinfolds on the upper limb. The importance of this is lessened by the fact that a similar pattern exists in the apparently healthy men, with the notable exception of the difference in subscapular skinfold.

Prominent findings in this study were the significant differences between patients and controls for all girth measures of abdominal obesity and the very large stature-normalised z-values for the waist and abdominal girths of the patients. These stature-normalised z-values were also significantly greater in the patients than the controls. Waist circumference cut-off points for men of 94.0 cm (Lean *et al.*, 1995) and 100cm (Lemieux *et al.*, 1996) have been proposed. The mean waist girth of the patients, but not the controls, was much greater than the lower of these figures and almost equal to the higher. The SD of the stature-normalised waist girth of the patients indicates that more than 95 % of these men had proportionally large waist girths (z-value > 1.0). When these girth measurements were normalised to body mass the

deviations from the Phantom were still positive but much smaller. This is due to the increased body mass of both groups, particularly the patients.

The body-mass normalised skinfolds showed no difference between the patients and controls with regard to the direction of the z-values. The front mid-thigh, subscapular and suprailiac sites were significantly different with respect to the size of the z-values. Normalised for body mass, the suprailiac and thigh skinfolds were proportionally smaller in the patients than the controls but the subscapular skinfold was greater in the patients. Except for the subscapular skinfold in the controls and the negative deviation of the abdominal skinfold, the skinfold pattern for both groups was essentially one of proportionally small skinfolds on the limbs and large skinfolds on the torso. An interpretation of the relatively small abdominal skinfold is that in genetically-susceptible men, increasing age is associated with the accumulation of intra-abdominal AT (Bouchard *et al.*, 1993). This augments the pressure within the abdomen, which increases the tension of the skin and reduces the skinfold thickness. This is analogous to increasing the pressure within a cylinder, which increases the circumferential tensile stress on the wall.

Other studies that have used angiography patients in comparison to controls have reported no difference in skinfold thickness (Flynn *et al.* 1994), waist and abdominal girths (Hauner *et al.*, 1994; Flynn *et al.*, 1994; Hodgson *et al.*, 1994). The difference in the findings of this study appears to be due to the size of the girth measurements in the controls, as the values of the patients are very similar to these previous studies. Our control subjects were recruited from a University health-screening programme and were asymptomatic with regard to CAD. The controls of these other studies were patients who, having undertaken angiography, were found to have clinically insignificant coronary stenosis. In effect, whilst some of these controls

may have had no CAD, others had angiographic evidence of CAD but below an arbitrary value. This may explain the lack of a statistical difference between the groups. In our study, this was avoided by using a scoring system that allowed us to exclude from the analysis only those patients who had a zero myocardial score. Kahn *et al.* (1996) also found a significant difference between patients and controls when they recruited asymptomatic control subjects from the same community as the patients. Thus, it appears that waist circumference is able to discriminate between CAD patients and healthy controls, but not between patients who are all hospitalised for investigative coronary angiography and who may have greater or lesser degrees of CAD. Enlarged waist circumference may be an indicator of visceral fat accumulation as this depot, but not the abdominal subcutaneous, seems to be enlarged in CAD patients compared to controls (Nakamura *et al.*, 1994).

With regard to skinfolds, Flynn *et al.* (1994) found no difference between CAD patients and controls at several sites. Furthermore, Kahn *et al.* (1996) suggested that a greater sum of 3 skinfolds actually conferred some protection against CAD in older individuals. With regard to unadjusted subcutaneous adiposity, this study revealed that CAD patients differed from controls only in biceps and subscapular skinfold thickness. Thus, in agreement with other studies, an increased subscapular skinfold thickness appears to be a prominent feature of CAD. When normalised for stature or body mass, a large subscapular skinfold remained a prominent feature of CAD patients compared to controls.

These results suggest that increased body mass, ASD, waist and abdominal girths, and subscapular skinfold thickness are features of CAD patients but not increased subcutaneous adiposity. Adjusting for stature had no effect on these results but adjusting for body mass removed the difference in the girth measurements.

Following the adjustment for differences in body mass, subscapular skinfold remained significantly larger in the patients but front mid-thigh and suprailiac skinfolds became significantly greater in the controls. Thus, CAD patients have proportionally large waist and abdominal girths for their stature but not for their mass.

4.4 SKINFOLDS AND ANTHROPOMETRIC INDICES OF ABDOMINAL OBESITY IN MEN. THE INFLUENCE ON SERUM GLUOCSE AND LIPIDS AND THE EFFECT OF ADJUSTING FOR BODY SIZE VARIATION.

The aim of this study was an examination of the relationship between anthropometric indices of adiposity and serum glucose, lipids and lipoproteins in the healthy men (it was not possible to perform this analysis in the CAD men as a significant number were taking lipid-lowering medication). This was done using regression analysis and by investigating potential differences in these metabolic variables in the upper and lower halves of the distribution for the anthropometric variables. The 50^{th} percentile or median value of each anthropometric variable was used to divide the entire sample (N = 68) into two groups of equal number i.e. 34 men with a skinfold or girth equal to or below the median and 34 men with a skinfold or girth greater than the median value. Differences in the metabolic variables between these two groups were then tested for statistical significance.

As in the previous section, a proportionality technique was also applied to the anthopometric variables to see whether this had any effect on the ability of the anthropometric variables to discriminate between men with higher and lower glucose and lipid levels. In other words, it was of interest to discover whether the absolute or relative size of the adiposity measurements were most closely related to metabolic fitness.

Table I (4.4) presents mean values ± (SD) of age, body mass, stature, BMI, skinfolds, waist and abdominal girths, and metabolic variables. Median values that were calculated for all skinfolds and girths are also shown.

Means, SD's and median values for the size-adjusted variables are shown in table II (4.4). With the exception of the suprailiac, mid-thigh and calf skinfolds, waist girth and stature-adjusted abdominal girth, the anthropometric measurements were within ± 1.00 of a z-value of zero, i.e. these variables were of similar proportions to the hypothetical model.

TABLE I (4.4). Age, anthropometric and metabolic characteristics of the subjects (N = 68).

Variable	Mean ± (SD)	Median
Age (years)	43.9 (9.1)	
Body mass (kg)	75.9 (9.4)	
Stature (cm)	174.4 (5.6)	
BMI ($kg.m^{-2}$)	25.8 (3.2)	
<u>Skinfolds (mm)</u>		
Triceps	15.4 (5.2)	14.6
Biceps	8.6 (4.9)	7.3
Subscapular	21.4 (8.1)	20.0
Suprailiac	32.5 (9.9)	33.5
Supraspinale	21.6 (8.7)	20.5
Abdominal	27.5 (9.5)	26.3
Mid-thigh	20.5 (7.2)	20.2
Medial calf	10.9 (3.3)	11.0
Σ 8 skinfolds	158.2 (43.2)	156.0
Σ 4 torso skinfolds	103.0 (29.4)	102.0
Σ 4 limb skinfolds	55.2 (17.7)	52.0
Σ torso / Σ limb skinfold ratio	1.95 (0.51)	1.88
<u>Girths (cm)</u>		
Waist	89.2 (8.4)	87.0
Abdominal	93.4 (8.3)	91.6
<u>Metabolic variables</u>		
Glucose ($mmol.L^{-1}$)	5.30 (0.36)	
Total cholesterol ($mmol.L^{-1}$)	4.97 (0.93)	
Triglyceride ($mmol.L^{-1}$)	1.58 (1.16)	
HDL-cholesterol ($mmol.L^{-1}$)	1.21 (0.26)	
LDL-cholesterol ($mmol.L^{-1}$)	3.09 (0.86)	
LDL:HDL	2.65 (0.95)	

TABLE II (4.4) Descriptive statistics of the anthropometric characteristics following adjustment for differences in stature and body mass. Skinfolds and girths were adjusted to the Phantom stature (170.18 cm) and body mass (64.58 kg). (N = 68).

	Mean ± (SD)	Median
Skinfolds		
Triceps (stature)	-0.07 (1.1)	-0.29
Triceps (mass)	-0.51 (0.95)	-0.68
Biceps (stature)	0.15 (2.38)	-0.41
Biceps (mass)	-0.39 (2.13)	-0.84
Subscapular (stature)	0.72 (1.55)	0.45
Subscapular (mass)	0.17 (1.27)	-0.04
Suprailiac (stature)	3.66 (2.16)	3.71
Suprailiac (mass)	2.73 (1.78)	2.8
Abdominal (stature)	0.19 (1.19)	0.04
Abdominal (mass)	-0.25 (1.00)	-0.33
Mid-thigh (stature)	-0.84 (0.85)	-0.83
Mid-thigh (mass)	-1.15 (0.72)	-1.16
Calf (stature)	-1.14 (0.80)	-1.10
Calf (mass)	-1.43 (0.70)	-1.38
Girths		
Waist (stature)	3.43 (1.98)	3.44
Waist (mass)	1.06 (1.97)	0.98
Abdominal (stature)	1.74 (1.22)	1.57
Abdominal (mass)	0.15 (1.24)	0.21

Tables III (4.4) to IX (4.4) show differences in the serum concentrations of glucose, TC, TG, HDL-C and LDL-C according to skinfold thickness. Differences in the LDL-C : HDL-C ratio are also shown in each table. For all skinfolds, the mathematical direction of all the differences in these metabolic variables was in accordance with the hypothesis that greater adiposity is associated with higher levels of glucose, TC, TG and LDL-C and lower HDL-C. For unadjusted limb skinfolds [Table III (4.4)], the biceps was the best discriminator for revealing significant differences in glucose and lipids. Serum concentrations of glucose ($P < 0.05$), TC ($P < 0.01$), TG ($P < 0.01$) and LDL-C ($P < 0.01$) were all significantly higher in the group of men comprising the upper 50% of the biceps skinfold distribution. The LDL-C : HDL-C ratio was also significantly higher in this group ($P < 0.001$), whereas the HDL-C concentration was lower ($P < 0.01$). Other significant differences in glucose and lipids found using limb skinfolds were as follows. The LDL-C : HDL-C ratio was significantly greater ($P < 0.05$) in men with thicker triceps and calf skinfolds. LDL-C concentration was greater ($P < 0.05$) in the men above the median value according to calf skinfold.

TABLE III (4.4) Metabolic variables (mmol.L^{-1}) in men according to limb skinfold thickness. Values are means ± (SD). (N = 68).

		Triceps *(14.6 cm)*[a]	Biceps *(7.3 cm)*	Mid-thigh *(20.2 cm)*	Calf *(11.0 cm)*
Glucose	1[b]	5.24 (0.33)	5.19 (0.32)*	5.28 (0.37)	5.26 (0.31)
	2[c]	5.36 (0.39)	5.40 (0.38)	5.31 (0.36)	5.34 (0.41)
TC	1	4.80 (0.90)	4.64 (0.85)**	4.90 (0.96)	4.78 (1.03)
	2	5.13 (0.94)	5.30 (0.90)	5.04 (0.91)	5.16 (0.77)
TG	1	1.63 (1.39)	1.20 (0.77)**	1.63 (1.35)	1.67 (1.39)
	2	1.53 (0.91)	1.96 (1.37)	1.52 (0.93)	1.48 (0.87)
HDL-C	1	1.24 (0.23)	1.30 (0.24)**	1.24 (0.24)	1.24 (0.24)
	2	1.17 (0.29)	1.11 (0.26)	1.17 (0.28)	1.17 (0.28)
LDL-C	1	2.89 (0.84)	2.81 (0.76)**	3.00 (0.93)	2.84 (0.93)*
	2	3.29 (0.85)	3.40 (0.87)	3.18 (0.79)	3.33 (0.71)
LDL-C : HDL-C	1	2.36 (0.83)*	2.18 (0.60)***	2.50 (1.01)	2.35 (0.95)*
	2	2.92 (1.00)	3.14 (1.01)	2.79 (0.88)	2.94 (0.86)

* P < 0.05, ** P < 0.01, *** P < 0.001 between 1 and 2.

[a]Values in italics are median values for skinfold.

[b]1 represents the sub-group of subjects with skinfold thickness equal to or less than the median value for that skinfold.

[c]2 represents the sub-group of subjects with skinfold thickness greater than the median value for that skinfold.

Using the unadjusted torso skinfold values [Table IV (4.4)], there were significant differences in TC (P < 0.05), TG (P < 0.01), HDL-C (P < 0.05) and the LDL-C : HDL-C ratio (P < 0.01) for the supraspinale site. The only other significant difference was for TC (P < 0.05) using the suprailiac skinfold.

TABLE IV (4.4) Metabolic variables (mmol.L^{-1}) in men according to torso skinfold thickness. Values are means ± (SD). (N = 68).

		Subscapular *(20.0 cm)*[a]	Suprailiac *(33.5 cm)*	Supraspinale *(20.5 cm)*	Abdominal *(26.3 cm)*
Glucose	1[b]	5.26 (0.34)	5.23 (0.33)	5.23 (0.35)	5.26 (0.36)
	2[c]	5.33 (0.40)	5.35 (0.39)	5.36 (0.37)	5.33 (0.37)
TC	1	4.86 (0.96)	4.74 (0.99)*	4.72 (0.92)*	4.86 (1.03)
	2	5.08 (0.90)	5.19 (0.81)	5.21 (0.89)	5.07 (0.81)
TG	1	1.34 (0.81)	1.36 (0.82)	1.22 (0.75)**	1.37 (0.96)
	2	1.85 (1.43)	1.80 (1.40)	1.93 (1.38)	1.78 (1.32)
HDL-C	1	1.26 (0.24)	1.23 (0.27)	1.27 (0.22)*	1.26 (0.26)
	2	1.15 (0.28)	1.18 (0.25)	1.13 (0.28)	1.16 (0.26)
LDL-C	1	3.02 (0.92)	2.92 (0.93)	2.91 (0.90)	3.02 (0.99)
	2	3.18 (0.79)	3.27 (0.75)	3.28 (0.78)	3.17 (0.70)
LDL-C : HDL-C	1	2.48 (0.91)	2.48 (0.98)	2.32 (0.81)**	2.50 (1.02)
	2	2.85 (0.97)	2.83 (0.90)	3.00 (0.98)	2.81 (0.86)

* $P < 0.05$, ** $P < 0.01$ between 1 and 2.
[a]Values in italics are median values for skinfold.
[b]1 represents the sub-group of subjects with skinfold thickness equal to or less than the median value for that skinfold.
[c]2 represents the sub-group of subjects with skinfold thickness greater than the median value for that skinfold.

Table V (4.4) shows differences in the metabolic variables according to Σ 8 skinfolds, Σ 4 torso skinfolds, Σ 4 limb skinfolds and the torso-to-limb skinfold ratio. Men with a lower total subcutaneous adiposity (lower Σ 8 skinfolds) had a greater HDL-C concentration ($P < 0.05$) and lower LDL-C : HDL-C ratio ($P < 0.01$). Similarly, men with greater torso subcutaneous adiposity (Σ 4 torso skinfolds) had a greater serum TG concentration ($P < 0.05$) and ratio of LDL-C-to- HDL-C ($P < 0.05$).

TABLE V (4.4) Metabolic variables (mmol.L^{-1}) in men according to the Σ 8 skinfolds, Σ 4 torso skinfolds, Σ 4 limb skinfolds and the ration of torso-to-limb skinfolds. Values are means ± (SD). (N = 68).

		Σ 8 skinfolds *(156.0 cm)*[a]	Σ 4 torso skinfolds *(102.0 cm)*	Σ 4 limb skinfolds *(52.0 cm)*	torso-to-limb ratio *(1.88)*
Glucose	1[b]	5.26 (0.35)	5.27 (0.35)	5.24 (0.34)	5.29 (0.37)
	2[c]	5.34 (0.38)	5.32 (0.38)	5.35 (0.38)	5.30 (0.36)
TC	1	4.77 (0.98)	4.79 (0.99)	4.86 (0.98)	5.08 (1.02)
	2	5.16 (0.84)	5.14 (0.84)	5.06 (0.89)	4.84 (0.82)
TG	1	1.43 (1.10)	1.31 (0.82)*	1.70 (1.40)	1.35 (0.81)
	2	1.72 (1.22)	1.85 (1.39)	1.48 (0.91)	1.81 (1.43)
HDL-C	1	1.27 (0.24)*	1.26 (0.26)	1.23 (0.23)	1.23 (0.28)
	2	1.14 (0.27)	1.15 (0.26)	1.19 (0.29)	1.19 (0.24)
LDL-C	1	2.90 (0.93)	2.96 (0.93)	2.94 (0.93)	3.25 (0.90)
	2	3.27 (0.74)	3.23 (0.77)	3.21 (0.79)	2.91 (0.79)
LDL-C : HDL-C	1	2.32 (0.83)**	2.43 (0.91)*	2.44 (0.95)	2.73 (0.97)
	2	2.98 (0.96)	2.89 (0.96)	2.82 (0.93)	2.55 (0.94)

* P < 0.05, ** P < 0.01 between 1 and 2.
[a]Values in italics are median values for skinfold.
[b]1 represents the sub-group of subjects with skinfold thickness equal to or less than the median value for that skinfold.
[c]2 represents the sub-group of subjects with skinfold thickness greater than the median value for that skinfold.

After adjusting the limb skinfolds for differences in stature, a similar pattern of differences can be seen with respect to the metabolic variables [Table VI (4.4)]. Men with greater stature normalised biceps skinfold thickness had higher serum concentrations of glucose, TC and LDL-C ($P < 0.05$) and a lower HDL-C concentration ($P < 0.01$). The LDL-C : HDL-C ratio was also significantly greater in these men ($P < 0.001$) as it was when the stature normalised calf skinfold was used.

TABLE VI (4.4) Metabolic variables (mmol.L^{-1}) in men according to limb skinfold thickness following adjustment to the Phantom stature of 170.18 cm. Values are means ± (SD). (N = 68).

		Triceps *(-0.29)*[a]	Biceps *(-0.41 cm)*	Mid-thigh *(-0.83 cm)*	Calf *(-1.10 cm)*
Glucose	1[b]	5.24 (0.33)	5.20 (0.32)*	5.29 (0.36)	5.24 (0.31)
	2[c]	5.36 (0.39)	5.37 (0.36)	5.30 (0.37)	5.34 (0.40)
TC	1	4.80 (0.90)	4.69 (0.88)*	4.90 (0.97)	4.80 (1.04)
	2	5.13 (0.94)	5.19 (0.85)	5.02 (0.90)	5.13 (0.78)
TG	1	1.66 (1.38)	1.37 (1.11)	1.66 (1.36)	1.69 (1.40)
	2	1.50 (0.92)	1.81 (1.19)	1.49 (0.93)	1.46 (0.80)
HDL-C	1	1.24 (0.23)	1.29 (0.23)**	1.23 (0.24)	1.23 (0.24)
	2	1.19 (0.30)	1.11 (0.25)	1.19 (0.28)	1.18 (0.28)
LDL-C	1	2.89 (0.83)	2.82 (0.78)*	3.00 (0.94)	2.86 (0.93)*
	2	3.28 (0.85)	3.30 (0.81)	3.18 (0.78)	3.30 (0.73)
LDL-C : HDL-C	1	2.38 (0.81)	2.19 (0.60)***	2.52 (1.02)	2.83 (0.95)*
	2	2.90 (1.02)	3.09 (1.04)	2.76 (0.88)	2.90 (0.89)

* P < 0.05, ** P < 0.01, *** P < 0.001 between 1 and 2.

[a]Values in italics are median values for skinfold.

[b]1 represents the sub-group of subjects with skinfold thickness equal to or less than the median value for that skinfold.

[c]2 represents the sub-group of subjects with skinfold thickness greater than the median value for that skinfold.

Using the stature-adjusted torso skinfolds, the only significant difference in either serum glucose or lipid concentrations was for HDL-C ($P < 0.05$) using the subscapular skinfold [Table VII (4.4)].

TABLE VII (4.4) Metabolic variables ($mmol.L^{-1}$) in men according to torso skinfold thickness following adjustment to the Phantom stature of 170.18 cm. Values are means ± (SD). (N = 68).

		Subscapular *(0.45 cm)*[a]	Suprailiac *(3.71 cm)*	Abdominal *(0.04 cm)*
Glucose	1[b]	5.25 (0.34)	5.27 (0.34)	5.26 (0.36)
	2[c]	5.34 (0.38)	5.32 (0.39)	5.33 (0.37)
TC	1	4.88 (0.98)	4.80 (1.03)	4.86 (1.03)
	2	5.05 (0.88)	5.13 (0.79)	5.07 (0.82)
TG	1	1.33 (0.83)	1.51 (1.19)	1.37 (0.96)
	2	1.83 (1.39)	1.65 (1.15)	1.79 (1.32)
HDL-C	1	1.27 (0.24)*	1.23 (0.27)	1.26 (0.26)
	2	1.14 (0.27)	1.18 (0.25)	1.16 (0.26)
LDL-C	1	3.03 (0.94)	2.92 (0.95)	3.02 (0.99)
	2	3.16 (0.77)	3.25 (0.74)	3.17 (0.70)
LDL-C : HDL-C	1	2.46 (0.92)	2.49 (1.00)	2.50 (1.02)
	2	2.85 (0.95)	2.81 (0.89)	2.81 (0.86)

* $P < 0.05$ between 1 and 2.
[a]Values in italics are median values for skinfold.
[b]1 represents the sub-group of subjects with skinfold thickness equal to or less than the median value for that skinfold.
[c]2 represents the sub-group of subjects with skinfold thickness greater than the median value for that skinfold.

Table VIII (4.4) shows the values of serum glucose and lipids according to the body mass normalised limb skinfold values. Again the biceps skinfold was the best for revealing significant differences in these metabolic variables. Men with smaller mass-adjusted biceps skinfolds had significantly lower fasting values for serum glucose ($P < 0.05$), TC ($P < 0.05$), LDL-C ($P < 0.05$) and the LDL-C : HDL-C ratio ($P < 0.001$). HDL-C was significantly higher in these men ($P < 0.01$). TC ($P < 0.05$) and

LDL-C ($P < 0.01$) were also significantly higher in men with greater mass-adjusted calf skinfold. Using mass-adjusted torso skinfolds, the only significant difference was found using the suprailiac skinfold and was for LDL-C concentration ($P < 0.05$), which was lower in men with smaller suprailiac skinfolds [Table IX (4.4)].

TABLE VIII (4.4) Metabolic variables (mmol.L^{-1}) in men according to limb skinfold thickness following adjustment to the Phantom body mass of 64.58 kg. Values are means ± (SD). (N = 68).

		Triceps *(-0.68)*[a]	Biceps *(-0.84 cm)*	Mid-thigh *(-1.16 cm)*	Calf *(-1.38 cm)*
Glucose	1[b]	5.27 (0.35)	5.20 (0.32)*	5.33 (0.36)	5.33 (0.32)
	2[c]	5.32 (0.38)	5.39 (0.38)	5.26 (0.36)	5.37 (0.40)
TC	1	4.87 (0.96)	4.73 (0.89)*	4.90 (0.97)	4.69 (0.96)*
	2	5.06 (0.91)	5.20 (0.93)	5.03 (0.90)	5.26 (0.81)
TG	1	1.67 (1.37)	1.34 (1.11)	1.75 (1.37)	1.62 (1.28)
	2	1.49 (0.93)	1.82 (1.18)	1.40 (0.90)	1.53 (1.03)
HDL-C	1	1.22 (0.21)	1.30 (0.23)**	1.18 (0.23)	1.20 (0.24)
	2	1.19 (0.31)	1.12 (0.26)	1.23 (0.29)	1.22 (0.28)
LDL-C	1	2.97 (0.89)	2.88 (0.79)*	3.01 (0.94)	2.80 (0.87)**
	2	3.21 (0.83)	3.30 (0.88)	3.17 (0.78)	3.40 (0.73)
LDL-C : HDL-C	1	2.45 (0.84)	2.22 (0.61)***	2.65 (1.08)	2.46 (1.07)
	2	2.83 (1.03)	3.07 (1.04)	2.66 (0.83)	2.85 (0.76)

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ between 1 and 2.

[a]Values in italics are median values for skinfold.

[b]1 represents the sub-group of subjects with skinfold thickness equal to or less than the median value for that skinfold.

[c]2 represents the sub-group of subjects with skinfold thickness greater than the median value for that skinfold.

TABLE IX (4.4) Metabolic variables (mmol.L^{-1}) in men according to torso skinfold thickness following adjustment to the Phantom body mass of 64.58 kg. Values are means ± (SD). (N = 68).

		Subscapular *(-0.04 cm)*[a]	Suprailiac *(2.80 cm)*	Abdominal *(-0.33 cm)*
Glucose	1[b]	5.28 (0.35)	5.26 (0.36)	5.30 (0.38)
	2[c]	5.31 (0.38)	5.33 (0.36)	5.29 (0.35)
Total Cholesterol	1	4.79 (1.00)	4.76 (1.02)	4.97 (1.09)
	2	5.14 (0.83)	5.18 (0.78)	4.97 (0.76)
TG	1	1.38 (0.82)	1.53 (1.17)	1.39 (0.94)
	2	1.78 (1.41)	1.63 (1.17)	1.76 (1.34)
HDL-C	1	1.23 (0.23)	1.21 (0.25)	1.24 (0.26)
	2	1.17 (0.29)	1.20 (0.28)	1.17 (0.26)
LDL-C	1	2.95 (0.95)	2.89 (0.93)*	3.13 (1.03)
	2	3.24 (0.74)	3.30 (0.73)	3.05 (0.65)
LDL-C : HDL-C	1	2.46 (0.94)	2.51 (1.00)	2.62 (1.05)
	2	2.84 (0.94)	2.80 (0.88)	2.68 (0.85)

* $P < 0.05$ between 1 and 2.
[a]Values in italics are median values for skinfold.
[b]1 represents the sub-group of subjects with skinfold thickness equal to or less than the median value for that skinfold.
[c]2 represents the sub-group of subjects with skinfold thickness greater than the median value for that skinfold.

Differences in serum glucose and lipids according waist and abdominal girths are shown in Table X (4.4). With the exception of serum glucose concentration, significant differences in all metabolic variables were found. TC, TG and LDL-C were significantly lower in the men characterised by a smaller waist and abdominal girth ($P < 0.05$). LDL-C : HDL-C was also significantly lower in men with smaller waist ($P < 0.001$) and abdominal girths ($P < 0.01$). HDL-C was significantly higher in the men with narrower waist ($P < 0.001$) and abdominal girths ($P < 0.01$).

Table X (4.4). Metabolic variables (mmol.L^{-1}) in men with different levels of abdominal obesity determined using waist and abdominal girth measurements. (N = 68).

Variable		Waist girth *(87.0)*[a]	Abdominal girth *(91.6)*
Glucose	1[b]	5.23 (0.31)	5.24 (0.31)
	2[c]	5.36 (0.40)	5.36 (0.40)
TC	1	4.73 (0.96)*	4.74 (0.92)*
	2	5.20 (0.84)	5.20 (0.90)
TG	1	1.15 (0.43)*	1.31 (0.83)*
	2	2.01 (1.47)	1.85 (1.38)
HDL-C	1	1.31 (0.22)***	1.29 (0.25)**
	2	1.10 (0.26)	1.12 (0.26)
LDL-C	1	2.90 (0.90)*	2.87 (0.92)*
	2	3.30 (0.77)	3.32 (0.79)
LDL-C : HDL-C	1	2.27 (0.83)***	2.31 (0.92)**
	2	3.07 (0.92)	3.01 (0.86)

* $P < 0.05$, **$P < 0.01$, *** $P < 0.001$ between 1 and 2.
[a]Values in italics are median values for waist and abdominal girth.
[b]1 represents the sub-group of subjects with a waist or abdominal girth equal to or less than the median value for that girth.
[c]2 represents the sub-group with a girth measurement greater than the median.

After adjustment for the variation in stature, the magnitude of the differences in serum glucose and lipids appeared to be diminished. Significant differences remained for TC ($P < 0.05$) using stature normalised waist girth, TG ($P < 0.01$) and HDL-C ($P < 0.05$) using both waist and abdominal girths, and LDL-C : HDL-C ($P < 0.05$ using stature normalised waist girth and $P < 0.01$ using stature normalised abdominal girth) [Table XI (4.4)].

Table XI (4.4). Metabolic variables (mmol.L^{-1}) in men with different levels of abdominal obesity determined using waist and abdominal girth measurements normalised to a Phantom stature (170.18 cm). (N = 68).

Variable		Waist girth *(3.44)*[a]	Abdominal girth *(1.57)*
Glucose	1[b]	5.21 (0.31)	5.24 (0.32)
	2[c]	5.37 (0.40)	5.34 (0.40)
TC	1	4.73 (0.98)*	4.77 (0.99)
	2	5.20 (0.84)	5.13 (0.85)
TG	1	1.16 (0.49)**	1.15 (0.44)**
	2	1.97 (1.45)	1.96 (1.45)
HDL-C	1	1.29 (0.23)*	1.28 (0.21)*
	2	1.13 (0.27)	1.14 (0.28)
LDL-C	1	2.92 (0.91)	2.98 (0.92)
	2	3.26 (0.78)	3.20 (0.79)
LDL-C : HDL-C	1	2.35 (0.89)**	2.37 (0.83)*
	2	2.96 (0.92)	2.92 (0.99)

* $P < 0.05$, ** $P < 0.01$ between 1 and 2.
[a]Values in italics are median values for stature normalised waist and abdominal girths.
[b]1 represents the sub-group of subjects with a waist or abdominal girth equal to or less than the median value for that girth.
[c]2 represents the sub-group with a girth measurement greater than the median.

Following adjustment for differences in body mass, there were no significant differences between any of the metabolic variables using either waist or abdominal girths [Table XII (4.4)].

Table XII (4.4). Metabolic variables (mmol.L^{-1}) in men with different levels of abdominal obesity determined using waist and abdominal girth measurements normalised to a Phantom body mass (64.58 kg). (N = 68).

Variable		Waist girth *(0.98)*[a]	Abdominal girth *(0.21)*
Glucose	1[b]	5.23 (0.30)	5.22 (0.31)
	2[c]	5.36 (0.41)	5.37 (0.39)
TC	1	4.90 (0.96)	4.95 (0.97)
	2	5.03 (0.91)	4.99 (0.90)
TG	1	1.43 (1.00)	1.40 (0.99)
	2	1.72 (1.30)	1.74 (1.29)
HDL-C	1	1.18 (0.23)	1.18 (0.23)
	2	1.24 (0.29)	1.23 (0.29)
LDL-C	1	3.12 (0.91)	3.17 (0.90)
	2	3.07 (0.82)	3.00 (0.82)
LDL-C : HDL-C	1	2.75 (1.04)	2.79 (1.03)
	2	2.55 (0.86)	2.51 (0.86)

All differences not significant (P > 0.05)
[a]Values in italics are median values for stature normalised waist and abdominal girths.
[b]1 represents the sub-group of subjects with a waist or abdominal girth equal to or less than the median value for that girth.
[c]2 represents the sub-group with a girth measurement greater than the median.

Table XIII (4.4) shows simple bivariate correlations between fasting serum glucose and lipid concentrations and skinfold measurements. Glucose was related to abdominal skinfold only (r = 0.268, P < 0.05). Fasting TC, however, was significantly related to all torso skinfolds as follows: subscapular (r = 0.258); suprailiac (r = 0.267); abdominal (r = 0.277) (all P < 0.05); supraspinale (r = 0.312, P < 0.01). HDL-C was inversely correlated with all skinfolds. This relationship was significant (P < 0.05) with respect to biceps (r = - 0.239), suprailiac (r = - 0.264), abdominal (r = - 0.242)

and mid-thigh (r = - 0.326, P < 0.01) skinfolds. LDL-C was also significantly related to biceps (r = 0.270), suprailiac (r = 0.239), supraspinale (r = 0.299) and abdominal skinfolds (all P < 0.05). The largest correlations were between biceps (r = 0.341), suprailiac (r = 0.370) and abdominal (r = 0.377) skinfolds with the LDL-C : HDL-C ratio (all P < 0.01). This ratio was also related to the mid-thigh (r = 0.313) and calf (r = 0.307) skinfolds (both P < 0.05).

TABLE XIII (4.4). Correlation coefficients showing the relationship between fasting serum glucose and lipid concentrations and skinfolds in healthy men (N = 68).

	Glucose	TC	TG	HDL-C	LDL-C	LDL-C : HDL-C
Triceps	-0.229	-0.016	0.016	-0.058	-0.024	0.042
Biceps	0.088	0.206	0.068	-0.239*	0.270*	0.341**
Mid-thigh	-0.007	0.156	0.213	-0.326**	0.151	0.313*
Calf	-0.016	0.129	-0.038	-0.233	0.204	0.307*
Subscapular	0.191	0.258*	0.247*	-0.139	0.177	0.200
Suprailiac	0.092	0.267*	0.307*	-0.264*	0.239*	0.370**
Supraspinale	0.176	0.312*	0.127	-0.055	0.299*	0.219
Abdominal	0.268*	0.277*	0.148	-0.242*	0.301*	0.377**

* P < 0.05; ** P < 0.01

Table XIV (4.4) shows correlations between the metabolic variables and the sum of eight skinfolds, the sum of torso skinfolds, the sum of limb skinfolds and the torso-to-limb skinfold ratio. Although individual limb skinfolds were unrelated to TC, when the sum of limb skinfolds was used, a significant relationship was observed (r = 0.311, P < 0.01). Other significant (P < 0.01) correlations were found between HDL-C and the sum of eight skinfolds (r = - 0.417) and between LDL-C : HDL-C with the sum of eight skinfolds (r = 0.355), the sum of torso skinfolds (r = 0.412), the sum of limb skinfolds (r = 0.389) and the torso : limb skinfold ratio (r = 0.359).

TABLE XIV (4.4). Correlation coefficients showing the relationship between fasting serum glucose and lipids and various skinfold parameters in healthy men (n = 68).

	Glucose	TC	TG	HDL-C	LDL-C	LDL-C : HDL-C
Σ 8 skinfolds	0.122	0.156	0.307*	-0.417**	0.152	0.355**
Σ 4 torso skinfolds	0.154	0.305*	0.193	-0.285*	0.320**	0.412**
Σ 4 limb skinfolds	0.162	0.311**	0.240*	-0.268*	0.306*	0.389**
Torso : limb skinfold ratio	0.107	0.228	0.073	-0.249*	0.272*	0.359**

* $P < 0.05$; ** $P < 0.01$

Correlations between fasting serum glucose, lipids and stature-normalised skinfolds are shown in Table XV (4.4). TC was significantly related to biceps (r = 0.251), subscapular (r = 0.263) and suprailiac (r = 0.302) skinfolds ($P < 0.05$). TG was significantly related to biceps (r = 0.244) and subscapular (r = 0.301) skinfolds ($P < 0.05$), and HDL-C was inversely related to abdominal skinfold (r = -0.323, $P < 0.01$). LDL-C : HDL-C showed the greatest association with the stature-normalised subcutaneous adiposity. Abdominal (r = 0.300), mid-thigh (r = 0.296) (both $P < 0.05$), triceps (r = 0.331), subscapular (r = 0.360) and medial-calf (r = 0.353) (all $P < 0.01$) skinfolds were all significantly related to this CAD risk ratio.

TABLE XV (4.4.). Correlation coefficients showing the relationship between fasting serum glucose and lipid concentrations and stature-normalised skinfolds in healthy men (N = 68).

	Glucose	TC	TG	HDL-C	LDL-C	LDL-C : HDL-C
Triceps	0.109	0.199	0.071	-0.237	0.264*	0.331**
Biceps	0.204	0.251*	0.244*	-0.140	0.173	0.195
Mid-thigh	0.004	0.121	-0.040	-0.232	0.197	0.296*
Calf	0.218	0.233	-0.003	-0.197	0.306*	0.353**
Subscapular	0.111	0.263*	0.301*	-0.259	0.237	0.360**
Suprailiac	0.201	0.302*	0.118	-0.047	0.291*	0.203
Abdominal	0.013	0.148	0.209	-0.323**	0.197	0.296*

*P < 0.05; ** P < 0.01

The relationship between the metabolic variables and skinfolds adjusted for body mass are presented in Table XVI (4.4). Significant relationships were found between subscapular skinfold and TG concentration (r = 0.301), abdominal skinfold and HDL-C (r = - 0.298), and between LDL-C : HDL-C and both subscapular (r = 0.293) and calf (r = 0.254) skinfolds (all P < 0.05).

TABLE XVI (4.4). Correlation coefficients showing the relationship between fasting serum glucose and lipid concentrations and body mass-normalised skinfolds in healthy men (N = 68).

	Glucose	TC	TG	HDL-C	LDL-C	LDL-C : HDL-C
Triceps	0.097	0.121	0.052	-0.177	0.158	0.205
Biceps	0.196	0.186	0.214	-0.097	0.100	0.117
Mid-thigh	-0.011	0.046	-0.056	-0.191	0.105	0.201
Calf	0.195	0.164	-0.014	-0.145	0.215	0.254*
Subscapular	0.101	0.210	0.301*	-0.234	0.161	0.293*
Suprailiac	0.211	0.222	0.094	0.028	0.184	0.071
Abdominal	0.002	0.062	0.209	-0.298*	0.034	0.206

*P < 0.05

The final results in this section are presented in table XVII (4.4). This shows the relationship between the metabolic variables and waist and abdominal girths. Also shown are the results obtained following adjustment of these girth measurements by the Phantom stature and body mass. Generally, the relationship between waist and abdominal girths and the lipid variables was stronger than the relationship with skinfolds. This relationship was strongest using the unadjusted waist and abdominal girths. After adjustment for stature the magnitude of the correlations were slightly reduced. However, after adjustment for body mass, correlations were dramatically reduced and only one remained significant. Fasting serum glucose was associated with stature-normalised waist ($r = 0.260$, $P < 0.05$) and abdominal girths ($r = 0.243$, $P < 0.05$) but was independent of these girth measurements in the unadjusted or body mass-adjusted forms.

TABLE XVII (4.4). Correlation coefficients showing the relationship between fasting serum glucose and lipid concentrations and waist and abdominal girths. Also shown are the correlations with stature and body mass-normalised waist and abdominal girths (N = 68).

	Glucose	TC	TG	HDL-C	LDL-C	LDL-C : HDL-C
Waist	0.196	0.253*	0.414**	-0.440**	0.226	0.421**
Abdomen	0.169	0.289*	0.384**	-0.437**	0.276*	0.464**
Waist / Ht	0.260*	0.235	0.378**	-0.394**	0.213	0.372**
Abdomen / Ht	0.243*	0.272*	0.356**	-0.396**	0.263*	0.417**
Waist / Wt	0.197	-0.035	0.252*	-0.182	-0.124	-0.005
Abdomen / Wt	0.172	-0.029	0.217	-0.162	-0.111	-0.001

Waist / Ht and Abdomen / Ht are waist and abdominal girths normalised to the Phantom stature (170.18cm).
Waist / Wt and Abdomen / Wt are waist and abdominal girths normalised to the Phantom body-mass (64.58 kg).
*P < 0.05, ** P < 0.01

Many studies have, in the past, examined the relationship between anthropometrically-described AT distribution and indices of metabolic fitness. However, none have adjusted for differences in body size as this study has done.

The mathematical direction of the differences in glucose and lipids between the two groups formed for this analysis were as expected. Whether using skinfolds or girth measurements, leaner men were more likely to have a metabolic profile that presents them with less risk of CVD than fatter men. In many instances in this study, these differences were statistically significant and in line with previous research. However, a few surprising results were also generated. For example, when skinfolds were used in their unadjusted form, biceps appeared to be the best skinfold for identifying differences in all of the metabolic variables tested. With this kind of analysis, torso skinfolds were relatively insensitive to differences in glucose and lipids. As stated previously, subscapular skinfold has appeared as an independent

predictor of CVD in several prospective studies. However, when men were divided according to subscapular skinfold thickness, there were no differences in any of the metabolic variables. Supraspinale was the best torso skinfold for identifying men more likely to have an adverse metabolic profile.

Previously, Pouliot *et al.* (1992) found a higher fasting glucose concentration in obese compared to lean men. Rates of glucose disposal and hepatic glucose output have also been found to be related to torso skinfolds (Abate *et al.*, 1995). Krotkiewski *et al.* (1983) found a highly significant relationship between waist girth and fasting glucose. In this study however, fasting glucose was not higher in men with greater subcutaneous adiposity nor was it related to skinfolds or girths. The one exception to this finding was with respect to the waist and abdominal girths adjusted for stature. Both of these measurements had a significant, if low, correlation with fasting glucose. Why men with a relatively large waist or abdominal girth for their height have a higher fasting glucose concentration is not immediately clear. Bearing in mind that skeletal muscle is the major site of non-oxidative glucose disposal, one possibility is that these men have an increased hepatic glucose output associated with their abdominal obesity but a low muscle mass.

With the exception of the consistent, if surprising, finding that biceps was the best skinfold for identifying differences in serum lipids, individual skinfolds seemed to be of little use for this purpose. Sums of skinfolds were no better, although Σ torso skinfolds was able to identify a difference in serum TG that Σ limb, or Σ 8 skinfolds was not. The torso-to-limb skinfold ratio was equally ineffective. In the past, Leclerc *et al.*, (1983) found that BMI, skinfolds and total body fat were equally related to TG and HDL-C. Despres *et al.* (1985) found that abdominal and subscapular skinfolds were highly related to TG and HDL-C. The relationship between torso skinfolds and

HDL-C was independent TG (Despres *et al.*, 1988). Of the lipid variables measured in this study, differences in the ratio of LDL-C to HDL-C were the most consistently identified using skinfolds and girths. Triceps, biceps, calf, supraspinale, Σ 8 skinfolds, Σ 4 torso skinfolds, waist and abdominal girths were all able to identify a difference in this CVD risk ratio. The difference in LDL-C : HDL-C, observed using biceps skinfold and waist girth to distinguish the men, was highly significant ($P < 0.001$). Standardising biceps skinfold for stature and body mass, and waist girth for stature had no effect on this finding. However, when waist girth was adjusted for body mass, no difference existed. Likewise, waist and abdominal girth were significantly related to the LDL-C : HDL-C ratio, TG and HDL-C in the non-standardised and stature-adjusted forms. When these girths were standardised for body mass, the size of the correlations was significantly diminished and they were no longer significant. The same phenomena could be observed for HDL-C, and to a lesser extent TG. Exactly why this occurs is unclear. Intuitively, the magnitude and consistency of the changes in the correlations seem too great to be explained as a random event. This finding illustrates the complexity of the relationship between blood lipids and physique and presents an intriguing opportunity for future research.

In summary, this study found that segregating individuals on the basis of anthropometric measures of total and regional subcutaneous adiposity was not a valid way of identifying subjects with elevated fasting serum glucose. With simple regression analysis, glucose was related to abdominal skinfold and also the waist and abdominal girths standardised for stature. However, these relationships were only weak. With regard to fasting serum lipids and lipoproteins, TC, TG, LDL-C, HDL-C and the LDL-C : HDL-C ratio all had significant relationships with subcutaneous adiposity. TC, TG, LDL-C and LDL-C : HDL-C are all positively associated with

adiposity. HDL-C is inversely related to adiposity. No discernible subcutaneous AT pattern appeared with respect to the relationship with lipids. Rather, it appeared that total subcutaneous adiposity was important. Abdomen and waist girths were also significantly related to the metabolic variables examined in this study. A physique characterised by a greater abdominal girth is evidently associated with increased CVD risk via elevated TG, LDL-C, LDL-C : HDL-C and a decreased HDL-C. Standardising these anthropometric methods for variation in body size did not improve the ability to identify subjects with an adverse risk profile, nor did it increase the strength of relationships. However, adjusting for variation in body mass did result in the appreciable decrease in the relationship between serum lipids, waist and abdominal girths. The physiological significance of this finding requires further analysis.

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CHAPTER 5

RESULTS & DISCUSSION

STUDIES FOCUSING ON SOMATOTYPE

5.1 SOMATOTYPE AND ADIPOSE TISSUE DISTRIBUTION OF MEN WITH ANGIOGRAPHICALLY-DETERMINED CAD

The aim of this study was to describe the somatotype of men with angiographically-determined CAD and to investigate the relationship between somatotype, adipose tissue distribution and CAD. Descriptive statistics of the anthropometric characteristics and angiographic assessment are presented in Table I (5.1).

TABLE I (5.1). Means and standard deviations for age, body size, somatotype, fat distribution and angiography results (N = 65).

Variable	Mean	SD
Age, years	61.5	8.7
Body mass, kg	81.02	13.00
Stature, cm	173.15	6.10
BMI, $kg.m^{-2}$	27.0	4.0
Abdominal circumference, cm	99.9	10.7
Hip circumference, cm	100.0	8.0
AHR	1.0	0.05
ASD, cm	26.4	3.6
Endomorphy	5.7	1.7
Mesomorphy	5.6	1.2
Ectomorphy	1.2	1.0
Sum of 8 skinfolds, mm	153.8	53.2
Sum of torso skinfolds, mm	100.7	34.4
Sum of limb skinfolds, mm	53.1	21.1
Torso/limb skinfold ratio	1.97	0.46
Myocardial score	6.70	3.58
Ventricular score	2.20	2.00

BMI - body mass index
AHR - abdomen-to-hip ratio
ASD - abdominal sagittal diameter

A mean somatotype (± SD) of 5.7 / 5.6 / 1.2 (1.7 / 1.4 / 1.0) illustrates a clear and equal dominance of endomorphy and mesomorphy with ectomorphy of only

minor significance. A breakdown of the somatotypes into defined categories (Carter and Heath, 1990) was as follows: mesomorphic-endomorphs (N = 24); endomorphic-mesomorphs (N = 20); mesomorph-endomorphs (N = 10); balanced endomorphs (N = 2); balanced mesomorphs (N = 1) and ectomorphic-endomorphs (N = 1). Furthermore, 35 (60%) somatotypes could be considered as extremes for their particular category (Carter and Heath, 1990).

The results of a zero-order correlation analysis between the somatotype components, indices of obesity and adipose tissue distribution, and the angiographic findings are shown in table II (5.1).

TABLE II (5.1). Pearson product-moment correlation coefficients between the somatotype components, indices of obesity and adipose tissue distribution, and angiographic findings.

	somatotype component		
Variable	Endomorphy	Mesomorphy	Ectomorphy
Age	-0.37**	-0.08	0.19
BMI	0.71***	0.74***	-0.82***
Abdominal circumference	0.77***	0.50***	-0.66***
Hip circumference	0.64***	0.53***	-0.59***
AHR	0.64***	0.18	-0.47***
ASD	0.74***	0.56***	-0.70***
Σ of 8 skinfolds	0.94***	0.42**	-0.51***
Σ of torso skinfolds	0.92***	0.38**	-0.52***
Σ of limb skinfolds	0.85***	0.44***	-0.45***
Torso/limb skinfold ratio	0.01	-0.11	-0.05
Myocardial score	0.01	0.12	-0.08
Ventricular score	-0.08	-0.06	0.08

*** P < 0.001, ** P < 0.01, * P < 0.05

Mesomorphy and ectomorphy, but not endomorphy, were independent of age. The somatotype components were not related to the torso-to-limb skinfold ratio, but endomorphy, as expected, was highly significantly correlated with the sum of 8 skinfolds ($r = 0.94$, $P < 0.001$), the sum of 4 torso skinfolds ($r = 0.92$, $P < 0.001$) and the sum of 4 limb skinfolds ($r = 0.85$, $P < 0.001$). Endomorphy was also related to abdominal adiposity as indicated by the correlations with abdominal circumference ($r = 0.77$, $P < 0.001$), AHR ($r = 0.64$, $P < 0.001$) and ASD ($r = 0.74$, $P < 0.001$). Mesomorphy was significantly related to BMI ($r = 0.74$, $P < 0.001$), this correlation being slightly greater than the correlation between endomorphy and BMI ($r = 0.71$, $P < 0.001$). Mesomorphy was equally related to an increased abdominal circumference ($r = 0.50$, $P < 0.001$), ASD ($r = 0.56$, $P < 0.001$) and hip circumference ($r = 0.53$, $P < 0.001$) but was not associated with the AHR ($r = 0.18$, $P > 0.05$). Ectomorphy was inversely associated with all measures of adiposity. None of the zero-order correlations between the somatotype components and the angiography findings were statistically significant ($P > 0.05$).

As the somatotype components were significantly interrelated ($P < 0.01$) (correlations shown later) further correlation analysis was performed using second-order partial correlations [(Table III (5.1)]. These correlations indicate the strength of the relationship between each somatotype component and the dependent variables after statistically controlling for the effects of the other two somatotype components. Generally, this had the effect of reducing the strength of the correlations.

TABLE III (5.1). Partial correlation coefficients showing the relationship between each somatotype component, indices of obesity and adipose tissue distribution, and angiographic findings after statistically controlling for the other two somatotype components.

Variable	somatotype component		
	Endomorphy	Mesomorphy	Ectomorphy
Age	-0.32*	-0.05	0.01
BMI	0.62***	0.58***	-0.52***
Abdominal circumference	0.65***	0.17	-0.26*
Hip circumference	0.49***	0.29*	-0.15
AHR	0.53***	-0.22	-0.26*
ASD	0.60***	0.25	-0.32*
Σ 8 skinfolds	0.92***	0.37**	0.27*
Σ torso skinfolds	0.90***	0.19	0.12
Σ limb skinfolds	0.83***	0.39**	0.31*
Torso/limb skinfold ratio	-0.02	-0.19	-0.15
Myocardial score	-0.04	0.09	-0.02
Ventricular score	-0.08	-0.06	0.08

*** $P < 0.001$, ** $P < 0.01$, $P < 0.05$

Canonical correlation analysis revealed no significant relationship ($P > 0.05$) between the first or second pairs of canonical variates with only 3% of the variance in angiography results explained by the Heath-Carter anthropometric somatotype [(Table IV (5.1)].

TABLE IV (5.1). Results of canonical correlation analysis between somatotype and angiographic findings.

	Canonical correlations	Squared canonical correlations	Chi-square	Degrees of freedom	Significance
First	0.168	0.03	1.790	6	0.938
Second	0.067	0.00	0.245	2	0.885

Table V (5.1) presents the loadings (correlations) between the original variables and their first and second canonical variates.

TABLE V (5.1). Correlations (loadings) between the somatotype components and the angiography results with their respective first and second canonical variates.

	First canonical variate	Second canonical variate
Endomorphy	0.390	-0.860
Mesomorphy	0.966	0.110
Ectomorphy	-0.825	0.424
Myocardial score	0.721	0.693
LV function	-0.419	0.908

For the first canonical variates, mesomorphy and endomorphy load positively (r = 0.966 and 0.390 respectively) and ectomorphy negatively on the somatotype variate (r = -0.825). On the variate that describes the angiography results, myocardial score loaded positively (r = 0.721) and ventricular score negatively (r = -0.419). These

correlations suggest that the first somatotype variate is best interpreted as one of high mesomorphy, moderate endomorphy and low ectomorphy. The first angiography variate is one of a high myocardial score and low ventricular score. The loadings on the second somatotype variate suggest that this should be interpreted as a measure of low endomorphy and moderate ectomorphy, and the second angiography variate is one of high myocardial and ventricular scores.

This is the first investigation into the somatotypes of men undergoing investigative coronary angiography, although other investigators have used this approach to study the influence of overweight, fat distribution and subcutaneous adiposity (Hauner *et al.*, 1990; Thompson *et al.*, 1991; Flynn *et al.*, 1993; Hodgson *et al.*, 1994; Ley *et al.*, 1994).

Previous studies by Gertler *et al.* (1950, 1951, 1967) and Spain *et al.* (1953, 1955) suggested that mesomorphy was the most significant somatotype component with regard to predisposition to CAD. However, this conclusion should be viewed with caution as these studies examined the somatotype not as a gestalt, but focused only on the dominant component. In a later study, Spain and colleagues stated that endo-mesomorphic individuals had the highest prevalence rate for CAD, suggesting that body fatness was also a characteristic of at risk individuals (Spain *et al.*, 1963). However, Spain *et al.* suggested that "relative muscle mass rather than an increase in adipose tissue probably has a more direct association with the prevalence of coronary atherosclerotic heart disease, especially in the absence of hypertension". One other study at this time also highlighted the precedence of endomorphy and mesomorphy in describing the physique of coronary cases (Paul *et al.*, 1963). These latter findings were supported by the study of Smit *et al.* (1979) who used the Heath-Carter technique and reported a mean somatotype of 4 - 5.5 - 1 for a group of cardiac

infarction patients. Using the same somatotype technique, this study has found an almost equal number of patients who are dominant in endomorphy and mesomorphy (30 patients were dominant in endomorphy, 26 dominant in mesomorphy and 2 exhibited equality of endomorphy and mesomorphy). Whilst there was a clear dominance of endomorphy and mesomorphy, men who exhibit ectomorphic dominance appear to be at little risk of CAD. Thus, patients with angiographically-determined CAD are characterised by a physique of relative muscularity and adiposity, whereas linearity of physique is evidently not a physical characteristic of CAD patients. These data would, therefore, appear to support the recent conclusion that with regard to CAD risk, linearity in males appears to be advantageous (Malina *et al.*, 1997).

In an attempt to explain the observations outlined above, the relationship between somatotype and angiographic findings was investigated with canonical correlation analysis. The aim was to consider all three components together rather than treat each component as an independent variable. This approach to the analysis of somatotype data has been used previously by Gordon *et al.* (1987) and Katzmarzyk *et al.* (1998). Gordon *et al.* (1987) found that somatotype was related to a set of serum lipids that included TC, LDL-C, HDL-C and TG in a group of young adult males. Katzmarzyk *et al.* (1998) reported that a Heath-Carter anthropometric somatotype characterised by high endomorphy and mesomorphy was associated with higher levels of TG, LDL-C and fasting glucose, and lower levels of HDL-C in male and female youths aged 9- to 18-years. This analysis showed that the two pairs of canonical variates representing somatotype and angiography results were not related. However, examination of the pattern of loadings between the original variables and their respective first canonical variates indicated that a somatotype of high mesomorphy,

moderate endomorphy and low ectomorphy, and an angiography variate represented by an increased myocardial score and a lower ventricular score were the linear combinations that provided the strongest possible correlation. Simple correlations between the somatotype components and the angiographic findings were also not significant. The absence of a significant relationship between somatotype and CAD may be due to the fact that CAD is an extremely complex disease with many biological, environmental and lifestyle risk factors. Also, rather than simply using clinical diagnostic criteria, a highly sensitive angiographic scoring system was employed to assess the severity of an occlusion. Variation in CAD severity established with this technique was clearly not of sufficient magnitude to be identifiable between different somatotypes.

Using simple correlation coefficients in this way is somewhat problematic as the relationship is confounded by the inter-relationship between somatotype components. In this study, correlations between the components were as follows: endomorphy and mesomorphy ($r = 0.36$, $P < 0.01$), endomorphy and ectomorphy ($r = -0.56$, $P < 0.001$) and ectomorphy and mesomorphy ($r = -0.66$, $P < 0.001$). Therefore, a partial correlation technique was used to investigate the relationship between the somatotype components and the dependent variables. This technique statistically controls for the confounding effect of the other two components. As recently noted, data analysis in which the components are treated individually, "dilutes the somatotype gestalt" (Malina *et al.*, 1997). However, it allows an evaluation of the relationship between the angiographic findings, adiposity indices and a somatotype component independently of the other two components.

In a study of 824 men, it was reported that those with an android fat distribution were more often classed as obese than gynoid fat men (Mueller and Joos, 1985).

Furthermore, the android obese men were significantly more mesomorphic and less endomorphic than the gynoid obese. This, it was suggested, means that android obesity is associated with "deep body obesity" (presumably referring to intra-abdominal adiposity) and "excess lean body mass". Interestingly, several case-control studies employing angiographic assessment, and data presented previously in this thesis, suggest that an android fat distribution is a notable characteristic of men with CAD (Hauner *et al.*, 1990; Thompson *et al.*, 1991; Flynn *et al.*, 1993; Hodgson *et al.*, 1994; Ley *et al.*, 1994). Other anthropometric indicators of upper trunk, android or abdominal obesity, have also been shown to be predictors of CVD or increased CVD risk. These include the ASD (Seidell *et al.*, 1994), waist circumference (Han *et al.*, 1995) and trunk skinfold thickness (Donahue *et al.*, 1987). In this study, the simple correlations between the somatotype components and the anthropometric measurements of total subcutaneous adiposity and AT distribution indicate that endomorphy is strongly and positively related to all indices. Mesomorphy is moderately and positively related to all indices except the AHR. Ectomorphy is quite strongly and inversely related to all indices. The exception to this finding is the torso-to-limb skinfold ratio that is not correlated with any of the somatotype components when analysed in this way. After adjustment for the inter-relationship between components, the correlations are generally reduced. However, endomorphy remained significantly positively related to abdominal circumference, AHR and the ASD, whilst mesomorphy was not significantly associated with any of these variables and, in fact, became inversely related to the AHR. Of further note is the finding that BMI, which is a widely used indicator of obesity in many epidemiological and clinical settings, was almost equally related to endomorphy and mesomorphy after partial adjustment.

This investigation has shown that men with angiographically-documented CAD exhibit an almost equal dominance of endomorphy and mesomorphy. Ectomorphy, however, is a physical characteristic that appears to be beneficial in terms of CAD risk. Probably the largest published samples of men of similar age who have been somatotyped with the Heath-Carter anthropometric technique are those of Canadian (Bailey *et al.*, 1982) and British men (King cited in Carter and Heath, 1990). These data showed the mean somatotype (± SD) of the Canadian men aged 50- to 59-years to be 4.1 - 5.4 - 1.6 (1.2 - 1.2 - 0.9) and the British men aged 50- to 64-years to be 3.9 - 5.9 - 1.3 (1.0 - 1.1 - 0.9). Recent data from the Quebec Family Study reported a mean somatotype of 4.0 - 5.6 - 1.5 (1.5 - 1.0 - 1.0) for 233 men aged 40 to 49-years (Malina *et al.*, 1997). In comparison to these data, the CAD patients in this study are approximately equal in mesomorphy, slightly less in ectomorphy and between 1.5 to 2.0 units greater in endomorphy. In general, the CAD patients in this study are also older than the Quebec subjects. It is possible, therefore, that increasing body fatness with age in mesomorphic individuals predisposes to CAD in later life. This conclusion is in agreement with an opinion forwarded more than 30 years ago suggesting that mesomorphs are prone to excessive weight gain and should adopt an active lifestyle to maintain energy balance (Gertler, 1967).

The biological mechanisms that associate obesity (represented by a high endomorphy rating) with CAD have been delineated in some detail (Kissebah and Krakower, 1994). A biological role for mesomorphy (representing lean body mass), however, is less clear. Two possible explanations are proposed.

As obese individuals also have a large absolute lean body mass (Forbes, 1977), the high mesomorphy rating reported for CAD patients is simply an artefact. That is, endomorphy is biologically relevant in CAD risk and mesomorphy is coincidental.

Given the substantial body of evidence that is now available suggesting that skeletal muscle plays an important role in metabolic disease risk (Basset, 1994), this seems unlikely. Therefore, the following explanation is more likely.

The physiological significance of skeletal muscle fibre-type in the aetiology of insulin resistance and a metabolic syndrome that includes hypertension, insulin resistance and android obesity has been outlined by several authors (Basset, 1994; Kelley and Simoneau, 1997; Simoneau and Kelley, 2000). Type IIb skeletal muscle fibre proportion has been shown to be negatively correlated with insulin-stimulated glucose uptake (Lillioja *et al.*, 1987). Furthermore, in comparison to type I fibres, type II fibres have a lower capillary density (Lillioja *et al.*, 1987) and reduced capacity for the oxidation of NEFA's (Kelley and Simoneau, 1997). Theoretically, therefore, individuals with a high proportion of type IIb fibres are predisposed to insulin resistance and fat accumulation in adipose tissue. Mesomorphy may, therefore, have a more direct role in CAD risk if, in genetically susceptible individuals, it is associated with this particular fibre type. Conversely, ectomorphs would be 'protected' against obesity, insulin resistance and their consequences by a having a high proportion of type I fibres. They are ectomorphic because they are high fat 'burners'. Current evidence from studies of skeletal muscle characteristics, obesity and insulin resistance suggests that this is a reasonable supposition and would explain the predisposition of mesomorphs for body fat gain.

Thus, chronically inactive, ageing mesomorphs may be susceptible to abdominal obesity, insulin resistance, hypertension and a dyslipidemia that includes elevated TG, apo B and the atherogenic small dense LDL particles and reduced HDL-C. This cluster of metabolic factors has been described previously (Despres, 1995). It was not possible to assess insulin sensitivity in these patients, but this metabolic

derangement has been previously documented in patients undergoing angiography (Shinozaki *et al.*, 1996). Individuals characterised by ectomorphic dominance appear to have a low risk of CAD as this component is associated with leanness and a favourable risk factor profile.

With regard to application of these findings, it would seem sound advice to endo-mesomorphs and meso-endomorphs that they endeavour to become leaner (more ectomorphic) at the cost of endomorphy and that the mesomorphic component, i.e. the lean body mass, should be kept physically active. Interestingly, recent findings from the Aerobics Center Longitudinal Study in Dallas, Texas have suggested a lower relative all-cause mortality risk in obese men (% body fat $\geq$ 25) classified as 'fit' in comparison to lean (% body fat < 16.7), 'fit' men (Lee *et al.*, 1999). Individuals characterised by higher levels of ectomorphy should aim to maintain this characteristic and avoid becoming more endomorphic with advancing age. A study of CAD risk factors in individuals high in mesomorphy but low in endomorphy and ectomorphy is needed to completely delineate the relevance of mesomorphy in CAD.

5.2 SOMATOTYPE OF MEN WITH CAD AND HEALTHY AGE-MATCHED CONTROLS.

The aim of this study was the somatotype comparison of the men with CAD and a group of men who were apparently healthy and matched for age. The mean (± SD) ages of the CAD patients and healthy men were 53.2 (6.5) and 51.2 (4.0) respectively (P = 0.77). As MANOVA revealed a significant difference in somatotype between these men (Wilks' lambda = 0.887; F (3, 71) = 3.013; P = 0.036), further examination was undertaken using a univariate F-test to reveal which components where significantly different. These results are presented in table I (5.2) below.

Table I (5.2). Means ± standard deviations of the somatotypes of men with angiographically-documented CAD (n = 27) and healthy, age-matched men (n = 38)

Variable	Mean ± (SD)	F (df)	Significance
Endomorphy			
CAD	6.32 (1.62)	4.456 (1, 73)	0.038
Healthy	5.57 (1.43)		
Mesomorphy			
CAD	5.72 (1.46)	2.079 (1, 73)	0.154
Healthy	5.28 (1.18)		
Ectomorphy			
CAD	0.91 (0.91)	7.851 (1, 73)	0.006
Healthy	1.61 (1.17)		

(df) degrees of freedom

Although the mean somatotypes of these groups of men were similar (both exhibit high ratings for endomorphy and mesomorphy with the ectomorphic

component of only minor importance) there are statistically significant differences for endomorphy and ectomorphy. The CAD patients were significantly greater in endomorphy ($P = 0.038$) and lesser in ectomorphy ($P = 0.006$).

The small but significant differences in endomorphy and ectomorphy in the age-matched samples are also in agreement with the notion that increased fatness and, therefore, weight-for-height are physical characteristics that predispose to CAD.

5.3 SOMATOTYPE AND METABOLIC FITNESS

The results in section 5.1 show that men reporting consecutively for coronary angiography exhibit high ratings, and an almost equal dominance, of endomorphy and mesomorphy. In this investigation, canonical correlation analysis was used to investigate the relationship between somatotype and the results of the angiographic assessment. It was suggested that this multivariate technique allows an important aspect of somatotype data analysis to be upheld; i.e. the somatotype is treated as a gestalt.

The aim of this subsequent investigation was to examine the association between somatotype and fasting concentrations of serum glucose, TC, LDL-C, HDL-C, the HDL:LDL ratio and TG in a group of apparently healthy adult males. These biochemical parameters have been suggested to be important indicators of metabolic fitness (Katzmarzyk *et al.*, 1998). Metabolic fitness, which includes parameters such as blood lipids and lipoproteins, fasting and post-prandial glucose and insulin levels, is a term that was first introduced a short time ago and is an important component of health-related fitness (Bouchard and Shephard, 1994).

Table I (5.3) shows the age, anthropometric characteristics and metabolic profile of the subjects. The mean somatotype rating is defined as an endomorph-mesomorph i.e. endomorphy and mesomorphy are dominant and equal (or do not differ by more than 0.5) and ectomorphy is of minor significance. A breakdown of the somatotypes into defined categories (Carter and Heath, 1990) was as follows: endomorphic-mesomorphs (n = 24); mesomorphic-endomorphs (n = 24); mesomorph-endomorphs (n = 12); central (n = 2); balanced endomorphs (n = 2); mesomorphic-ectomorphs (n = 1); ectomorphic-mesomorphs (n = 1); balanced ectomorphs (n = 1) ectomorphic-endomorphs (n = 1).

Table I (5.3). Descriptive statistics (means ± standard deviations) for age, anthropometric variables and indicators of metabolic fitness (n = 68).

Variable	Mean	SD
Age (years)	43.9	9.1
Body mass (kg)	75.9	9.4
Stature (cm)	174.4	5.6
Endomorphy	5.5	1.4
Mesomorphy	5.3	1.3
Ectomorphy	1.7	1.1
Glucose ($mmol.L^{-1}$)	5.30	0.36
TC ($mmol.L^{-1}$)	4.97	0.93
LDL-C ($mmol.L^{-1}$)	3.09	0.86
HDL-C ($mmol.L^{-1}$)	1.21	0.26
HDL:LDL	2.65	0.95

Table II (5.3) shows the results of the canonical correlation analysis. As correlations of ≤ 0.30 explain less than 10% of the variance between canonical pairs, and statistical significance is largely dependent on sample size, only canonical correlations greater than this level are interpreted (Tabachnick and Fidell, 1989). In this analysis, as only the first canonical correlation was > 0.30 the second and third canonical correlations have been ignored. The first canonical correlation marginally failed to reach significance but suggests that somatotype accounts for 24% of the variation in metabolic fitness ($r_c = 0.496$, $P = 0.06$).

Table II (5.3). Results of canonical correlation analysis showing the relationship between somatotype and metabolic fitness.

First canonical correlation	Squared canonical correlation	Chi-square	Degrees of freedom	Significance
0.495	0.24	24.328	15	0.06

Figure 1 (5.3) presents the loadings or correlations between the original (standardised) variables and their first canonical variate. Again correlations of ≥ 0.30 were interpreted. For the somatotype variate, endomorphy and mesomorphy both load negatively and ectomorphy positively. For the metabolic fitness variate, TC, TG, LDL-C and glucose all load negatively and HDL-C loads positively. The size of the correlation indicates the relative contribution that each variable makes to its respective variate. These loadings suggest that the first somatotype variate is best interpreted as one of high endomorphy, moderate mesomorphy and low ectomorphy. The first metabolic fitness variate is one of moderately high glucose, TC, TG and LDL-C and moderately low HDL-C.

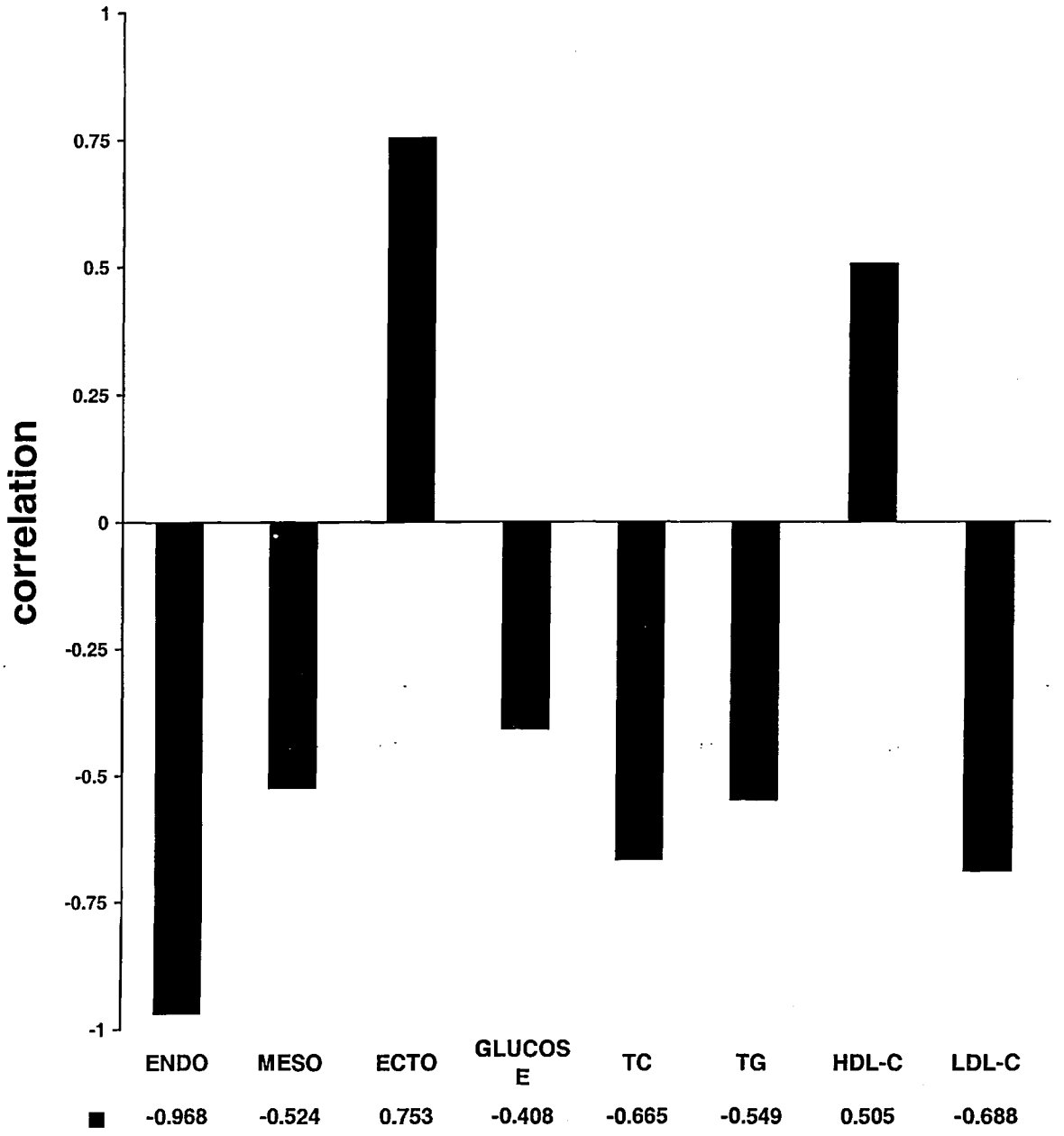

Figure 1 (5.3). Loadings (correlations) between the somatotype components, indicators of metabolic fitness and their respective first canonical variates.

Table III (5.3) shows third-order partial correlations between the individual somatotype components and the indicators of metabolic fitness. Third-order partial correlations were used to adjust for the confounding effect of age and the inter-relationship between the somatotype components. Endomorphy was positively and significantly related to TC (P = 0.09), TG (P = 0.05), LDL-C (P = 0.001) and the

HDL-C:LDL-C ratio (P = 0.001). Mesomorphy was inversely related to HDL-C (P = 0.05) and ectomorphy was positively related to HDL-C (P = 0.02) and inversely related to the HDL-C: LDL-C ratio (P = 0.001).

Table III (5.3). Third-order partial correlations showing the relationship between the individual somatotype components and the indicators of metabolic fitness after adjusting the confounding interrelationship between the somatotype components and age. Significance values are shown in parentheses.

	Somatotype component		
	ENDO	MESO	ECTO
Glucose	0.214 (0.09)	0.138 (0.27)	-0.140 (0.26)
TC	0.317 (0.01)	0.043 (0.74)	-0.187 (0.13)
TG	0.238 (0.05)	0.094 (0.46)	-0.218 (0.08)
HDL-C	-0.222 (0.07)	-0.250 (0.05)	0.273 (0.02)
LDL-C	0.331 (0.001)	0.088 (0.48)	-0.212 (0.09)
HDL-C:LDL-C	0.430 (0.001)	0.241 (0.05)	-0.356 (0.001)

The association between somatotype and disease of metabolic origin has now been examined in several studies. Fredman (1972) studied a relatively small group of Tamil Indians who were diabetic, prediabetic or healthy and, although the data were not subjected to the rigour of statistical analysis, it was suggested that there was no difference in the somatotype of these sub-groups. In a later study, Fredman (1974) indicated that diabetic Tamil Indians were significantly more mesomorphic than controls and that mesomorphy, but not endomorphy or ectomorphy, was positively correlated with fasting glycaemia. Earlier in this thesis, a mean somatotype that was characterised by high ratings of endomorphy and mesomorphy, and a low rating for ectomorphy was reported for men with CAD. This was in agreement with several previous studies that also emphasised the importance of these first two components in describing men with CAD (Spain *et al.*, 1963; Paul *et al.*, 1963; Smit *et al.*, 1979).

With regard to the dominance of endomorphy and mesomorphy in this investigation, the findings are similar to previous quite large studies of Canadian (Bailey *et al.*, 1982) and British men (King, cited in Carter and Heath, 1990). However, there does appear to be a difference in the size of the endomorphic component that was reported to be 4.1 ± 1.2 for the Canadian men and 3.9 ± 1.1 for the British men (means ± SD). Recent data from the Quebec Family Study reported a mean somatotype for men of a comparable age that was approximately equal for mesomorphy and ectomorphy but 1.5 units lower for endomorphy (Malina *et al.*, 1997). As these studies employed the same somatotype method as this study, this difference could be due to either systematic bias in skinfold measurements or it may reflect the recent increased prevalence of obesity that has been well documented (Fehily, 1999). In comparison to the mean somatotype of men with angiographically-

documented CAD in this study, the mean somatotype of this apparently healthy cohort suggests they are a group at high risk of CAD.

The use of canonical correlation analysis in this investigation is because neither physique nor metabolic fitness can be adequately described by a single variable (Katzmarzyk *et al.*, 1998). In this study, the first canonical correlation suggested that approximately 24% of the variance in metabolic fitness could be explained by variation in somatotype. This is similar to a previous investigation of adult males (Gordon *et al.*, 1987) that was conducted using a larger sample. The explained variance seems to be smaller in boys aged from 9- to 18-years, but this study was also based on a larger sample (Katzmarzyk *et al.*, 1998). In a study of 233 males of similar genetic background, somatotype was found to be weakly associated with CAD risk factors that included blood pressure and fasting serum glucose and lipids (Malina *et al.*, 1997). However, at the extremes of the risk factor distributions, there was a clear delineation between somatotypes. Those with an adverse risk factor profile tended to be more endomorphic and mesomorphic and less ectomorphic than those with a better profile who were more ectomorphic.

There are two reasons for exploring the loadings between the variables and their respective canonical variates. Firstly, the significance of the canonical correlation is highly dependent on sample size. Secondly, an examination is necessary to evaluate the biological significance of the correlation. The size and directions of the loadings are in agreement with those previously reported for younger subjects (Katzmarzyk *et al.*, 1998). An interpretation of the loadings is that a somatotype of high endomorphy, moderately high mesomorphy and low ectomorphy is associated with higher fasting serum concentrations of glucose, TC, TG and LDL-C and a low HDL-C level.

Alternatively, a somatotype of high ectomorphy and low endomorphy is associated with a greater HDL-C concentration and lower levels of glucose, TC, TG and LDL-C.

Support for this conclusion can be derived from the third-order partial correlation analysis that was performed in order to examine the influence of each individual component independently of the other two, and age. Analysis of this kind is preferred to simple correlations because of the inter-relationship between the components. Whilst recognising that this destroys the meaning of the somatotype, i.e. it does not treat it as a gestalt, it facilitates the biological interpretation of the data. Significant positive correlations between endomorphy and TC, TG, LDL-C and the HDL-C : LDL-C ratio can be explained by the metabolic disturbances that are associated with obesity (Kissebah and Krakower, 1994). Conversely, relative leanness or linearity is associated with a higher HDL-C and an increase in the ratio of HDL to LDL cholesterol.

In conclusion, this investigation has shown that somatotype and metabolic fitness are not significantly related in a group of men whose mean age was 43.9 ± 9.1 years. However, a somatotype characterised by high endomorphy and low ectomorphy is associated with an adverse metabolic profile which includes high TC, TG, LDL-C, and glucose and a low HDL-C concentration. A moderately high mesomorphy rating also appears to be associated with this adverse metabolic profile, although not to the same extent as endomorphy. A high degree of ectomorphy appears to be protective against CAD and this is partly mediated by a favourable metabolic profile, most noticeably a high HDL-C. These data reaffirm that, as part of a healthy living strategy, men should endeavour not to accumulate excess body fat. Furthermore, individuals who have high ratings in endomorphy should attempt to lose

body fat and, as ectomorphy is defined as a lack of weight-for-height, possibly mass *per se* in order to become more ectomorphic.

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CHAPTER 6

SUMMARY, CONCLUSIONS AND DIRECTIONS FOR FUTURE RESEARCH

6.1 SUMMARY, CONCLUSIONS AND DIRECTIONS FOR FUTURE RESEARCH

This thesis is a compendium of studies that were performed using data that were collected on two separate occasions with a view to studying the association between physique, CAD and CAD risk. On the first occasion, men undergoing investigative coronary angiography for suspected atherosclerosis were measured with a variety of anthropometric procedures. The anthropometric measurements were examined in relation to an angiographic scoring system that is designed to account not only for the extent of coronary stenosis, but also the anatomical distribution of lesions within the coronary arteries. Thus, by considering the portion of the myocardium that is affected by the stenosis, it more precisely measures the severity of coronary atherosclerosis in comparison to methods that ignore which artery, and which part of the vessel, is affected. Furthermore, it treats atherosclerotic severity as a continuous rather than a dichotomous variable. For example, two patients could have a single arterial blockage of equal size. One blockage may be at a distal site in a small arterial branch the other could be at the top of the left main stem. Clearly, the latter of these is of greater clinical significance than the former. The system used in these studies, however, is not able to account for coronary artery plaque dynamics i.e. the stability of an atherosclerotic plaque. As this study and others have now shown that physique is associated with CAD, future studies should focus on the relationship between physique and plaque morphology.

In agreement with previous investigations reviewed in this thesis, the data presented in Chapter 4 suggests that waist and abdominal girths are the simplest anthropometric measurements for identifying people at risk of CAD. However, they are not sensitive enough to distinguish between those with severe and those with less

severe CAD. This is probably due to the complex multi-factorial nature of the disease. An increased visceral AT is thought to present obese subjects with the greatest risk of CVD. Whilst they will be expensive and difficult to perform, a definitive answer to the role of fat distribution in CVD risk will only be found when large prospective studies that measure visceral fat (or predict it very accurately) are completed.

With regard to which indirect predictor of visceral AT is best from a public health perspective, it appears that waist or abdominal girths are equally useful. They are easily measured, well understood by the public and cut-off points for CVD risk are in existence. Whether these cut-off points are valid across all populations irrespective of factors such as age, race and physical level remains to be seen.

One aspect of the relationship between anthropometry and CVD risk that has not received much attention is that of proportionality. Put simply, are waist girth measurements above a recognised level related to CVD in all individuals or is the relationship modified by size? Are the relationships between measures of adiposity and CVD risk factors independent of size? Studies outlined in this thesis suggest that the absolute size of adiposity indices (girths and skinfolds), and the stature-adjusted values are equally related to fasting serum glucose, TG, LDL-C and HDL-C. However, adjusting for body mass significantly reduces the strength of this relationship. The exact meaning of this finding requires further explanation but it appears that adiposity and body mass interact in the relationship with metabolic fitness.

Somatotype and CAD severity are apparently unrelated, although men with CAD have a somatotype that is high in endomorphy, high in mesomorphy and low in ectomorphy. However, the significance of this should not be over-stated as the healthy men exhibited a similar somatotype. Because of the small number of subjects used in

this comparison, further studies are required to clarify the significance of somatotype in CAD. One area that should be given specific attention is the role of a large muscle mass in CVD risk. The role of fibre type has been outlined in Chapter 2 of this thesis, but the significance of muscle mass *per se* has not been examined. The canonical loadings of the somatotype components on the metabolic variables suggests that mesomorphy as well endomorphy is associated with higher fasting serum glucose, TC, TG and LDL-C and a lower HDL-C.

APPENDIX

Papers and Presentations Emanating from this Research

SRP Williams, E Jones, W Bell, B Davies, MW Bourne.
Body habitus and coronary heart disease in men. A review with reference to methods of body habitus assessment.
European Heart Journal 1997. 18: 376-393.

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