THE RELATION BETWEEN OBESITY AND HAEMOSTATIC VARIABLES, STANDARD CARDIOVASCULAR RISK FACTORS AND MORTALITY

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Abstract

Analysis of data from around 3000 participants in the Northwick Park Heart Study, a prospective study of males and females recruited from three occupational groups in North West London, showed that amongst the males obesity was associated with an increased risk of fatal ischaemic heart disease. Overall an increase in obesity, measured as weight/height^2, by 1 kg m^{-2} resulted in a mean increase in the relative risk of fatal IHD of 13%. Insufficient cases for analysis occurred in the females. Obesity was related at entry examination to four cardiovascular risk factors; blood pressure, serum cholesterol, factor VII and plasma fibrinogen in both sexes. The association between cholesterol, factor VII and fibrinogen on the one hand and obesity on the other was stronger amongst the younger than the older males. Changes in weight between entry and follow up examination (on average around 6 years later) were significantly correlated with changes in blood pressure, serum cholesterol and factor VII. The relation between obesity at entry and fatal IHD persisted when the associations between obesity and the measured cardiovascular risk factors were taken into account suggesting that other mechanism(s) were also involved.

The association between the distribution of body fat as measured by the thickness of four skinfolds (forearm, triceps, subscapular and suprailiac) and cardiovascular risk factors was examined. In the case of systolic blood pressure, cholesterol and factor VII in males, both forearm and either suprailiac or subscapular skinfold thickness were independently associated. In the case of females these three variables were independently associated only with centrally located fat (either suprailiac or subscapular skinfold thickness). Plasma fibrinogen was associated particularly with centrally located fat in both sexes.

The relation between obesity and haemostatic variables, standard cardiovascular risk factors and mortality

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Chapter 1

Introduction

The ability to store energy in the form of fat has been of major importance in evolution. It has allowed greater mobility and independence from a constant food supply than other forms of stored energy. For instance if energy was stored as glycogen instead of fat a 180 lb man with 30 lb of fat would weigh 900 lbs! (Powers 1980). In times of inadequate food supply the ability to store large reserves of fat must have been of considerable survival value but in developed countries at the present time this capacity may become a liability. No specific 'cause' has has been found for the majority of cases of obesity. Specific endocrinological or metabolic lesions only account for a small proportion. There appear to be familial factors involved which may be both environmental and genetic. There may be family patterns of relative overfeeding or sedentary life style, but in addition studies on identical twins reared apart show that there is a closer relationship between their weights than non identical twins reared in the same house (Sheilds 1962).

There has been controversy over the contribution of obesity to premature mortality, particularly from ischaemic heart disease (IHD). The results of the Framingham study suggested that a 20% reduction in weight might result in a 40% reduction in the chances of

coronary heart disease (Kannel and Gordon 1974). On the other hand Keys et al (1972a) found that obesity was unrelated to the incidence of definite cardiovascular disease in men from seven countries except amongst Northern European men. Although there has been a great deal of published data about the association between blood pressure and cholesterol and obesity little is known about the relation of obesity to haemostatic variables, particularly factors VII and VIII and fibrinogen, which have recently been found to be independent risk factors for cardiovascular death in a prospective study (Meade et al 1980). There have recently been suggestions that centrally located body fat may be particularly important in determining blood pressure (Blair et al 1984) but little is known about the role of the distribution of body fat in determining other cardiovascular risk factors. This thesis, which is based on data from the Northwick Park Heart Study (NPHS) with which the author has been involved for 8 years, addresses these three areas. Additionally, many previous studies which have examined the association between cardiovascular risk factors and obesity have focussed solely on cross-sectional data. This thesis includes both cross-sectional and longitudinal data from individuals measured on average 6 years apart.

The measurement of obesity

Overweight is not necessarily synonymous with obesity which indicates excessive fat deposition. For instance, in a study of professional football players it was shown that these men, although overweight compared with ideal weight tables derived from Life Insurance data, also had a greater than average specific gravity indicating a lower than average fat content (Walham and Bahnke 1942).

There are several laboratory methods for determining body fat. The three best established indirect methods are measurements of total body water, body density and total body potassium. These methods are based on the principle that fat contains no water or potassium and is less dense than the fat free mass. Total body water can be calculated by a dilutional technique using tritiated water (Pace et al. 1945). Total body potassium can be measured using a whole body counter which measures radio-activity due to the presence of the naturally occurring isotope K^{40} (Womersley et al. 1972). Density is usually measured by underwater weighing using Archimedes' principle. A comparison of all three techniques (Krywieki et al. 1974) showed a correlation of 0.8 between body fat determined by total body potassium and densitometry in 323 soldiers. They considered that all three methods

were equally reliable. These methods may not be entirely valid however at the extremes of age or in the chronically sick. None of these methods are suitable for large scale epidemiological studies and other less direct methods are therefore used.

A variety of different measurements have been used to quantify obesity in population studies. There are two main requirements for any valid measure of obesity, firstly it should be independent of height, secondly it should correlate well with one of the accepted laboratory measurements of obesity. As well as being a valid indicator of obesity it should be able to be measured reproducibly by different observers.

Two types of weight index are used for assessing fatness. Relative weight is the weight expressed as a percentage of the weight of an 'ideal' person of the same sex, height and perhaps frame size. The values for ideal weight are generally derived from data collected during the examination of applicants for life insurance policies. The ideal weight is determined by the life expectancy of policyholders.

Tables of desirable weight for men and women based on the mortality experience from U.S. Life Insurance Data have been published (Metropolitan Life Insurance

Company 1959). These tables give desirable weights for three frame sizes, small, medium and large. However in view of the lack of agreement about the classification of frame size, the Fogarty Conference in 1973 recommended that the upper limit of desirable weight for the large frame size be used in expressing results (Bray 1973). There are obviously considerable advantages in having a uniform system for expressing obesity which allows comparison between populations.

The other type of weight index is derived by attempting to take height into account by means of expressions such as W/H, W/H^2, W^3/H, $W^{0.33}/H$. The term $W^{0.33}/H$, and its inverse ($H/W^{0.33}$) which was introduced by Sheldon and colleagues in studies of somatotypes (Sheldon, Stephens & Tucker 1940) have been found to be highly correlated with height and therefore are no longer considered a valid index of obesity.

The index which comes closest to being independent of height is W/H^2 (Florey 1970) which was originally described by Quetelet and is sometimes known as Quetelet's Index or Body Mass Index. Whilst W/H^2 does not reflect body fat with absolute accuracy it has been shown that there is a strong correlation between W/H^2 and body density. The correlation coefficient was 0.67 for a group of U.S. business executives and 0.85 for a

group of male students (Keys et al 1972b). Nevertheless no more than half the total variance of body fatness was accounted for by the regression of body density on W/H^2. The agreement may be closer in females; (Webster, Kesp and Garrow 1984) have found a correlation of over 0.9 between three measurements of body fat and W/H^2 in a group of obese females. W/H^2 has the advantage that it does not require a reference standard and does not require any assumptions about what constitutes normal or excessive weight. It may not be applicable for children and adolescents unless different standard values of p are used in the expression W/H^p.

The measurement of skinfold thickness can also be used in the assessment of obesity. Its use depends upon the assumption that subcutaneous fat constitutes a predictable proportion of total body fat. The correlation coefficient between skinfold thickness and body density has generally been found to be between 0.7 - 0.9 (Durnin and Womersley 1974, Keep et al. 1972, Damon and Goldman 1964). The relation is not linear in either sex, in more obese subjects relatively large increments in total skinfold thickness are associated with only small changes in body density. The use of a logarithmic transformation of total skinfold values however results in a linear relation with body density. The relationship between skinfold thickness and body fat

varies with age and sex. Women appear to have a more even subcutaneous distribution of body fat than men and also appear to have a larger proportion of internal body fat than men. The equivalent fat content, as a percentage of body weight, for a given value of the sum of four skinfolds (triceps, subscapular, suprailiac and forearm) tends to be higher in older than in younger individuals. It may be that a higher proportion of body fat it deposited internally with increasing age.

Definition of obesity in epidemiological studies

The limits of 'normality' in studies of obesity have been defined in several ways. The limits should ideally be based upon a precise knowledge of the relation between obesity and morbidity and mortality since it is this relationship which constitutes the most powerful argument for defining 'normality'.

At present the definiton of overweight in adults is based on actuarial data that indicate the weight range for each height category that appears to correspond with the lowest mortality rate in an insured population. This range is taken as the optimal and those who exceed the upper limit are 'overweight'. Some workers have defined overweight as 110-119% of these standards and obesity as 120% or more. The standards themselves are derived from Metropolitan Life Insurance Company data

(1959 and 1960) and based on the Build and Blood Pressure study (Society of Actuaries 1959). Despite the recommendations of the Fogarty Conference mentioned earlier many studies continue to express results in terms of frame sizes and a second report by an expert group in the USA (Bray 1979) referred to an acceptable weight range which took into account all three frame sizes. The acceptable average value for W/H^2 for males was 22.0 and the range 20.1 - 25.0. Obesity was defined as a W/H^2 of 30.0 or over (120% of the upper limit of the acceptable range). For females the corresponding values were 20.8, 18.7 - 23.8 and 28.6.

Since many studies indicate that there is a rise in obesity with age there is a question as to whether this should be allowed for in calculating acceptable weights. Studies do indicate that obesity may be particularly deleterious at younger ages (for discussion see later) and there is still uncertainty over whether the standards used are applicable at all ages. There is however evidence that weight gain in adult life may be disadvantageous and at the present time the weight standards are used for adults of all ages.

Height, weight and obesity in the UK population

There have been several studies of obesity in the UK. In 1943 a large study of 27,500 males and 33,500 females was undertaken (Kemsley 1950). The population studied consisted of industrial workers in large and small firms (both male and female), miners (male) and housewives. The results of this survey, which was undertaken during wartime are unlikely to be representative of the population at the present time. Weight for height standards derived from this population were published some time after the original publication (Kemsley et al. 1962). The low and high weight for each height category given in this paper represented the lower and upper 25 per cent of the weight distribution. Data on the heights and weights of men in two industrial populations (one in Birmingham measured in 1960 and one in Port Talbot, South Wales measured in 1965) showed that, compared with national samples in 1930 and 1943, there appeared to have been secular increase of about 1 inch in height per generation (25 years) since 1850 and that the increase was still continuing. Weight seemed to be increasing at a greater rate than height so that the adult male population was becoming progressively more obese (Khosla and Lowe 1968). Young and middle aged men were about 15 lbs heavier than men of the same age and height thirty years before. Obesity appeared to increase up to age 35 and flatten off. A study of

10,300 employees of British Petroleum Company Limited (7,400 males and 2,900 females) serving in the London office and overseas between 1964 and 1966 also showed that the participants were taller and heavier than those in earlier studies. (Montegriffo 1968). This study also indicated that 48% of males and 46% of females were above the desirable weight as given by mortality statistics of the Metropolitan Life Insurance Company (1960) for U.S. Life Insurance policy holders.

A study of obesity in the London Borough of Richmond showed that 37% of males and females were greater than 10% above desirable weight using the medium frame of the Metropolitan Life tables (McLean Baird et al. 1974). Although the participants were recruited by random sampling of general practitioners' lists the response rate was only 36% of those requested to attend for measurement and weighing. A random sample of non respondents was visited at home and somewhat fewer of them were found to be obese compared with respondents.

Obesity and cardiovascular disease

It has been suggested for many years that obesity predisposes to death from cardiovascular disease. Two main sources of data have been used to examine the relationship between obesity and mortality. Firstly, life insurance companies have, since 1897, constructed

tables relating obesity to mortality. Information from this source is available for very large numbers of insured lives but despite this life insurance policy holders are not representative of the general population because those insured tend to be male and middle class and individuals with pre-existing hypertension, diabetes, ischaemic heart disease etc. may have difficulty in obtaining cover. The second major source of information on obesity and mortality has been from epidemiological studies of a variety of populations particularly in North America and Europe. These studies have resulted in data on smaller numbers of individuals than that available from life insurance policyholders but the participants were, by and large, unselected at least as regards their history of vascular disease and associated conditions.

The Build and Blood Pressure Study (Seltzer 1966) was based on the experience of over 4 million insured lives between 1935 and 1954 and included males between 20 and 59 years of age. Obesity was expressed in terms of $H/\sqrt[3]{w}$, using inches and pounds respectively, (although this has now been shown to be markedly dependent on height). An exponential curvilinear rise in mortality was noted below a value of 12, i.e. with increasing obesity. A review of the experience of both British and American life insurance companies (Donald

1973) concluded that at all ages overweight was associated with increased mortality and that the level of excess mortality varied more or less in proportion to the degree of obesity. In addition it was found that among the obese with no other recorded impairment deaths from cardiovascular and renal disease were 50% more than those expected; coronary artery disease mortality showed an excess of 40% and the mortality rate due to diabetes was four times normal. The mortality of hypertensives who were also obese and of those with a family history of cardiovasular disease who are overweight was significantly higher than those of normal weight with similar risk factors. The excess mortality of obese policyholders increases during the 20 year period after the issue of the policy. It then tends to level off but excess risks can still be demonstrated for at least 30 years after the issue of the policy.

Although the relative excess risk appears to occur in all age groups in life insurance data it seems to be higher in younger age groups (Blair and Haines 1966, Society of Actuaries 1979).

In 1959 the American Cancer Society conducted a study of 750,000 men and women who were recruited by 68,000 volunteer workers and followed up until 1972 (Lew and Garfinkel 1979). Over 90% of those originally

interviewed were successfully traced at the end of this period. Unfortunately however the study used self reported height and weight. The lowest mortality was found amongst those whose weight was 80-109% of the average for their age and sex. Mortality among men and women 30-40% heavier than average weight was nearly 50% higher than those of average weight. Among those more than 40% above average weight mortality was 90% higher than those of average weight. Coronary heart disease was the major cause of excess mortality in the obese. Cancer mortality was only elevated amongst those who were 40% or more above average weight.

Some smaller studies based mainly on populations examined for cardiovascular risk factors and followed prospectively have shown a U or J shaped relationship of obesity with total mortality which has tended to be higher than that in studies of insured lives. For instance the Chicago Peoples Gas Company Study of 1233 males aged between 40-59 found that the lowest mortality occurred in those who were around average weight for the population which was 25-32% above their desirable body weight (Dyer et al. 1975). The Framingham study found a similar relationship between obesity and mortality among both males and females (Sorlie et al. 1980). There was a significant univariate relationship with CHD incidence amongst females only.

The Pooling Project Research Group report (1978) which examined data from the following studies, Albany, Chicago Gas Company, Chicago Western Electric, Framingham and Tecumseh and included over 8000 males aged between 40-64, found a moderate gradient of relative weight on CHD incidence only for men age 40-49 with no significant relationship for older men (Pooling Project 1978).

The Health Insurance Plan Study included 110,000 males and females aged between 35-64 and found a significant association between relative weight and non fatal MI in males only and angina (in both males and females). Weight increase in adult life appeared to be a more sensitive indicator of risk in males (Shapiro et al. 1969). The Japan and Hawaii heart study of males between 45 and 68 found a significant relationship between 'definite' CHD (fatal and non fatal combined) and both relative weight and skinfold thickness considered separately, (Robertson et al. 1977). Paffenbarger et al. (1970) in their study of over 3,000 U.S. longshoremen aged 35-64 found that there was an increase in death rate due to CHD in those men who were above mean weight for height. A study of 1,500 Swedish women aged 38-60 in Gothenburg (Noppa et al. 1980) showed that there was an increased incidence of angina and fatal MI in the fattest quintile but overall there

was a negative relationship between total mortality and skinfold thickness. Pelkonen et al. (1977) in a prospective study of 1648 middle aged Finnish men showed that obesity was only associated with an increased risk of cardiovascular death when combined with raised serum lipids. Cochrane et al. (1980) found a significant relationship between W/H^2 and CHD mortality in a prospective study of a small group of women (n = 253) aged 55-64 in South Wales. A study of 4,000 males in Manitoba, Canada found a relationship between CHD incidence (particularly sudden death) and W/H^2 only in young men under aged 40. The relationship only appeared after prolonged (more than 20 years) follow up (Rabkin et al. 1977).

Other studies have found no statistically significant relationship between obesity and CHD. An early report from the Whitehall Civil Servants study of 18,000 males age 40-64, for instance, found no relationship with CVD mortality or angina (Reid et al. 1976). Studies in Oslo (Westlund et al. 1972), Evans County, Georgia (Heyden et al. 1971), the Western Collaborative study (Rosenman et al. 1976) as well as the International Co-operative study of Cardiovascular Epidemiology, which included men from Northern and South Europe and the USA, likewise all found no significant relationship overall with definite CHD. In the latter

study there was however a statistically significant association between obesity and definite CHD in Northern European men. (Keys et al. 1972). A recent report from the Honolulu Heart study (Rhoads and Kagan 1983) throws light on the apparent discrepancies between the results of various studies on the relation between obesity and CHD and between obesity and total mortality. The authors found that the excess deaths in the top quintile of W/H^2 were due primarily to CHD which was directly and positively related to W/H^2. In the bottom two quintiles excess mortality was due to cancer and "other" causes and was confined to men who had lost weight between aged 25 and examination. This suggested that excess mortality in thin middle aged men was due to occult disease rather than to any adverse affect of leaness. When W/H^2 at age 25 was considered the men in the bottom quintile had the lowest mortality in middle age.

Recently, a further report from the Whitehall Study showed that for 10 year mortality there was an association between cardiovascular (and total) mortality and obesity in younger males (aged 40-49) (Jarrett, Shipley and Rose 1982). The apparent relationship of mortality to obesity may therefore depend on the age of the population and the length of follow-up, the adverse effects of obesity may only become manifest after considerable periods. In addition some studies have not

taken into account the confounding effects of cigarette smoking which is associated in many studies with a lower body weight but also increases cardiovascular risk (for discussion see later).

There is comparatively little information on the effect of voluntary weight loss on the risks of obesity. No randomised trials of weight reduction involving large numbers with long-term follow up have been undertaken. There is some evidence from a study of the mortality experience of 2300 people who were first charged additional premiums for obesity and who were later insured at the normal rate because they had reduced to normal weight range (Dublin 1953). It appeared that the expected excess mortality based on their original weight was reversible by weight reduction.

Obesity and cardiovascular risk factors

Hypertension

Reports on the relationship between body weight and hypertension go back over half a century (Terry 1923). In a study of the whole adult population of Bergen, Norway, the correlation between blood presure and weight was low and persons with very high blood pressure were only slightly heavier than average (Boe et al. 1957). Systolic pressure increased by about 3mm and diastolic pressure by about 2 mm for every 10 kg increase in body

weight. A similar relationship was found in the Framingham study (Kannel and Gordon 1974).

It seems unlikely that differences in obesity explain much of the international differences in the incidence of hypertension. In the Seven Country study for instance there were large international differences in body fatness and relative weight but these did not explain the observed differences in blood pressure. Thus thin Finns had higher blood pressures than fat Americans and fat Mediterranean Europeans had even lower blood pressures (Keys 1970).

It has been known for many years that if the bladder in the blood pressure cuff is too small to encircle 75% of the arm circumference a spuriously high measurement of blood pressure is likely to be obtained (Kirkendall et al. 1980). The standard size bladder in blood pressure cuffs in the UK is only 23 cm, this is insufficent for many arms. Obesity does however appear to have a true effect on blood pressure even when cuff size and arm circumference are taken into account (Khosla and Lowe 1965). Blood pressure appears to be more closely correlated with body weight than with body fat (Whyte 1959 and Kannel et al. 1967). More recently however in a study in Goteborg, Sweden, it has been found that fat free mass was not related to blood

pressure but that about 10% of the variance in blood pressure was explained by the relationship with body fat (Larsson 1978).

In the Framingham study there was a consistent relationship between weight changes over time and changes in blood pressure for both males and females (Ashley and Kannel 1974). The initial relative weight seemed to have no significant effect on the magnitude of the changes involved. Amongst males about 5% of the variance of the change in systolic blood pressure over time was explained by changes in relative weight, the percentage was somewhat lower, about 3%, in females.

Several other studies have shown that overweight in young adult life increases the risk of hypertension later (Miall et al. 1968, Paffenbarger et al. 1968). Weight reduction in intervention studies has also been shown to be associated with a fall in blood pressure as long ago as 1922 (Rose 1922).

The response of blood pressure to weight reduction is however quite variable. Some subjects appear to show no fall and others a dramatic reduction of blood pressure. The mean reduction of blood pressure in different studies range from a reduction of 26 mm Hg in systolic pressure for a 12 lbs weight reduction

(Terry 1923), to a 7 mm Hg reduction in mean systolic blood pressure for a 10 lbs mean weight reduction (Fletcher 1954, Adlersberg et al. 1954) and a mean reduction of 3.5 mm Hg for a 10 lbs mean weight loss (Martin 1953). Some of these discrepencies may be due to a failure to take into account the fall in blood pressure which occurs with repeated measurements.

A randomised trial of weight reduction in 127 hypertensives with a mean blood pressure of 167/102 from a screened community showed that at one year follow up there was an average decline of 18 mm Hg systolic pressure in the treatment group and 12 mm Hg in the control group (a statistically significant difference). The mean weight loss was 18 lbs and 4 lbs respectively (Tyroler et al. 1975) This study suggests a modest effect of weight loss on blood pressure but the interpretation is complicated by the inclusion of salt restriction in the weight reduction regime.

In a Chicago coronary prevention evaluation programme 67 males who were 15% or more overweight were studied for 5 years. Moderate weight loss (5-6% of body weight) appeared to influence blood pressure more or less uniformly independently of initial weight (Stamler et al. 1980). The possible relation of changes of salt intake to blood pressure changes in patients undertaking

weight reduction was investigated by Reisen et al. (1981). They showed that a mean reduction of 9.5 kg was associated with a fall in blood pressure of 18 mm Hg systolic and 20 mm Hg diastolic in the presence of an unchanged salt intake. A randomly selected control group showed no change in weight or blood pressure. The magnitude of blood pressure reduction was correlated with the reduction in weight. Unfortunately the investigators used a blood pressure cuff with a bladder of only 22 cm in length with may have lead to spuriously high blood pressure in the obese and therefore possibly an exaggerated fall in blood pressure on weight reduction. However it seems likely that this methodological deficiency could only account for a part of the observed fall (King 1967) and the study is evidence for the role of weight reduction in lowering blood pressure.

The mechanism of the association between obesity and hypertension has been extensively investigated (Messerli 1982). Obesity increases metabolic demand and hence total body oxygen consumption. As a consequence cardiac output and stroke volume increase to meet the metabolic requirements, intravascular volume expands and peripheral resistance falls. Because of the increased stroke volume left ventricular end diastolic volume and filling pressure increase in parallel (Kaltman and

Golding 1976). Adipose tissue appears to be relatively underperfused compared with lean tissue, for instance as total body fat increases the ratio of intravascular volume to body weight falls to approximately 45 ml/kg compared with 95-100 ml/kg in underweight persons. (Feldschuh and Enson 1977). Cardiac output appears to be elevated disproportionately to the amount required for adipose tissue perfusion. No single factor has been identified as directly linking hypertension and obesity.

Obesity in relation to serum lipids

Several studies have shown a weak relationship between serum cholesterol and obesity (Kahn et al 1969, Garcia Palmieri et al. 1972, Keys and Fidanza 1960 and Shapiro et al. 1969). The relationship between serum triglycerides is considerably stronger and more consistent (Carlsson and Lindstedt 1968, Albrink, Meigs and Granoff 1962). In the Goteborg study no relationship was found between serum cholesterol and body weight, body fat, fat cell size or number in men aged 50 and 60. In contrast there was a correlation between serum triglycerides and body weight ($r = 0.3$), body fat ($r = 0.3$) mean fat cell weight ($r = 0.3$). There was a relationship between serum triglycerides and both waist circumference and subscapular skinfold but not triceps skinfold suggesting a closer relationship with central than peripheral adiposity. Change in

weight between the age of 50 to 60 but not initial weight was significantly associated with change in serum triglycerides but not cholesterol (Carlsson 1978).

In the Framingham study however there was a weak positive correlation between change in relative weight over time and serum cholesterol. Changes in relative weight accounted for about 4% of the variance in cholesterol over time in males and 2% in females (Ashley & Kannel 1974). In a study of 5,800 rural and urban subjects in Puerto Rico correlation coefficients between relative weight and serum cholesterol of 0.22 for rural and 0.13 for urban participants were found (Garcia Palmieri et al., 1972). A survey of 10,000 Israeli men found a correlation coefficient of 0.15 for serum cholesterol and weight/height^2 (Goldbourt & Medalie 1974).

Studies of the effect of weight reduction have shown a reduction in serum cholesterol which is not consistent in all individuals (Berkowitz 1964) but in some cases is quite marked, for instance a small study of six obese adults with a mean weight loss of 24 lbs showed a mean decrease in serum cholesterol of 54 mg/100ml (Galbraith et al. 1964). A study of four medical students who gained and then lost weight over a short period of time (Mann et al. 1955) showed that a

mean weight gain of 18 lb was associated with a mean increase in serum cholesterol of 57 mg/100 ml and a mean decrease of 14 lb with a fall in serum cholesterol of 43 mg/100 ml. A group of 78 factory workers who had gained 4.5 kg or less since age 25 had a considerably lower mean serum cholesterol than a group of 137 who had gained more than 4.5 kg. The mean levels of serum cholesterol were 218 and 240 mg/100 ml respectively (Albrink, Meigs and Granoff 1962).

Changes in relative weight over time seem to exert a more potent effect on both blood pressure and cholesterol than the general level of adiposity. Whilst only a small percentage of the variation in these variables is 'explained' by changes in relative weight the effect is nevertheless substantial and clinically relevant. For instance a change in relative weight from 120% to 80% in males aged 35-44 would result in a change in relative odds of CHD from 1.86 to 0.57 using the multiple logistic model (Ashley and Kannel 1974). In men, following a 10% reduction in relative weight a fall of 20% in coronary incidence would be anticipated. The effect is slightly less pronounced in older than in younger persons and in females than males.

The Framingham Offspring Study investigated the relationship between lipoproteins and obesity in over

4000 young adults of both sexes (Garrison et al. 1980). The strongest association between obesity and LDL cholesterol was found in males aged 20-29 and the weakest in 40-49 year old males. In contrast, in women, the relationship appeared stronger in the older (40-49) age group. The paucity of lean males in the 40-49 age group may have been responsible for the apparently weaker association in this group. An inverse relationship between high density lipoprotein (HDL) cholesterol and obesity was of similar strength in all age groups in both sexes. There were substantial differences in the ratio of total cholesterol to HDL cholesterol in lean and obese young males.

The Honolulu Heart Study found a strong inverse association between HDL cholesterol and skinfolds and a positive correlation between LDL and skinfolds in men aged 50-72 (Rhoads et al. 1976).

Cigarette smoking

The relationship between weight and CHD is partly confounded by the fact that cigarette smokers tend to be lighter than non smokers (Larsson 1978, Hjerman et al. 1976, Gordon et al. 1975). There is a tendency for a curvilinear relationship between smoking and weight, with moderate smokers being lightest and non smokers and heavy smokers being somewhat heavier. Individuals who

stop smoking tend to gain more weight than non smokers and persistent smokers. In a longitudinal study in Goteborg, Sweden, for instance men who stopped smoking in a ten year period gained an average of 3.5 kg in weight compared with 1.4 kg for non smokers (Larsson 1978).

Haemostatic variables

Studies of the aetiology of ischaemic heart disease have focussed primarily on the role of smoking, hypertension and lipids. However, recently there has been greater attention given to the importance of factors predisposing to thrombosis, in particular to the importance of coagulation factors and other elements of the haemostatic system.

It has recently been shown in a prospective study that factors VII and VIII and fibrinogen are higher in those who die of CHD than those who do not (Meade et al. 1980). The association with cardiac death appears to be independent of the relation between serum cholesterol and fatal CHD and, in the case of factor VII and fibrinogen, of similar or greater magnitude. The general epidemiology of factors VII and VIII and fibrinogen is, with few exceptions, consistent with the hypothesis that they are causally related to cardiovascular death. Increasing age, diabetes and its

complications, smoking and oral contraceptive use all appear to increase the levels of one or more of these three clotting factors (Chakrabarti et al. 1975, Fuller et al. 1979, Meade et al. 1979, Meade et al. 1977). Moderate alcohol consumption, black ethnic group and vegetarianism are all associated with a reduced risk of CHD and decreased levels of factor VII or fibrinogen (Kozararevic et al. 1980, Meade et al. 1978, Phillips et al. 1978, Haines et al. 1980).

Although there have been some preliminary reports of the association between obesity and factor VII (Haines et al 1980) and fibrinogen (Meade et al 1979) no detailed analysis of the relation between obesity and haemostatic variables appears to have been undertaken.

Distribution of body fat and cardiovascular risk factors

It has been shown that fat laid down in adult life tends to accumulate on the trunk rather than the periphery (Vague 1956, Ashwell et al 1978). Adult onset obesity, unless severe, tends to be associated with fat cell hypertrophy rather than hyperplasia (Hirsch and Batchelor 1976). Several studies show that centralised rather than a generalised pattern of subcutaneous fat deposition is associated with disorders of lipid and carbohydrate metabolism (Vague 1956, Kissebah et al 1982). An analysis of the Framingham data by

Damon et al (1969) suggested that mean subscapular skinfold thickness was higher in males with evidence of coronary heart disease unassociated with myocardial infarction and that mean triceps skinfold was lower. Recently it has been shown that, using data from the First U.S. Health and Nutrition Examination Survey (HANES) on adults between ages 30-59, subscapular skinfold was a better predictor of blood pressure than triceps skinfold. The observation was consistent in males and females and in both blacks and whites throughout all age groups (Blair et al 1984).

Obesity as an independent risk factor

Most studies of cardiovascular disease and obesity have concluded that the risks of obesity are mediated through the effects of obesity in raising cardiovascular risk factors. However a few studies, particularly those involving relatively long term follow up, have suggested a deleterious effect of obesity independently of its effect on the risk factor profile (Hubert et al 1983, Rabkin et al 1977, Robertson et al 1977).

Conclusion

There are several areas of uncertainty regarding the relation of obesity with cardiovascular disease to which this thesis addresses itself. In particular it examines the association between obesity and haemostatic

variables as well as with 'standard' cardiovascular risk factors. The issue of whether the association between obesity and cardiovascular mortality is solely related to its effect on cardiovascular risk factors is examined. The relevance of the distribution of body fat in determining cardiovascular risk factors has also been investigated. Most other studies have used skinfold thickness at only two sites, usually triceps and subscapular, to measure fat distribution. NPHS has the advantage that four sites of measurement were used. Finally, the Northwick Park Heart Study permits examination of relationships between obesity and both cardiovascular risk factors and other variables likely to be of importance in influencing obesity such as age, smoking and menopause, in both cross-sectional and longitudinal data.

Chapter 2

The Northwick Park Heart Study (NPHS)

Description of NPHS - Methods and design

The main purpose of NPHS study is to determine the relationship between haemostatic variables and the development of clinical IHD. Those who enter the study are followed up and participants who develop IHD are compared with those who do not in terms of values for haemostatic and other variables in blood taken at recruitment. In addition the participants are currently in the process of re-examination which is on average about 6 years after their initial examination.

Most of the participants in the study were recruited from the headquarters and main London production site of a food-processing company. All those who had worked for the company for at least 12 months were asked to take part in the study. The employees of the food processing company were not considered eligble for the study unless and until they had been with the company for at least a year. This decision was taken because of the very high turnover among those with the company for only a short time. Those who had been at the company for at least a year, or whose time with the

company rose above the one year cut-off during the course of the study, were considered eligible for NPHS provided they were on the day shift (men and women) or on the night shift (men only). However, it proved very difficult accurately to determine the numbers in these categories. There were always quite a large number of people, particularly men, who were transferring - often for very short periods, before they transferred back - from one category to another. This involved transfer not only between the day and night shifts but also between these two shifts and other "split" shifts where the hours involved made it impossible for those concerned to attend for recruitment into NPHS. This difficulty will not have affected the response rate calculations very much but the figures for the men, particularly the day men, should be regarded as being accurate to within about 2 or 3% rather than as very precise estimates. With these provisos in mind, response rates were:

day men	75%
night men	91%
women	80%

The largest group was the day men and, taking this into account, the overall response rate was 78%.

Recruitment at the food processing company took place between 1972 and 1976 and during the earlier part of this period, many industrial groups seemed ready to let their work force take part in studies like NPHS in the company's time. Towards the end of that period, however, the increasingly difficult financial circumstances facing industry altered the willingness of companies to help with medical research. For a while, it looked as though no further groups within reasonable reach of Northwick Park Hospital could be recruited and it was only just before recruitment at the food processsing company finally ended that agreement was secured with the office staff of the London Boroughs of Harrow and Brent to participation in NPHS. In order to ensure a continuous supply of entrants to the study, recruitment in these London Borough groups and, subsequently, in the employees of British Telecom was based on a call for volunteers (strengthened by periodic reminders and further calls) rather than on the random selection from a previously established nominal roll that had been the basis for recruitment at the food processing company. No formal estimates of response was made among the Harrow, Brent or British Telecom groups. Continuing recruitment without a break was considered more important than the advantages of accurate response rate estimates, together with random selection from a nominal roll, as the latter would have entailed halting

the recruitment process for some weeks and possibly months. However, informal estimates (confirmed by the impressions of the staff member in each of the three groups responsible for liaison with NPHS) suggest that the response rate in these other groups was about the same as at the food processing company.

Ages at recruitment range from 18-64 for males and 18-59 for females. Recruitment commenced in 1972 and was completed by 1978. Re-examination was started in 1979 and will continue until the autumn of 1985. The majority (2962) of participants are white and all results shown are for whites only. Day workers were seen at between 0830 and 1100 hours and night workers (food processing factory only) between 0700 and 0830 hours. The numbers in the different occupational groups are as follows

	Food Processing company					
	Harlesden	Hayes	Harrow	Brent	Post Office	Total
M	857	330	170	229	533	2119
F	215	249	116	178	85	843
	1072	579	286	407	618	

Participants were interviewed in a standard fashion by trained nursing sisters. Information was collected on smoking and drinking habits, medication, social class (Registrar General's classification), menopausal status and oral contraception (for females). In addition all participants were interviewed by a doctor to determine whether there was any history of clinical IHD, claudication or hypertension. A standardised physical examination was performed on all participants at recruitment and follow up. The following measurements were recorded:

Height (metres)

Weight (kg)

Peak expiratory flow rate

Blood pressure

Pulse rate

Skinfold thickness at the following sites -

- Triceps
- Forearm
- Suprailiac
- Subscapular

Peripheral arterial pulses

Standard 12 lead electrocardiogram (ECG)

Methods of measurement

Height and weight were measured using a Steven's beam balance with a height attachment. The participants were in underclothing only.

Blood pressure was measured before and after venepuncture and the mean of two readings used in statistical analyses. In the initial examination a standard sphygmomanometer was used with a 12 x 23 cm bladder. At the follow up examination a random zero sphygmomanometer was used with two cuff sizes, one for normal (12 x 23 cm bladder) and one for obese arms (15 x 33 cm bladder). The arm circumference was measured 10cm above the medial epicondyle of the humerus. In the event of the arm circumference being 30 cm or above the larger cuff was used. The blood pressure was always measured in the left arm with the participant lying on a couch. Peak expiratory flow rate was recorded as the best of three attempts using a Wright peak flow meter.

Skinfold thickness was measured to the nearest 0.2 mm using Holtain skinfold calipers. The measurements were made on the right side of the body with the participant standing. The triceps skinfold was measured halfway between the inferior border of the coracoid process and the tip of the olecranon process. The forearm skinfold was picked up on the lateral aspect of

the forearm at the mid-point of the radius. The subscapular skinfold was measured at an angle of 45^{o}' to the vertical parallel to the medial edge of the scapula and just below it. The suprailiac skinfold was just above the iliac crest in the mid axillary line. In each case the skinfold was picked up between thumb and forefinger and the caliper jaws applied. The reading was taken as soon as the needle on the gauge appeared stable.

Laboratory measurements

Blood samples were taken following a normal breakfast during the recruitment examination, at follow up participants were asked to have a fat free breakfast (except the night shift workers) and given written instructions. At the recruitment examination blood was taken before and after a standard period of exercise which consisted of stepping on and off a chair 20 times (except in those with ECG evidence of IHD). Fibrinolytic activity and factor $VIII_C$ were measured on the pre and post exercise sample, the other variables were measured on the pre-exercise sample only.

A range of haemostatic variables have been assayed:

Factor V: automated one-stage biological assay (Brozovic et al. 1976)

Factor VII_C: automated one-stage biological assay (Brozovic et al. 1974)

Factor $VIII_C$: semi-automated two-stage biological assay (Stirling et al 1978). Results for the three clotting factors are expressed as % of standard. Six different standards were used during the recruitment period and a further five standards have been used in the follow up. Conversion values were derived to allow results obtained against each successive standard to be expressed in terms of the first standard.

Fibrinogen (clottable): gravimetric method (Fearnley and Chakrabarti, 1966)

Fibrinolytic activity: whole blood dilute clot lysis time method (Fearnley and Chakrabarti 1962). Results are expressed as 100 x the reciprocal of the clot lysis time in hours. Clots are reviewed either by eye or photographically. Those which

are not lysed at 24 hours are all assigned this lysis time, this gives a fibrinolytic activity of 4.2 (100/24).

Antithrombin III: a) biological assay method (Hensen and Loeliger (1963)
b) immunological assay by immuno electrophoresis (Laurell 1972)

In addition platelet count (Coulter Thrombocounter) and platelet adhesiveness to glass beads (at recruitment only) were routinely carried out.

Serum cholesterol was also measured by the method of Van der Honing et al. (1968) until 1976 when it was replaced by the enzymatic method of Richmond (1973) using the chromogenic technique described by Trinder (1969). Triglycerides were measured by the method of Eggstein and Kuhlmann (1974).

Statistical methods

Data was stored and analysed on a Digital DEC 20 computer. Standard statistical packages were used for statistical analyses; namely p-STAT for tabulations, Biomedical Computer Programmes (BMDP) for multiple regression analyses and Generalised Linear Interactive

Model (ling) (GLIM) for logistic regression analyses. The distribution of W/H^2 and total skinfold thickness is skewed and therefore log transformation was undertaken to improve the normality of the distribution. The use of log transformed data however made little difference to the results of analyses and for convenience arithmetic (untransformed) means are shown in tables and text unless indicated. Regression coefficients are given as % change in the dependent variable per unit change in the independent variable because of the use of logatithmic transformations.

The program for multiple regression analyses uses a forward stepping algorithm in which the first independent variable to be entered into the equation is the one with the highest absolute correlation with the dependent variable. When a variable has been entered into the equation its contribution is computed and the potential contribution of each of the variables not yet entered is also computed. If any of the variables which have been entered subsequently have a weaker relationship because of overlap with other entered variables that variable will generally be deleted from the equation (the F value to delete is below a threshold of 3.9). A variable which has been deleted at one step may be re-entered later on. This process continues until either too many steps have occurred due to

enter/delete oscillation or no entered variable can be deleted and no remaining variable can be entered or alternatively until all variables have been entered.

Logistic regression analysis as described by Walker and Duncan (1967) was used to analyse data with a binary endpoint, specifically it has been used to determine the association of a range of variables with mortality. The dependent variable can only take one of two values (0 or 1, present or absent).

In those cases where a non linear relationship appeared possible, either from inspection of the data or because previous studies had suggested this possibility (e.g. the association between obesity and total mortality) quadratic terms were introduced into the regression analysis to determine whether these made an independent contribution to the regression equation (for details see later).

Follow up of participants

Comprehensive notifications of deaths are received from the National Health Service Central Register and further information on the cause of death has been ascertained from the patients' general practitioner and/or hospital consultant. At follow up participants are interviewed in a standard fashion to determine

whether any cardiovascular events may have occurred since the initial examination. Specifically, questions are asked about the occurrence of chest pain, any hospital admissions or major illness and investigations. Since follow up is still underway incidence data are incomplete and the subsequent analyses relate to cardiovascular disease noted to be present at entry examination and to the fatalities during the subsequent follow up which are continuously notified to NPHS. Clinical and necropsy reports are assessed by three doctors independent of the study according to standard criteria.

Definitions: Prevalence Cases

Definite Myocardial Infarction:

(a) Typical history, typical ECG changes and elevated enzyme levels.

or (b) History typical or atypical, equivocal ECG but elevated enzyme levels.

or (c) ECG shows typical serial changes.

or (d) Typical history, negative ECG but elevated enzyme levels.

or (e) Typical history, typical ECG, but no enzyme changes reported.

Possible Myocardial Infarction:

(a) Typical pain; ECG and enzyme levels performed, but equivocal or normal.

or (b) Intermediate coronary syndromes, e.g. coronary insufficiency, myocardial ischaemia; terms sometimes used to describe episodes of prolonged chest pain, with (i) or without (ii) ECG changes and not necessarily related to exertion, that fall short of frank infarction but are more prolonged and intense than angina.

Criteria: (i) ECG information available (either copied from original tracing or referred to in a clinical summary) that shows ST/T wave or LBBB changes compatible with ischaemia, or is clearly reported on as ischaemic. No enzyme changes. Prolonged chest pain reported, which may or may not have been typical in site, quality, etc.

(ii) ECG information and enzyme levels not performed, or not available. Prolonged chest

pain reported; typical of ischaemic cardiac pain in site and quality.

Angina Pectoris

Definite Angina Pectoris: Typical history of angina pectoris confirmed by other evidence, clinical and/or investigatory (e.g. in a G.P. or hospital letter) that is independent of the opinion of the Unit's examining doctor.

Possible Angina Pectoris: Independent evidence of angina pectoris equivocal or absent, but symptoms could be those of angina.

Intermittent Claudication

Definite Intermittent Claudication: As for Definite Angina Pectoris (substituting Intermittent Claudication).

Possible Intermittent Claudication: As for Possible Angina Pectoris (substituting Intermittent Claudication).

N.B. Examination details of peripheral pulses may be consulted in assessing cases for intermittent claudication.

Diagnosis of fatal ischaemic heart disease

Data was available from several sources on those participants who died during the follow up. Death certificates were available for the National Health Service Central Registry and further information was collected from general practitioners, hospital clinicians and coroners where appropriate. The decision to classify a participant as dying of ischaemic heart disease was taken without knowledge of their personal characteristics or risk factors. All relevant data was reviewed by myself without knowledge of the laboratory results. Of the 54 fatal cases of IHD amongst white males on whom the statistical analyses were undertaken, 34 had post mortems. In all of these cases the autopsy results corroborated the clinical diagnosis.

My role in NPHS

I have been involved in NPHS since 1976. I have examined and interviewed a large number of participants at recruitment and at follow up and made the measurements of blood pressure and skinfold thickness. I have been responsible for initiating several other studies based on use of data from NPHS including the comparison of haemostatic variables and other cardiovascular risk factors in NPHS participants with a group of vegetarians (Haines et al 1980), the relation between ABH secretor status and pulmonary function

(Haines, Imeson and Meade 1982) psychoneurotic profiles in smokers and non smokers (Haines, Imeson and Meade 1981) and the association between breath methane concentration and obesity (Haines, Imeson and Wiggins 1984). No systematic analysis of the NPHS results on obesity had been undertaken previously and I was responsible for initiating and supervising the analysis of the data. I received computing and statistical assistance from Mr J. D. Imeson, my colleague in the MRC Epidemiology and Medical Care Unit at Northwick Park Hospital.

Dr T W Meade initiated NPHS and continues to supervise the overall progress of the study. He and Dr R Chakrabarti were the other two observers besides myself who examined most of the participants. The haemostatic variables were assayed in the Coagulation laboratory, MRC Epidemiology and Medical Care Unit and the cholesterol and triglycerides in the Clinical Chemical laboratory, Northwick Park Hospital.

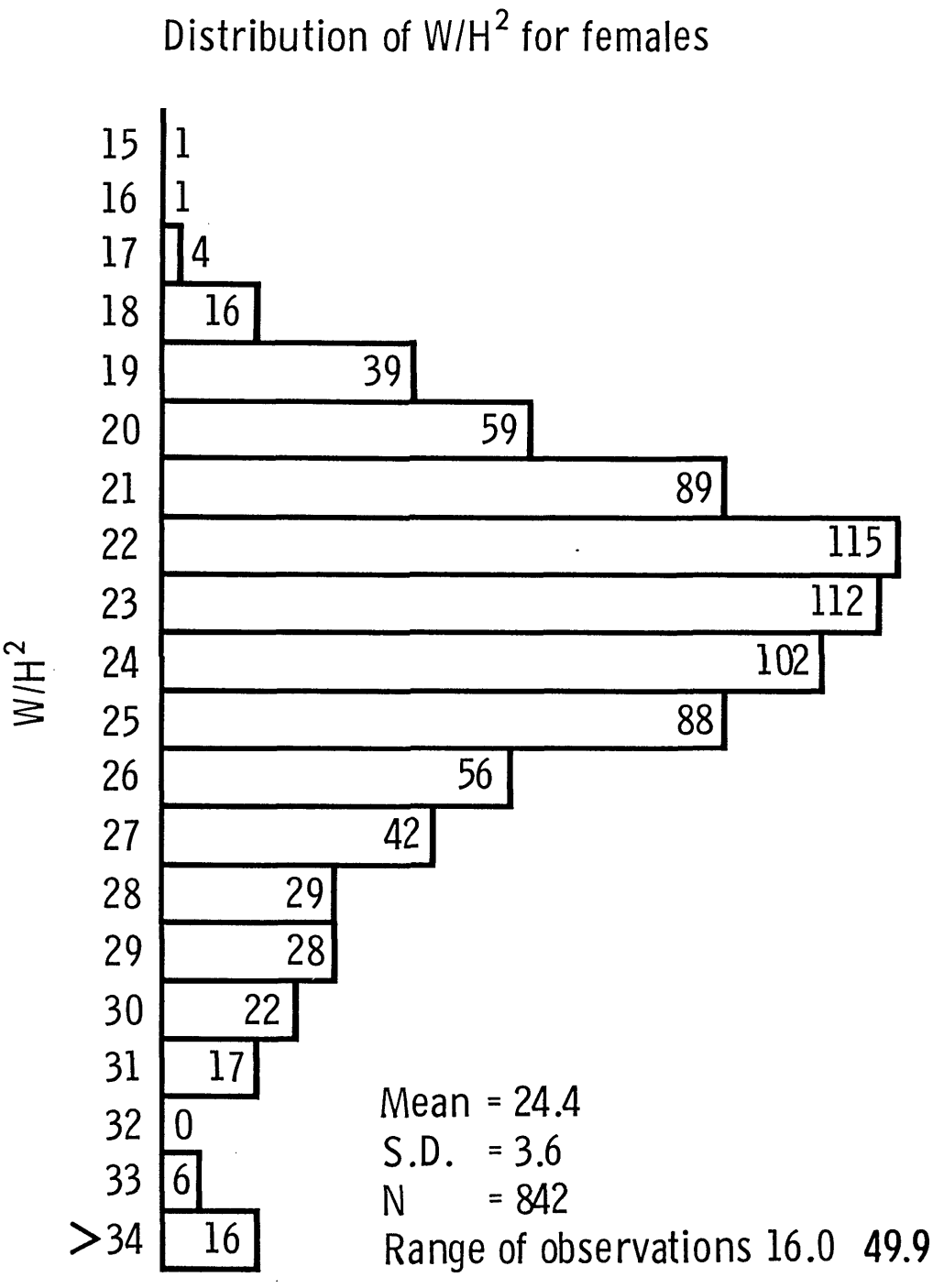
Chapter 3

Obesity and its association in NPHS

The distributions of W/H^2 at recruitment to NPHS for females and males are shown in figures 1 and 2 respectively. The distributions are slightly skewed for both males and females. There is a greater range of values for females than males. Using the values for the upper limit of desirable weight for the large frame size obtained from the Metropolitan Life Insurance tables (1959) about 49% of the males and about 30% of the females exceed the limits (the limits of W/H^2 are 24.9 for males and 24.6 for females). The upper limits of acceptable values for W/H^2 (Bray 1979) are 25.0 and 23.8 for males and females respectively. Thus 48% of the males and 39% of females are overweight or obese by this definition. The mean value of W/H^2 is lower for females than males.

Histograms of total skinfold thickness are shown for females and males in figures 3 and 4 respectively, again there is a greater range for females than males. The mean value is considerably greater for females than males. The distributions of both variables are moderately skewed. The distributions appear rather more irregular in the case of skinfold thickness than W/H^2. There is a tendency for older participants to have

Figure 1



N.B. Lowest observation = 15.98

Figure 2

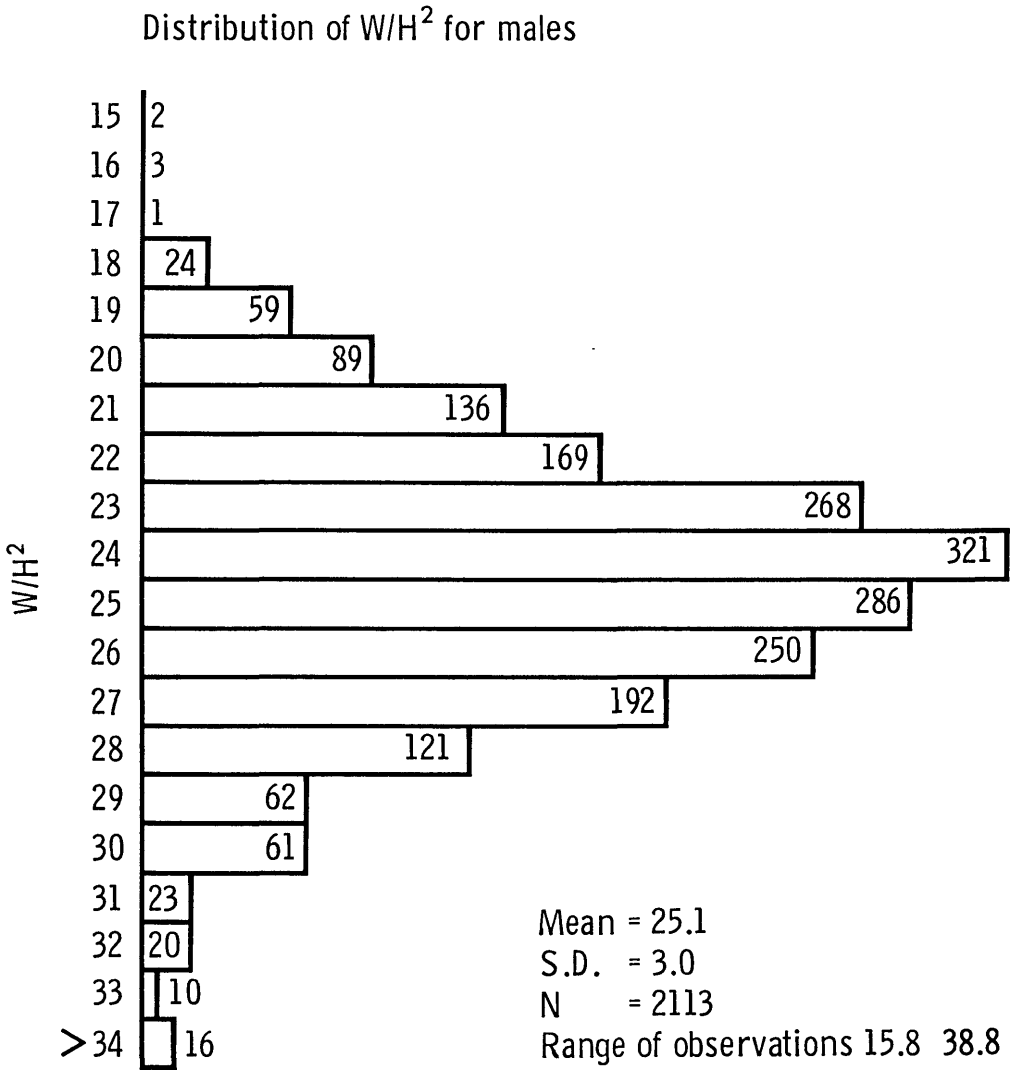

Distribution of W/H^2 for males
W/H^2
15 2
16 3
17 1
18 24
19 59
20 89
21 136
22 169
23 268
24 321
25 286
26 250
27 192
28 121
29 62
30 61
31 23
32 20
33 10
>34 16
Mean = 25.1
S.D. = 3.0
N = 2113
Range of observations 15.8 38.8

Figure 3

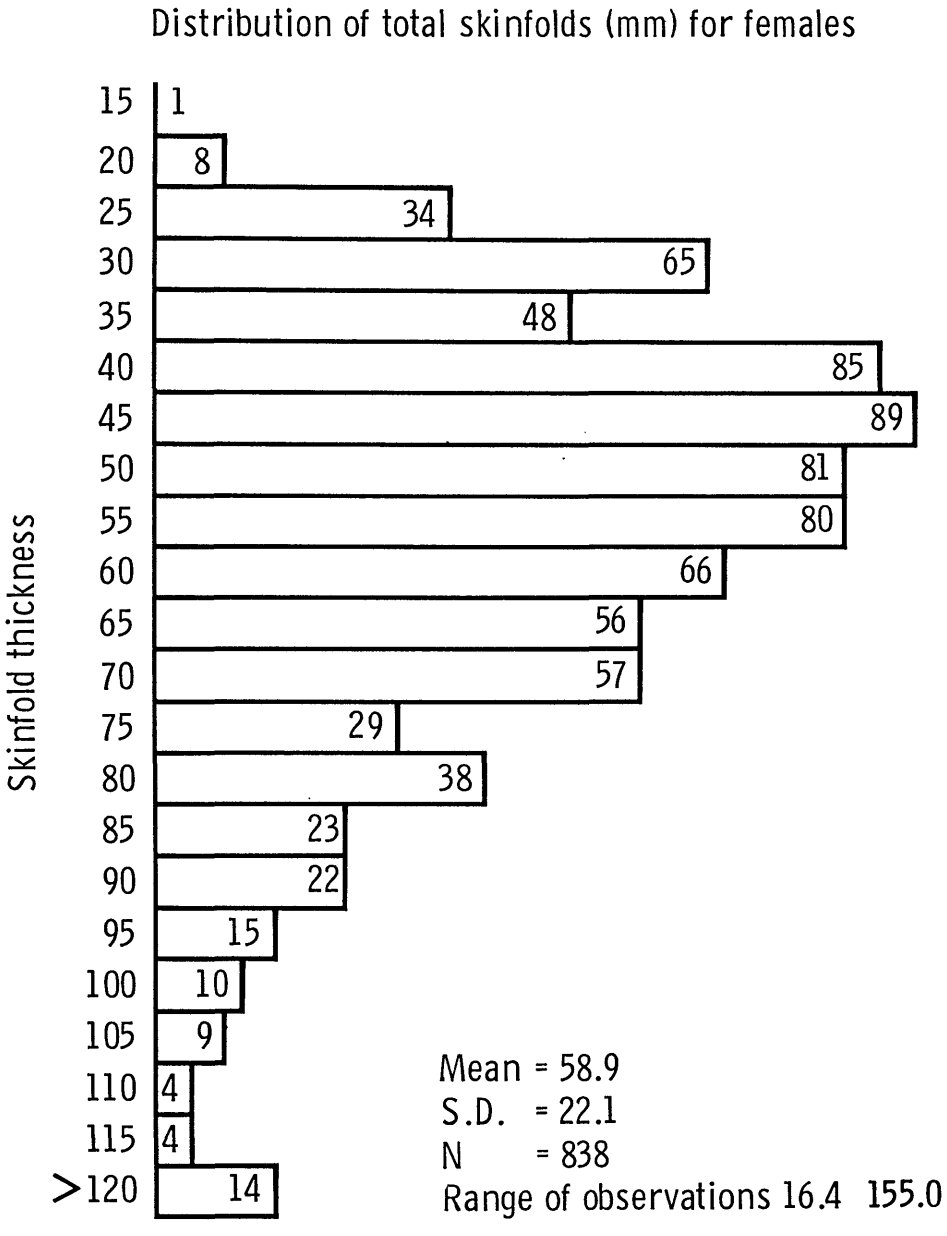

Distribution of total skinfolds (mm) for females
Skinfold thickness
15 1
20 8
25 34
30 65
35 48
40 85
45 89
50 81
55 80
60 66
65 56
70 57
75 29
80 38
85 23
90 22
95 15
100 10
105 9
110 4
115 4
>120 14
Mean = 58.9
S.D. = 22.1
N = 838
Range of observations 16.4 155.0

Figure 4

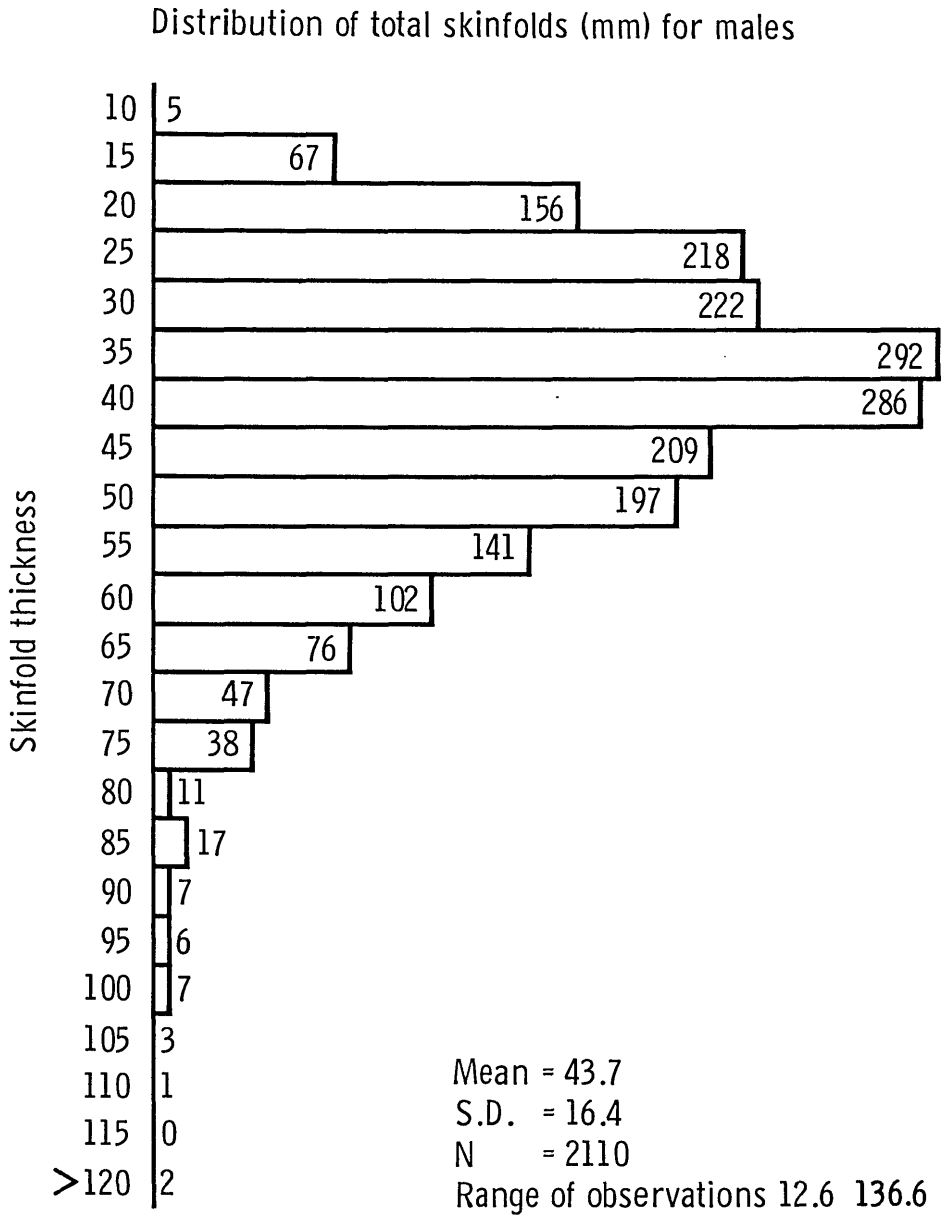

Distribution of total skinfolds (mm) for males
Skinfold thickness
10 5
15 67
20 156
25 218
30 222
35 292
40 286
45 209
50 197
55 141
60 102
65 76
70 47
75 38
80 11
85 17
90 7
95 6
100 7
105 3
110 1
115 0
>120 2
Mean = 43.7
S.D. = 16.4
N = 2110
Range of observations 12.6 136.6

Table 1

W/H^2 by age and sex (kg/m^2)

		<30	30-39	40-49	50-59	60-69	Total
Male	N	300	281	580	697	252	2110
	M	23.6	24.4	25.4	25.6	25.4	25.1
	SD	2.9	2.9	3.0	2.9	2.9	3.0
Female	N	115	92	254	350	31	842
	M	22.3	23.8	24.3	25.3	24.4	24.4
	SD	2.6	4.5	3.4	3.6	2.8	3.6
Total	N	415	373	834	1047	283	2952
	M	23.3	24.3	25.1	25.5	25.3	24.9
	SD	2.9	3.4	3.2	3.2	2.9	3.2

Table 2

Total skinfolds (mm) by age and sex

		<30	30-39	40-49	50-59	60-69	Total
Male	N	300	281	577	698	251	2107
	M	38.9	40.4	45.1	46.2	42.9	43.7
	SD	17.6	15.9	16.5	15.8	14.7	16.4
Female	N	114	92	253	348	31	838
	M	45.2	54.8	59.5	64.1	58.1	58.9
	SD	14.0	21.7	21.9	22.8	18.1	22.1
Total	N	414	373	830	1046	282	2945
	M	40.6	43.9	49.5	52.2	44.5	48.0
	SD	16.9	18.5	19.5	20.2	15.8	19.4

higher values for both W/H^2 and total skinfolds (Tables 1 and 2). However the mean values for both W/H^2 and skinfolds in the 50-59 age group are only slightly higher than those in the 40-49 age group for males. The 60-69 age group has slightly lower mean values for total skinfolds than both the 40-49 and 50-59 groups. In the case of the females the mean values for W/H^2 in the 40-49 and 60-69 age groups are similar and total skinfold thickness is slightly lower in the oldest age group although the numbers are small. The mean W/H^2 is somewhat higher amongst males than females at all ages and the converse applies in the case of total skinfolds. The rise in W/H^2 with age flattens off somewhat later amongst females than males. Multiple regression analysis using a quadratic term for age showed that amongst males W/H^2 appeared to peak at 55.4 years (95% C.L. $\pm$ 5 years) Amongst females the peak value for W/H^2 appeared to be beyond the upper age limit of the study.

The following equations have been derived by Eddy for calculating the % fat from W/H^2 (quoted in Research on Obesity DHSS/MRC 1976):-

$$\text{Men} \quad \text{Fat\%} = 1.281 \ (W/H^2) - 10.13$$

$$\text{Women} \quad \text{Fat\%} = 1.48 \ (W/H^2) - 7.0$$

Table 3

Ratio of trunk skinfolds (suprailiac and subscapular) to arm (triceps and forearm)

		<30	30–39	40–49	50–59	60–69	Total
Male	N	300	281	577	698	251	2107
	M	1.65	1.77	1.90	1.96	1.89	1.87
	SD	0.49	0.53	0.57	0.58	0.60	0.57
Female	N	114	92	253	348	31	838
	M	1.06	1.15	1.18	1.21	1.18	1.17
	SD	0.32	0.43	0.41	0.49	0.34	0.44
Total	N	414	373	830	1046	282	2945
	M	1.49	1.61	1.68	1.71	1.81	1.67
	SD	0.52	0.57	0.62	0.65	0.62	0.62

Using these it can be calculated that for men the percentage fat ranges from a mean of 20.1 in the youngest age group to 22.6 in the 50-59 year age group. In the case of women the mean percentage fat amongst those aged <30 is 26.0 and for those aged 50-59 30.4.

The subcutaneous distribution of fat appears more uniform in females than males in that the ratio between trunk skinfolds (subscapular and suprailiac) and arm skinfolds (triceps and forearm) is much closer to unity in females (Table 3). There is a tendency for the ratio to increase with age amongst males (except perhaps in the oldest group) indicating that in older men subcutaneous fat is distributed relatively more on the trunk than in younger males. The partial correlation coefficient for total skinfold thickness and W/H^2 is 0.75 for both males and females. Around 56% of the variance in total skinfolds is accounted for by W/H^2 amongst males and 64% amongst females. Women have a greater total skinfold thickness at a given W/H^2 than men.

Three observers made the great majority of skinfold measurements on the participants and the relationship between W/H^2 as one measure of obesity and skinfold thickness as another was examined independently for the

Table 4

Relationship between W/H^2 and skinfold thickness for the three observers (x axis = W/H^2, y axis = SKF), females only

		W/H^2 + Forearm SKF	W/H^2 + Triceps SKF	W/H^2 + Subscap SKF	W/H^2 + Suprailiac SKF
Observer 1	Intercept	-6.5	-8.1	-24.5	-28.4
n = 54	Reg coeff	0.6	1.1	1.8	1.8
	Corr coeff	0.7	0.6	0.9	0.8
Observer 2	Intercept	-4.7	-8.9	-25.7	-21.7
n = 649	Reg coeff	0.5	1.1	1.7	1.5
	Corr coeff	0.6	0.6	0.8	0.7
Observer 3	Intercept	-1.3	-8.1	-21.3	-18.8
n = 63	Reg coeff	0.3	1.1	1.6	1.3
	Corr coeff	0.6	0.6	0.8	0.6

Table 5

Relationship between W/H^2 and skinfold thickness for the three observers (x axis = W/H^2, y axis = SKF), males only

		W/H^2 + Forearm SKF	W/H^2 + Triceps SKF	W/H^2 + Subscap SKF	W/H^2 + Suprailiac SKF
Observer 1	Intercept	-3.6	-7.8	-14.1	-13.0
n = 409	Reg coeff	0.4	0.7	1.3	1.1
	Corr coeff	0.5	0.5	0.7	0.5
Observer 2	Intercept	-4.7	-6.7	-25.2	-25.7
n = 1288	Reg coeff	0.4	0.6	1.6	1.5
	Corr coeff	0.6	0.5	0.7	0.7
Observer 3	Intercept	-1.8	-6.5	-21.9	-16.5
n = 283	Reg coeff	0.3	0.6	1.5	1.0
	Corr coeff	0.5	0.5	0.7	0.6

three observers to determine whether there were any marked between observer differences. Tables 4 and 5 show the intercepts, regression coefficients and correlation coefficients for W/H^2 and the four skinfold thickness measurements for the three observers. The totals in these two tables are slightly less than the number of individuals in the study because a few participants had measurements made by two other observers at the beginning of the study. The numbers however are too small to make meaningful comparison with the three main observers. There is a consistent tendency (except in the case of suprailiac skinfolds for observer 1) for the correlation coefficients to be higher for subscapular and suprailiac skinfolds and W/H^2 than for triceps and forearm skinfolds and W/H^2.

There is also a consistent tendency for the correlation coefficients between the limb skinfold thickness (triceps and forearm) and W/H^2 to be higher for females than males perhaps reflecting the more uniform distribution of fat in females and therefore the greater contribution of peripheral fat to total body fat.

Multiple regression analyses with individual skinfolds as the dependent variable and W/H^2, sex, age and other variables thought to be related to obesity

Table 6

Social class, smoking and W/H^2 (males)

Smoked		I	II	IIINM	III M	IV	V	Total
	N	78	156	73	151	62	5	525
Never	M	24.0	24.4	23.8	25.1	26.1	26.2	24.7
	SD	2.9	2.7	2.8	3.2	3.5	4.3	3.1
	N	63	152	56	191	66	14	542
Ex	M	25.6	25.6	25.5	25.8	25.9	26.9	25.8
	SD	2.8	2.9	2.4	2.9	2.6	2.1	2.8
	N	23	34	29	86	51	8	231
1-10 Cigs	M	24.5	25.6	24.2	25.2	24.8	23.7	25.0
	SD	2.0	2.5	3.4	3.5	3.2	3.0	3.1
	N	24	52	39	178	75	14	382
11-20 Cigs	M	25.0	25.3	24.0	24.6	24.1	25.0	24.6
	SD	3.6	2.7	3.1	3.0	3.5	3.5	3.2
	N	12	42	17	104	57	3	235
21+ Cigs	M	25.3	25.6	25.0	25.5	24.2	20.3	25.1
	SD	2.9	3.4	3.0	3.0	3.1	5.5	3.2
	N	13	33	3	19	10		78
Cigar	M	24.8	25.8	25.9	24.8	26.1		25.5
	SD	2.1	2.3	2.5	2.4	2.0		2.2
	N	17	30	15	43	11	2	118
Pipe	M	24.9	25.0	25.9	25.2	27.3	26.2	25.4
	SD	2.7	2.3	2.7	2.9	4.4	4.0	2.9
	N	230	499	232	772	332	46	2111
Total	M	24.8	25.2	24.6	25.2	25.1	25.2	25.1
	SD	2.9	2.8	2.9	3.1	3.3	3.5	3.0

Table 7

Social class, smoking and W/H^2 (females)

Smoked		I	II	III NM	III M	IV	V	Total
	N	33	94	96	118	32	4	377
Never	M	23.3	24.5	24.1	25.1	25.5	26.3	24.6
	SD	3.7	3.3	3.9	4.1	3.1	2.5	3.8
	N	8	35	36	32	17	2	130
Ex	M	25.4	24.4	25.1	24.7	25.8	24.9	24.9
	SD	4.0	2.7	3.7	3.9	4.0	0.9	3.5
	N	4	17	25	42	10		98
1-10 Cigs	M	24.6	24.4	25.2	24.5	24.1		24.7
	SD	2.1	4.0	5.1	3.6	2.9		4.0
	N	5	28	31	49	22	2	137
11-20 Cigs	M	24.6	23.6	23.0	24.4	24.0	25.1	23.8
	SD	1.3	3.1	2.9	3.6	3.0	1.3	3.2
	N	2	11	18	32	10	2	75
21+ Cigs	M	23.9	22.1	22.9	23.7	23.0	25.3	23.2
	SD	3.9	2.1	2.8	3.4	3.1	0.9	3.0
	N	52	185	206	273	91	10	817
Total	M	23.9	24.2	24.3	24.7	25.0	25.6	24.4
	SD	3.5	3.2	3.9	3.8	3.6	1.7	3.6

Table 8

Social class, smoking and total skinfolds (males)

Smoked		I	II	III NM	III M	IV	V	Total
	N	78	156	72	152	62	5	525
Never	M	40.9	42.0	40.7	44.4	45.0	40.7	42.7
	SD	14.8	16.3	13.8	17.7	18.00	17.3	16.4
	N	63	152	56	191	66	14	542
Ex	M	46.9	48.9	48.2	47.5	43.2	45.7	47.3
	SD	15.1	14.9	13.7	18.0	15.8	9.1	16.0
	N	23	34	29	86	51	8	231
1-10 Cigs	M	46.9	44.8	42.2	42.6	41.1	31.8	42.6
	SD	16.6	15.7	15.7	17.1	19.0	8.9	17.0
	N	24	52	39	178	75	14	382
11-20 Cigs	M	44.9	46.4	38.3	40.4	35.3	38.3	40.2
	SD	22.5	16.9	14.9	15.2	14.3	12.5	16.0
	N	11	42	17	104	56	3	233
21+ Cigs	M	43.9	42.9	42.7	44.5	37.0	27.5	42.0
	SD	13.1	13.3	11.7	16.9	15.5	17.2	15.7
	N	13	33	3	19	10		78
Cigar	M	45.4	50.6	59.8	46.2	43.4		48.1
	SD	16.3	14.2	17.2	14.6	10.9		14.5
	N	17	29	15	43	11	2	117
Pipe	M	45.5	47.0	43.7	43.8	51.4	39.7	45.5
	SD	17.1	13.9	14.6	17.4	26.0	8.3	16.9
	N	229	498	231	773	331	46	2108
Total	M	44.3	45.7	42.9	44.0	40.7	39.1	43.7
	SD	16.2	15.6	14.5	17.1	17.1	12.5	16.4

Table 9

Social class, smoking and total skinfolds (females)

Smoked		I	II	III NM	IIIM	IV	V	Total
	N	33	94	96	118	32	4	377
Never	M	55.7	61.7	59.7	61.3	64.7	77.6	60.9
	SD	18.7	21.9	24.5	22.5	20.4	16.1	22.3
	N	8	35	36	32	17	2	130
Ex	M	68.3	63.8	64.3	62.5	62.2	47.7	62.9
	SD	30.2	19.0	23.7	22.9	22.3	8.1	22.1
	N	4	16	25	42	10		97
1-10 Cigs	M	51.0	61.3	61.7	60.6	52.5		59.8
	SD	12.2	24.6	26.9	20.2	12.9		21.9
	N	5	28	31	49	21	2	146
11-20 Cigs	M	56.2	52.2	50.5	56.0	52.4	66.1	53.2
	SD	16.7	19.9	17.3	25.3	18.9	21.6	20.8
	N	2	11	18	31	10	2	74
21+ Cigs	M	40.5	46.6	50.5	53.8	52.2	63.9	51.4
	SD	21.6	13.2	17.3	22.6	20.5	28.7	19.6
	N	52	184	206	272	90	10	816
Total	M	56.8	59.3	58.6	59.5	59.1	66.6	58.9
	SD	20.5	21.4	23.5	22.8	20.6	19.3	22.1

(see later in this section for description) as independent variables showed that for forearm skinfolds there is a consistent difference between observer 2 on the one hand and observers 1 and 3 on the other ($p<0.01$ and $p<0.001$ respectively). In addition the slope of the regression (regression coefficient) for observer 3 is significantly different from that of observer 2 ($p<0.0001$). In the case of triceps skinfold observer 1 measured consistently differently from observer 2 ($p<0.005$). Both observers 1 and 3 measured the subscapular skinfold significantly differently from observer 2 ($p<0.0001$ and $p<0.05$ respectively) and similarly for suprailiac skinfold ($p<0.02$ and $p<0.0001$ respectively). Although some of the differences between observers appeared to be opposite directions in the two sexes, the differences are not statistically significant. Observers 1 and 3 examined a comparatively small number of women at recruitment and the comparisons between the observers are therefore based on data from both sexes combined.

Personal characteristics related to obesity in NPHS.

Amongst males there is no consistent relationship between obesity and social class, the standard deviation tends to be higher in the lower social class males

suggesting a wider scatter of values. Amongst females there is a trend toward increasing obesity with lower social class which is more consistent for W/H^2 than skinfolds but is not statistically significant for either measurement (Tables 6-9). Amongst never smokers of both sexes there is a fairly consistent trend for those in the lower social classes to be more obese than those in the upper social classes but this is also not statistically significant. Ex-smokers tend to be somewhat more obese than never and current cigarette smokers ($p<0.001$, males only). Amongst females there is an overall inverse relationship between number of cigarettes smoked per day and obesity ($p<0.0001$, for both W/H^2 and total SKF, multiple regression) but this is not apparent for males. Cigar and pipe smokers (males only) tend to be heavier than cigarette smokers and never smokers. Amongst males there is no overall difference in mean W/H^2 and total skinfolds between cigarette smokers and never smokers. However there is an interaction between social class, cigarette smoking and obesity in that amongst upper social class (I and II) males current cigarette smokers are more obese than never smokers (Summary Table 10) whilst male social class IV and V smokers are leaner than never smokers of the same social class ($p<0.001$ for comparison of difference in W/H^2 between current cigarette smokers and never smokers of social classes I and II combined on the

Table 10

Summary table

Social class, current and never cigarette smokers and W/H^2 (males)

Smoking		I	II	III NM	III M	IV	V	Totals
Never	N	78	156	73	151	62	5	525
	M	24.0	24.4	23.8	25.1	26.1	26.2	24.7
	SD	2.9	2.7	2.8	3.2	3.5	4.3	3.1
Current Cigarette Smokers	N	59	128	85	368	183	25	848
	M	25.0	25.5	24.3	25.0	24.4	24.0	24.8
	SD	2.9	2.9	3.2	3.1	3.3	3.7	3.2

Table 11

Multiple regression analysis of factors related to individual skinfolds

Forearm	Reg Coeff	S.E.
Sex F>M (mean difference)	2.7	0.11****
Age Per year	0.02	0.004****
Oral contraception (current) Yes/no (mean difference)	1.1	0.28****
Ex-smokers/never smokers (mean difference)	0.33	0.05**
Triceps		
Sex F>M (mean difference)	8.1	0.26****
Menopausal status Post/Pre (mean difference)	2.5	0.35****
Age per year	0.02	0.008*
Ex-smokers/never smoked (mean difference)	0.54	0.25*
Current cigarette smokers/ never smokers (mean difference)	-0.41	0.21*
Subscapular		
Age (per year)	0.13	0.01****
Sex F>M (mean difference)	1.2	0.30****
Current cigarette smoking/ never smokers (mean difference)	-0.83	0.29**
Suprailiac		
Current cigarette smoking/never smokers (mean difference)	-1.5	0.30****
Menopausal status Post/Pre (mean difference)	2.5	0.51****
Age per year	0.04	0.01***
Sex F>M (mean difference)	1.3	0.08**

* P < 0.05
** P < 0.01
*** P < 0.005
**** P < 0.0001

one hand and between social classes IV and V combined on the other hand). In the case of total skinfolds similar results were obtained for males. Amongst men those who worked on the night shift are somewhat more obese (by 1 kg/m^2) than those on the day shift ($p<0.05$) and women who consume alcohol are on average more obese than those who were teetotallers by 1 kg/m^2 ($p<0.002$) but there is no apparent relationship between stated amount consumed and obesity.

Factors related to individual skinfolds

a) Forearm

Multiple regression analysis with forearm skinfolds as the dependent variable taking into account the observer differences previously described revealed that four variables appeared to be related to forearm skinfold thickness. Females have a greater mean forearm skinfold thickness than males (Table 11), those women taking oral contraceptives have a greater mean forearm skinfold thickness than those who were not. Forearm skinfold thickness increases with age. Finally, ex-smokers have somewhat greater mean forearm skinfold thickness than never smokers. 22% of the variance is explained by the factors in the multiple regression analysis.

b) Triceps

Taking observer difference into account, there are five factors which appeared to be related to triceps skinfold thickness. Two factors, sex and menopausal status, are unequivocably related to triceps skinfold thickness and for three characteristics, age, current and previous cigarette smoking, there are weak associations of borderline statistical significance. 46% of the variance in triceps skinfold thickness is 'explained' by the variables in the multiple regression analysis.

c) Subscapular

Only three factors are related to subscapular skinfold thickness namely age, sex and current cigarette smoking, the latter characteristic having the weakest association. Only 9% of the variance is explained.

d) Suprailiac

Four characteristics are significantly related to suprailiac skinfold thickness, namely age, sex,current cigarette smoking and menopausal status. As with subscapular skinfold thickness only 9% of the variance is explained.

Obesity and blood pressure

As discussed previously it has been noted for many years that the measurement of blood pressure may be affected by using a standard size blood pressure cuff on a fat arm since in this case the bladder does not circle the arm sufficiently. The usual length of the bladder in the UK is only 23 cm. The American Heart Association has recommended that the bladder should encircle 75% of the arm circumference. In the recruitment phase of NPHS a standard cuff and sphygmomanometer were used, however this was replaced in the follow up examination by a random zero sphygmomanometer with both standard and oversize (33 cm) cuffs available. At follow up the standard cuff was marked with lines to demonstrate the maximal permitted arm circumference, the oversize cuff was used above this point. In addition, at the follow up examination, arm circumference was measured 10 centimetres above the medial epicondyle of the humerus.

The relationship between blood pressure and total skinfolds was analysed separately for the two examinations. The mean of two blood pressure readings (pre and post blood sample) was used on both occasions. In addition, in the follow up data, the relationships between blood pressure and the various measures of

Table 12

Age related quartiles of W/H^2

		1	2	3
Females				
	<30	20.5	21.9	24.1
	30-39	21.0	23.2	24.7
	40-49	22.1	23.8	26.0
	50-59	22.9	24.8	26.7
	60-69	22.0	24.5	26.6
	Overall	22.0	24.0	26.0
Males				
	<30	21.6	23.5	25.3
	30-39	22.5	24.3	26.3
	40-49	23.5	25.2	27.1
	50-59	23.7	25.6	27.4
	60-69	23.8	25.4	27.1
	Overall	23.0	25.0	27.0

obesity were examined taking into account arm circumference by multiple regression analysis.

The data for systolic blood pressure and other variables are displayed separately for the two sexes as mean values for each age specific quartile of W/H^2. The quartiles are given in Table 12. In addition similar tabulations were performed using the overall quartiles for the whole population given in Table 12 for males and females separately. This naturally resulted in larger numbers in the lower quartiles amongst the younger age groups and conversely larger numbers in the higher quartiles in the older age groups since obesity tends to increase with age. Whilst the use of overall quartiles had the advantage of more clearly separating the effects of age and obesity by using uniform quartiles in different age groups this approach did not substantially affect the interpretation of the findings and therefore only the tabulations using age specific quartiles have been shown.

Tables 13 and 14 show the relationship between entry systolic blood pressure and W/H^2 for males and females. Blood pressure increases consistently with increasing obesity in males. In females there appears

Table 13

Mean systolic blood pressure (SD) at entry
by quartiles of W/H^2 and age (males)

Age		1	2	3	4	Total
	N	74	75	76	74	299
<30	M	119.7	123.4	124.8	126.5	123.6
	SD	13.0	13.5	13.0	15.9	14.1
	N	70	71	71	69	281
30-39	M	122.1	126.1	127.1	127.3	125.7
	SD	12.2	13.2	15.0	18.8	15.0
	N	143	146	143	145	577
40-49	M	126.5	131.9	133.3	135.3	131.8
	SD	16.9	16.0	17.8	20.0	18.0
	N	171	175	175	172	693
50-59	M	135.2	139.4	142.8	144.3	140.4
	SD	18.7	18.5	22.7	21.0	20.6
	N	64	60	64	61	249
60-69	M	144.9	149.9	151.5	149.8	149.0
	SD	23.8	27.1	22.8	24.7	24.6
	N	522	527	529	521	2099
Total	M	130.1	134.5	136.6	137.7	134.7
	SD	19.2	19.4	21.1	21.8	20.6

Table 14

Mean systolic blood pressure (SD) at entry
by quartiles of W/H^2 and age (females)

Age		1	2	3	4	Total
	N	29	29	29	28	115
<30	M	117.7	116.7	115.1	118.8	116.9
	SD	15.8	13.4	14.0	14.6	14.3
	N	23	23	23	23	92
30-39	M	120.5	118.1	119.0	117.0	118.6
	SD	14.2	10.5	15.2	8.9	12.3
	N	63	64	64	63	254
40-49	M	124.0	130.2	127.1	134.9	129.1
	SD	15.2	20.3	15.6	21.2	18.6
	N	87	88	88	87	350
50-59	M	135.3	136.0	138.4	144.7	138.6
	SD	21.1	21.2	19.0	22.7	21.3
	N	8	8	7	7	30
60-69	M	135.5	153.6	159.1	166.7	153.1
	SD	13.3	33.6	28.6	26.4	27.7
	N	210	212	211	208	841
Total	M	127.8	130.3	130.4	135.8	131.1
	SD	19.5	21.4	20.0	23.5	21.2

to be little relationship with obesity in those under 40. In both sexes there is a marked rise in blood pressure with age at all levels of obesity. Multiple regression analyses of systolic blood pressure (SBP) at entry (with both total skinfolds and W/H^2 included) shows that for males when age, observer variability, alcohol consumption and smoking are taken into account, both total skinfolds and W/H^2 have an independent relation with SBP ($p<0.01$ for both). The multiple regression analysis was repeated with the four individual skinfolds. Of the individual skinfolds, the suprailiac skinfold is most closely ($p<0.001$) related to blood pressure followed by the forearm skinfold ($p<0.01$). Amongst females, the subscapular skinfold is most closely related to systolic blood pressure ($p<0.001$). Triceps skinfold thickness is not significantly associated with systolic pressure in females when the other skinfold measurements are taken into account. In males the relation is of borderline significance but in the opposite direction to that anticipated. (For summary of associations between cardiovascular risk factors and individual skinfolds see Tables 27 and 28).

In the case of data at the re-examination where arm circumference was also measured it was found that when W/H^2 was taken into account, arm circumference had a

Table 15

Mean serum cholesterol mmol/l (SD) by age related quartiles of W/H^2 (males)

Age		1	2	3	4	Total
	N	72	71	72	69	284
<30	M	4.8	5.0	5.3	5.5	5.1
	SD	1.0	1.0	1.0	1.1	1.0
	N	67	63	66	64	260
30-39	M	5.1	5.6	5.8	5.9	5.6
	SD	1.0	0.9	1.0	1.0	1.0
	N	140	140	133	138	551
40-49	M	5.8	5.9	6.3	6.2	6.1
	SD	1.0	1.0	1.3	1.2	1.1
	N	164	166	170	159	659
50-59	M	6.1	6.3	6.2	6.3	6.2
	SD	1.1	1.2	1.1	1.2	1.1
	N	57	60	61	61	239
60-69	M	5.9	6.2	6.3	6.4	6.2
	SD	1.0	1.0	1.3	1.2	1.1
	N	500	500	502	491	1993
Total	M	5.7	5.9	6.0	6.1	5.9
	SD	1.1	1.1	1.2	1.2	1.2

Table 16

Mean serum cholesterol mmol/l (SD) by age related quartiles of W/H^2 (females)

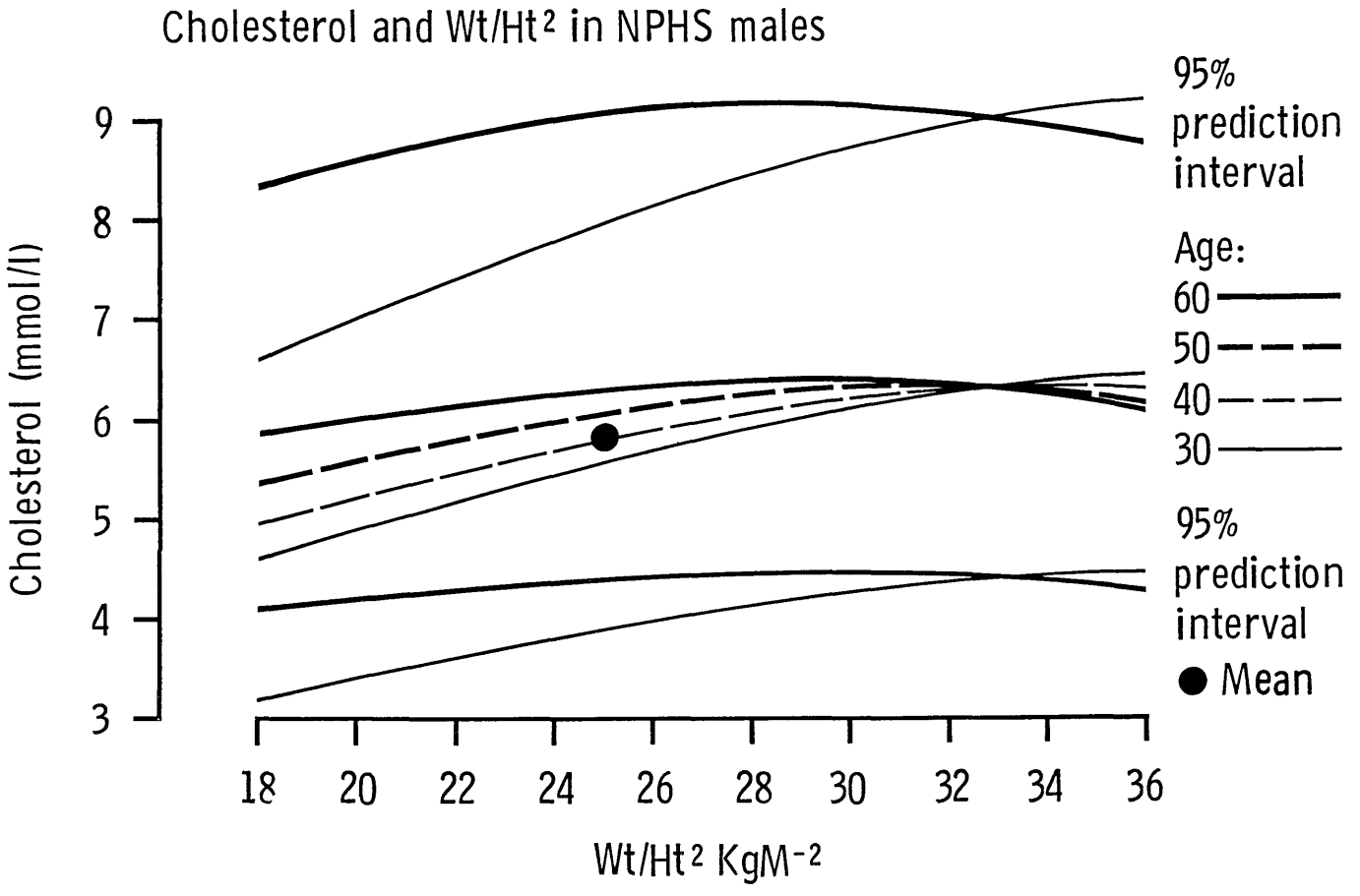
Age		1	2	3	4	Total
	N	23	26	26	25	100
<30	M	5.1	4.9	5.4	5.5	5.3
	SD	0.8	1.0	1.3	1.0	1.1
	N	21	20	20	19	80
30-39	M	5.5	5.5	5.6	5.3	5.5
	SD	1.5	0.8	1.0	1.0	1.1
	N	61	59	54	56	230
40-49	M	5.7	5.8	6.1	6.4	6.0
	SD	0.9	0.9	1.1	1.1	1.0
	N	79	77	78	74	308
50-59	M	6.6	6.8	6.9	7.1	6.8
	SD	1.0	1.1	1.1	1.5	1.2
	N	6	8	8	7	29
60-69	M	6.7	6.6	8.2	7.6	7.3
	SD	1.0	0.7	3.5	1.7	2.1
	N	190	190	186	181	747
Total	M	6.0	6.1	6.4	6.5	6.2
	SD	1.1	1.2	1.5	1.4	1.3

slight independent relationship with blood pressure in either sex ($p<0.05$). Systolic blood pressure rose by a mean of 0.7 mm Hg per centimetre increase in arm circumference when skinfold thickness and W/H^2 were taken into account. W/H^2 was significantly related to SBP at follow up ($P<0.001$). The regression coefficient was 1.7 mm Hg/Kgm^{-2} (SE = 0.18) for both sexes combined. However when total skinfold thickness and arm circumference were both included in the multiple regression analysis, the relationship between W/H^2 and blood pressure was no longer significant. Arm circumference and total skinfold thickness made similar contributions to the variance of systolic blood pressure in this analysis, (standard regression coefficient for both = 0.09). Since 118 individuals were known to have hypertension at entry and in most instances were receiving treatment for raised blood pressure this may have resulted in a slight underestimate of the association between obesity and blood pressure (for details see later).

Obesity and Lipids

Amongst both males and females there is a consistent relation between serum cholesterol on the one hand and obesity on the other. (Tables 15 and 16) In males the relation with obesity appears somewhat more

Figure 5


Cholesterol and Wt/Ht² in NPHS males
Cholesterol (mmol/l)
9
8
7
6
5
4
3
18
20
22
24
26
28
30
32
34
36
Wt/Ht² KgM⁻²
95% prediction interval
Age:
60
50
40
30
95% prediction interval
Mean

marked in those aged under 40 compared with those aged 40 and over, multiple regression analysis with an interaction term included for W/H^2 and age demonstrated that this tendency is statistically significant ($p<0.001$). In addition to the highly significant association between W/H^2 and cholesterol ($p<0.001$), in males only there is a statistically significant ($p<0.01$) independent association of cholesterol with $(W/H^2)^2$ when W/H^2 was taken into account. This resulted in the regression lines of cholesterol on W/H^2 for different age groups being somewhat convex for males (figure 5). Mean serum cholesterol appears higher in females than males over age 50. There is a pronounced tendency amongst females for serum cholesterol to be higher in the older age groups and this is apparent at all levels of obesity. In the case of males mean cholesterol levels seem to flatten off above age 40-49. A similar association was observed with total skinfolds and to avoid repetition only tabulations showing W/H^2 are displayed. Multiple regression analysis of serum cholesterol confirmed that in both sexes combined (there being no significant difference between the sexes in the relation) total skinfolds are related to serum cholesterol ($P<0.0001$). However the association was no longer significant when W/H^2 was taken into account. The association between cholesterol and individual skinfolds was also examined using multiple regression

Table 17

Mean serum triglycerides mmol/l (SD) by age related quartiles of W/H^2 (males)

Age		1	2	3	4	Total
	N	72	69	73	69	283
<30	M	1.0	1.0	1.4	1.7	1.3
	SD	0.4	0.5	1.0	1.0	0.8
	N	67	62	67	63	259
30-39	M	1.1	1.3	1.7	2.1	1.5
	SD	0.5	0.7	0.9	1.3	1.0
	N	134	142	136	138	550
40-49	M	1.4	1.7	2.2	2.2	1.9
	SD	0.8	1.0	1.5	1.2	1.2
	N	165	164	166	157	652
50-59	M	1.4	1.8	1.9	2.0	1.8
	SD	0.8	1.0	1.0	1.2	1.0
	N	56	61	58	61	236
60-69	M	1.5	1.7	1.7	2.4	1.8
	SD	0.9	0.9	0.8	1.4	1.1
	N	494	498	500	488	1980
Total	M	1.3	1.6	1.8	2.1	1.7
	SD	0.8	0.9	1.1	1.2	1.1

Table 18

Mean serum triglycerides mmol/l (SD) by age related quartiles of W/H^2 (females)

Age		1	2	3	4	Total
	N	23	26	27	25	101
<30	M	1.0	1.0	1.0	1.0	1.0
	SD	1.0	0.5	0.5	0.4	0.6
	N	21	20	21	19	81
30-39	M	1.0	0.9	1.1	1.4	1.1
	SD	0.5	0.4	0.5	0.6	0.5
	N	61	57	53	56	227
40-49	M	1.1	1.0	1.1	1.4	1.1
	SD	0.6	0.4	0.5	0.7	0.6
	N	76	77	79	72	304
50-59	M	1.1	1.4	1.3	1.7	1.4
	SD	0.5	0.8	0.6	0.8	0.7
	N	6	8	8	7	29
60-69	M	1.1	1.3	2.7	1.5	1.7
	SD	0.9	0.8	1.8	0.8	1.3
	N	187	188	188	179	742
Total	M	1.1	1.2	1.3	1.4	1.2
	SD	0.6	0.6	0.7	0.7	0.7

analysis. Subscapular ($p<0.001$) and forearm ($p<0.01$) skinfold thickness are independently associated with serum cholesterol in males but the association fell to borderline statistical significance when W/H^2 was taken into account. In the case of females, suprailiac skinfold ($p<0.001$) is the only individual skinfold related significantly to serum cholesterol and this association is no longer statistically significant when W/H^2 is taken into account (see also tables 27 and 28). In the case of triglycerides (Tables 17 and 18) males have a considerably higher mean level than females overall and this is consistent in all age groups. The difference between the leanest and heaviest quartiles in mean triglycerides is considerably less in females than males. There is a generally consistent trend towards higher mean triglycerides with increasing age in females but no further rise with age occurs in males beyond the 40-49 age group.

Obesity and haemostatic variables

The relations between obesity and factors V, VII_c, $VIII_c$, fibrinogen, antithrombin III (clotting and immunological) and fibrinolytic activity were examined. Significant relationships (all $p<0.001$) were found in the case of factors V and VII_c, fibrinogen and fibrinolytic activity for both sexes combined. In the

Table 19

Factor V% and W/H^2 (Males)

(Quartiles)

Age		1	2	3	4	Total
	N	74	72	73	69	288
<30	M	108.2	110.3	110.4	112.6	110.3
	SD	28.2	27.3	22.7	27.6	26.4
	N	66	66	69	65	266
30-39	M	118.3	119.8	111.0	122.2	117.7
	SD	28.0	31.0	27.1	27.8	28.7
	N	141	145	138	139	563
40-49	M	116.2	120.8	129.4	123.7	122.5
	SD	22.9	28.0	28.6	27.5	27.2
	N	164	167	168	165	664
50-59	M	126.8	126.7	122.2	127.3	125.7
	SD	29.6	29.8	22.5	28.4	27.7
	N	62	61	59	61	243
60-69	M	123.4	127.5	132.1	129.6	128.1
	SD	28.4	29.6	28.1	29.2	28.8
	N	507	511	507	499	2024
Total	M	119.6	121.9	122.0	123.9	121.9
	SD	27.9	29.5	26.7	28.4	28.2

Table 20

Factor V% and W/H^2 (females)
(Quartiles)

Age		1	2	3	4	Total
	N	27	24	25	24	100
<30	M	105.9	101.2	105.4	116.7	107.2
	SD	28.2	19.0	19.6	25.2	23.8
	N	19	19	19	20	77
30-39	M	119.8	132.9	126.9	127.4	126.8
	SD	39.6	58.7	24.3	25.6	38.9
	N	59	56	57	52	224
40-49	M	117.7	118.7	124.1	133.6	123.3
	SD	25.9	24.6	25.6	26.4	26.2
	N	80	81	83	78	322
50-59	M	123.3	129.8	120.2	128.2	125.3
	SD	25.8	23.6	25.7	35.3	28.0
	N	6	8	8	6	28
60-69	M	113.4	120.0	150.6	139.0	131.4
	SD	28.0	17.4	34.4	13.6	28.2
	N	191	188	192	180	751
Total	M	118.5	122.7	121.3	128.5	122.7
	SD	28.1	30.0	26.4	30.4	28.9

Table 21

Factor VII_C % and W/H^2 (males)
(Quartiles)

Age		1	2	3	4	Total
	N	73	71	70	69	283
<30	M	89.3	92.9	96.7	98.9	94.4
	SD	21.8	23.6	23.0	22.1	22.8
	N	67	66	69	64	266
30-39	M	91.6	98.1	106.4	115.4	102.8
	SD	19.8	26.8	25.7	30.1	27.1
	N	140	145	138	137	560
40-49	M	102.8	109.4	112.0	113.8	109.5
	SD	24.5	25.8	26.5	27.1	26.2
	N	164	168	168	163	663
50-59	M	108.2	110.0	114.2	115.2	111.9
	SD	21.9	26.6	26.3	26.8	25.6
	N	63	62	59	61	245
60-69	M	104.5	118.6	113.1	123.9	114.9
	SD	21.7	30.8	27.8	36.4	30.3
	N	507	512	504	494	2017
Total	M	101.4	106.9	109.9	113.6	107.9
	SD	23.3	27.5	26.6	28.8	27.0

Table 22

Factor VII_C % and W/H^2 (females)
(Quartiles)

Age		1	2	3	4	Total
	N	27	24	25	24	100
<30	M	103.4	96.5	102.7	101.5	101.1
	SD	34.4	35.2	38.4	36.2	35.6
	N	20	19	19	21	79
30-39	M	102.0	102.4	108.1	107.1	104.9
	SD	26.2	26.6	26.6	22.0	25.0
	N	59	56	57	52	224
40-49	M	105.8	107.3	109.2	122.2	110.9
	SD	25.5	22.8	26.3	28.9	26.5
	N	79	81	83	77	320
50-59	M	114.4	126.5	119.6	134.9	123.7
	SD	24.1	31.3	32.3	29.5	30.4
	N	6	8	8	6	28
60-69	M	111.6	120.2	126.5	131.6	122.6
	SD	29.1	22.9	16.8	31.9	24.6
	N	191	188	192	180	751
Total	M	108.8	114.3	113.4	123.5	114.9
	SD	26.8	30.8	31.0	31.8	30.5

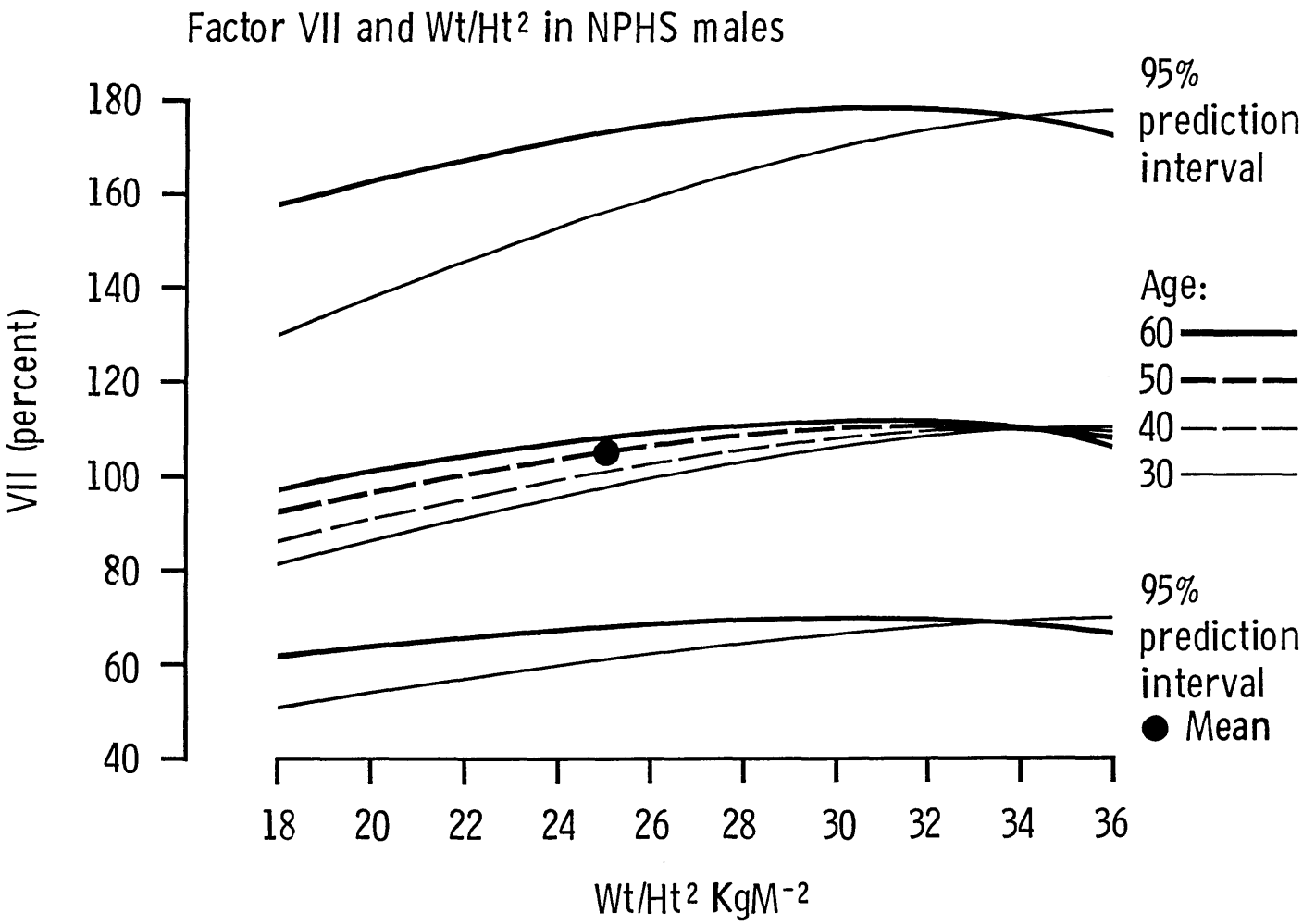

Factor VII and Wt/Ht² in NPHS males
VII (percent)
180
160
140
120
100
80
60
40
18
20
22
24
26
28
30
32
34
36
Wt/Ht² KgM⁻²
95% prediction interval
Age:
60
50
40
30
95% prediction interval
Mean

Figure 6

case of factors V and VII_c the results are shown by age and sex in Tables 19-22. Both factors V and VII_c show rises with age and obesity in males and females. The relationship between factor VII_c and obesity seems somewhat stronger than that for factor V and obesity especially in males. In the case of factor VII_c in males there is a significant interaction between age and obesity in the multiple regression analysis indicating that the association with obesity is stronger at younger ages ($p<0.02$). In addition there is a somewhat convex regression line of factor VII_c on W/H^2, just as with serum cholesterol, because of a quadratic relationship ($p<0.05$) between factor VII_c and W/H^2 (i.e. with $(W/H^2)^2$, figure 6. In the case of factor VII in males there is also an independent association with total skinfolds ($p<0.01$) when W/H^2 is taken into account. In view of the similarity between cholesterol and factor VII_c in their association with obesity, multiple regression analysis was performed with factor VII_c as the dependent variable and cholesterol, triglyceride, W/H^2 and those variables known to affect W/H^2 as independent variables. This showed that the independent association of factor VII_c and W/H^2 is highly significant ($p<0.001$) when all the other variables were taken into account. Both cholesterol and triglyceride are significantly associated with factor VII_c ($p<0.001$).

Table 23

Fibrinogen (mg/dl) and W/H^2 (males)
(Quartiles)

Age		1	2	3	4	Total
	N	72	72	71	69	284
<30	M	234.3	245.4	249.9	259.1	247.0
	SD	48.6	52.5	55.3	61.4	55.0
	N	68	66	70	66	270
30-39	M	250.2	258.1	269.5	274.3	263.0
	SD	52.4	55.4	60.8	54.7	56.5
	N	141	145	137	134	557
40-49	M	279.7	286.3	287.7	301.7	288.7
	SD	55.8	55.9	53.2	75.9	61.1
	N	161	169	167	166	663
50-59	M	315.3	313.6	311.3	317.6	314.4
	SD	75.7	70.2	65.1	58.8	67.6
	N	63	62	59	62	246
60-69	M	313.6	321.1	320.9	314.5	317.5
	SD	54.5	75.0	65.7	51.9	62.1
	N	505	514	504	497	2020
Total	M	285.0	290.4	291.6	299.0	291.5
	SD	68.6	68.4	64.3	66.2	67.1

Table 24

Fibrinogen (mg/dl) and W/H^2 (females)
(Quartiles)

Age		1	2	3	4	Total
	N	27	26	26	24	103
<30	M	264.0	270.5	258.9	283.1	268.8
	SD	52.6	63.0	78.9	97.5	73.7
	N	19	19	19	21	78
30-39	M	276.4	280.7	288.7	319.3	292.0
	SD	66.3	63.7	62.4	74.5	68.0
	N	61	58	56	53	228
40-49	M	266.8	284.6	292.4	316.1	289.1
	SD	51.2	46.8	66.3	56 7	57.9
	N	78	82	84	76	320
50-59	M	303.9	323.9	326.9	329.1	321.0
	SD	54.8	61.0	58.5	46.8	56.3
	N	6	8	8	6	28
60-69	M	346.0	326.6	351.0	368.7	346.7
	SD	73.6	30.2	56.6	74.2	57.6
	N	191	193	193	180	757
Total	M	285.0	300.7	305.0	319.3	302.3
	SD	58.5	60.4	68.5	64.4	64.1

Table 25

Fibrinolytic activity and W/H^2 (males)
(Quartiles)

Age		1	2	3	4	Total
	N	72	73	74	72	291
<30	M	41.0	39.2	36.5	28.4	36.3
	SD	14.0	23.0	16.3	14.7	17.9
	N	70	68	69	67	274
30–39	M	37.4	35.5	28.2	24.3	31.4
	SD	15.1	15.7	15.9	15.9	16.5
	N	138	140	136	138	552
40–49	M	33.7	30.1	24.8	23.4	28.0
	SD	16.4	15.9	15.8	15.3	16.3
	N	166	165	164	163	658
50–59	M	33.2	28.1	25.1	22.4	27.2
	SD	17.5	16.7	14.0	15.4	16.4
	N	60	61	60	59	240
60–69	M	30.6	34.4	26.6	24.2	29.0
	SD	14.9	23.3	14.1	17.2	18.1
	N	506	507	503	499	2015
Total	M	34.7	32.0	27.3	24.0	29.5
	SD	16.3	18.6	15.6	15.6	17.1

Table 26

Fibrinolytic activity and W/H^2 (females)
(Quartiles)

Age		1	2	3	4	Total
<30	N	29	26	26	24	105
	M	38.4	37.0	36.9	34.0	36.7
	SD	11.7	12.7	14.8	15.3	13.5
30–39	N	21	21	22	21	85
	M	42.8	29.5	35.6	29.7	34.4
	SD	19.3	16.2	21.3	13.0	18.3
40–49	N	62	59	60	56	237
	M	34.0	37.3	31.1	30.4	33.2
	SD	12.3	17.6	16.4	16.3	15.8
50–59	N	82	82	86	81	331
	M	35.2	34.4	27.5	24.4	30.3
	SD	17.7	15.9	12.2	15.1	15.9
60–69	N	6	8	8	6	28
	M	39.9	26.7	31.3	21.5	29.7
	SD	22.9	10.9	21.0	9.6	17.3
Total	N	200	196	202	188	786
	M	36.2	34.7	30.8	27.9	32.5
	SD	15.9	16.0	15.6	15.4	16.0

The standard regression coefficient for cholesterol is 0.153 and for triglycerides 0.209. The relationship between individual skinfolds and factor VII was examined using multiple regression analyses including all individual skinfolds (see Tables 27 and 28 for summary of association between individual skinfolds and cardiovascular risk factors). Subscapular and forearm skinfolds are associated with factor VII in males ($P<0.001$ and $p<0.05$, respectively) but the association only remains significant ($P<0.02$) for subscapular skinfold when W/H^2 is taken into account. In the case of females suprailiac and subscapular skinfolds are associated at a borderline level of significance ($p< 0.05$) with factor VII but these associations are no longer present when W/H^2 is taken into account.

In the case of plasma fibrinogen in males, the relation with obesity is only apparent in those under 50 (Table 23), in females it is present at all ages (Table 24). Plasma fibrinogen rises steadily with age in both sexes.

Fibrinolytic activity is inversely related to both age and W/H^2 in both sexes (Tables 25 and 26). There was no association between the difference in fibrinolytic acitivity between the pre and post exercise blood samples and W/H^2.

Table 27 Individual skinfolds and cardiovascular risk factors with and without W/H^2 in stepwise multiple regression analysis including all four skinfolds (Males)

	Skinfolds		Regression (95% C.L.) coefficient %/mm skinfold	Standard Reg Coefficient (in S.D. units per S.D. change in skinfold)	P value
SBP	Forearm	without W/H^2	5.1 (1.8- 8.3)	0.074	<0.01
		with W/H^2	4.0 (0.6- 7.4)	0.060	<0.05
	Suprailiac	without W/H^2	2.0 (1.0- 3.1)	0.090	<0.001
		with W/H^2	1.4 (0.2- 2.6)	0.063	<0.05
Cholesterol	Forearm	without W/H^2	7.6 (2.5-12.7)	0.082	<0.01
		with W/H^2	5.5 (0.4-10.6)	0.060	<0.05
	Subscapular	without W/H^2	4.1 (2.4- 5.7)	0.132	<0.001
		with W/H^2	2.2 (0.2- 3.9)	0.70	<0.05
Factor VII	Forearm	without W/H^2	6.7 (0.7-12.7)	0.058	<0.05
		with W/H^2	4.5 (-2.0-11.0)	0.039	n.s.
	Subscapular	without W/H^2	4.5 (2.3- 6.7)	0.115	<0.001
		with W/H^2	3.0 (0.6- 5.4)	0.060	<0.02
Fibrinogen	Suprailiac	W/H^2 not significantly associated when skinfolds included	3.7 (1.0- 5.2)	0.107	<0.01

Table 28 Individual skinfolds and cardiovascular risk factors with and without W/H^2 in stepwise multiple regression analysis including all four skinfolds (Females)

	Skinfolds		Regression (95% C.L.) coefficient %/mm skinfold	Standard Reg Coefficient (in S.D. units per S.D. change in skinfold)	P value
SBP	Subscapular	without W/H^2	2.6 (1.4-3.8)	0.134	<0.001
		with W/H^2	1.0 (-0.8-2.8)	0.051	n.s.
Cholesterol	Suprailiac	without W/H^2	3.7 (2.0-5.3)	0.142	<0.001
		with W/H^2	1.3 (-1.6-4.1)	0.049	n.s.
Factor VII	Subscapular	without W/H^2 (W/H^2 not significantly associated when skinfolds included)	3.4 (0.2-6.7)	0.099	<0.05
	Suprailiac	without W/H^2	3.3 (0.1-6.5)	0.099	<0.05
Fibrinogen	Subscapular	without W/H^2	4.4 (2.6-6.4)	0.162	<0.001
		with W/H^2	1.5 (-1.3-4.3)	0.055	n.s.

Association of individual skinfolds and cardiovascular risk factors

The association of the four cardiovascular risk factors (SBP, cholesterol, factor VII and fibrinogen) with fat distribution as measured by the individual skinfolds has been briefly outlined in the preceeding sections. The results are summarized in Tables 27 and 28 for males and females respectively. Multiple regression analysis was undertaken including all four skinfolds separately both with and without the inclusion of W/H^2. The values given in the table are for those skinfolds found to be significantly associated with the risk factors when all skinfolds were included in the regression analysis. In the case of males, both forearm and suprailiac skinfolds are independently associated with SBP, cholesterol and factor VII. The association is somewhat stronger with suprailiac (SBP) or subscapular (cholesterol and factor VII) than with forearm skinfold thickness. A further series of multiple regression analyses were performed including an interaction term for age and skinfold thickness to determine whether the association was stronger at different ages. These revealed a significant ($p<0.01$) interaction for age and forearm skinfold thickness in the case of serum cholesterol, indicating that the relation between forearm skinfold thickness and cholesterol was stronger in younger males. There is no

such relationship for factor VII or SBP. In the case of plasma fibrinogen in males suprailiac skinfold thickness is the only one of the four skinfolds independently associated. Amongst females only the central skinfolds, suprailiac and/or subscapular, are independently associated with the four risk factors. The inclusion of W/H^2 reduces and in some cases abolishes the association with the skinfolds in both sexes for most of the risk factors with the exception of plasma fibrinogen in males and factor VII in females. In these two cases the suprailiac and subscapular skinfold respectively explain more of the variance than W/H^2 which is therefore not included in the multiple regression.

In order to determine whether the lack of an independent association of peripheral skinfolds with cardiovascular risk factors in women is due to a closer intercorrelation between peripheral and central skinfolds in females than in males the intercorrelations between the individual skinfolds were examined. The strength of the associations are quite similar in both males and females and range from a correlation coefficient of 0.54 for triceps and subscapular skinfold in males to 0.62 in the case of forearm and subscapular skinfold also in males.

Table 29

Cross-sectional relationships with age and obesity in NPHS

		Wt/Ht^2 (% per kgm^2)	Age (% per year)
VII	Male	1.41 (1.05, 1.78)	0.40 (0.31, 0.49)
	Female	1.15 (0.64, 1.66)	0.67 (0.42, 0.92)
VIII	Male	0.34 (-0.16, 0.86)	0.59 (0.45, 0.73)
	Female	0.20 (-0.58, 0.99)	0.79 (0.52, 1.07)
Fibrinogen	Male	0.69 (0.38, 1.00)	0.67 (0.59, 0.75)
	Female	1.12 (0.70, 1.55)	0.30 (0.11, 0.49)
Cholesterol	Male	1.22 (0.94, 1.50)	0.40 (0.33, 0.48)
	Female	1.06 (0.70, 1.43)	0.63 (0.47, 0.80)
Systolic BP	Male	0.67 (0.48, 0.85)	0.40 (0.36, 0.45)
	Female	0.64 (0.38, 0.91)	0.53 (0.44, 0.62)

Regression coefficients (95% CI) for 2100 men and 800 women.

Overall relation of cardiovascular risk factors to obesity in the cross sectional data

The regression coefficients and 95% confidence intervals for the association of factor VII, fibrinogen, cholesterol and systolic blood pressure with W/H^2 and age are shown in Table 29. Factor VIII is included for comparison although no significant association with W/H^2 is present. The changes are expressed as % changes in the variable concerned per unit change in W/H^2 (i.e. per kg m^{-2}). This means, for example, that for a male with a factor VII level of 100% an increase of 1 unit in W/H^2 (equivalent to around 3kg for an average size male) would result in a 1.4% increase in factor VII level on average. Similarly for a female with a systolic blood pressure of 140 mm Hg a 1 unit increase in W/H^2 would result in an average increase in systolic blood pressure of 0.64% i.e. approximately 0.9 mm Hg. The regression coefficient for the effect of age on serum cholesterol in males is a considerable underestimate of the true relation in the younger males because serum cholesterol flattens off over age forty and the association between age and serum cholesterol is therefore markedly non linear. Similarly for factor VII in males the rise with age flattens off markedly over age 40 and the regression coefficient in the table is therefore an underestimate of the regression coefficient at ages under 40. In order to compare the relative effect of changes of W/H^2

Table 30

Standard regression coefficients
(Change in dependent variable in SD units per SD change in independent variable)

		W/H^2	Age
VII	Male	0.171	0.195
	Female	0.151	0.276
VIII	Male	0.026	0.175
	Female	0.018	0.212
Fibrinogen	Male	0.091	0.349
	Female	0.186	0.158
Cholesterol	Male	0.185	0.245
	Female	0.184	0.336
Systolic BP	Male	0.136	0.329
	Female	0.150	0.376

on the levels of these variables, standardised regression coefficients were also calculated (Table 30). These show rather similar results to the previous regression analysis except that the effect of W/H^2 on systolic blood pressure in comparison to its effect on the other variables was shown to be rather greater than using % changes. This is because the variance of systolic blood pressure somewhat lower than the other variables. The inclusion of the occupational groups in multiple regression analysis does not materially effect the relation of obesity with the cardiovascular risk factors.

Association of obesity with vascular disease detected at the entry examination.

At the entry examination 118 individuals were noted to have previously diagnosed hypertension, the majority of these were receiving treatment for this either from their general practitioner or a hospital. In addition there were 25 cases of intermittent claudication (19 males, 6 females) 42 cases of angina pectoris (35 males, 7 females), 17 possible (11 males, 6 females) cases of myocardial infarction and 42 definite cases (41 males, 1 female). The criteria used for diagnosis are given in the methods section. The mean age adjusted W/H^2 (to age 40) and total skinfold thickness in those who had no previous vascular event and those with different types

Table 31

W/H^2 (age adjusted) and prevalence of vascular disease at entry

Sex	No event	Hyperten-sion	Def IC	Def AP	Poss MI	Def MI	Total
	1920	87	19	35	11	41	2113
Male	24.647**	26.241**	25.313	25.042	24.877	25.152	24.716
	2.891	3.062	3.343	3.058	1.457	2.397	2.907
	791	31	6	7	6	1	842
Female	23.718	24.909	25.962	25.348	27.548	24.360	23.819
	3.372	3.498	2.374	3.146	7.294	00.000	3.427
Total N	2711	118	25	42	17	42	2955
Mean	24.376	25.891	24.469	25.093	25.820	24.157	24.461
S.D.	3.068	3.221	3.105	3.036	4.437	2.368	3.090

** P<0.001

Table 32

Total skinfolds (age adjusted) and prevalence of vascular disease at entry

Sex	No event	Hyperten-sion	Def IC	Def AP	Poss MI	Def MI	Total
	1917	87	19	35	11	41	2110
Male	42.094**	49.557**	46.863	45.097	40.429	41.671	42.477
	15.804	17.163	15.755	18.822	9.576	11.535	15.882
	787	31	6	7	6	1	838
Female	54.172*	62.483*	68.610	65.706	66.594	42.935	54.755
	19.367	22.010	18.186	29.357	29.908	00.000	19.727
Total N	2704	118	25	42	17	42	2948
Mean	45.609	52.953	52.082	48.532	49.664	41.701	45.967
S.D.	17.783	19.323	18.572	21.916	22.426	11.395	17.937

** P<0.001
* P<0.05

of vascular disease are shown in Tables 31 and 32. Only the hypertensives are significantly more obese than those with no vascular events. The difference is slighly more amongst the males than amongst the females.

Changes in weight over 6 year follow up.

In total complete data are available on computer (as of March 1984) on 1027 males and 416 females who have been examined on average around 6 years after entry. Incomplete data are available on a further 87 individuals. The response rate has been high amongst those requested to attend (over 80%) but cannot be exactly determined until recall for the follow up exam has ceased which will be towards the end of 1985. The results presented here for the follow up consist of workers at the food processing factory and telecommunications workers who were recruited into the study before the local government staff and were therefore recalled earlier. There was some variability in the time elapsed between initial exam and follow up which ranged from 5 - 7½ years in 95% of cases.

The mean increase in weight over the (on average) 6 year follow up was 1.4 kilos for men and 1.80 for women but there was a considerable range with considerable numbers gaining more weight and others losing weight. The outlying values were checked to exclude the

Table 33

Changes in weight and population characteristics of NPHS

	Men (n=1004)	Women (n=397)
Mean (kgs)	1.20 (0.13)	1.65 (0.23)
Gain in weight in kg per kg initial weight	0.046 (0.013)	0.13 (0.024)**
Age at entry (kgs per decade)	-1.06 (0.11)**	-0.64 (0.21)*
Stopping smoking (kgs)	+1.68 (0.43)**	+2.03 (0.61)**
Cigarette reduction (kgs per 10 cigs/day)	+0.62 (0.23)*	-
Alcohol increase (kgs per 20 gms/day)	+0.50 (0.15)*	-

Regression coefficients (Std Error)
* p< 0.01 ** p 0.001

Figure 7

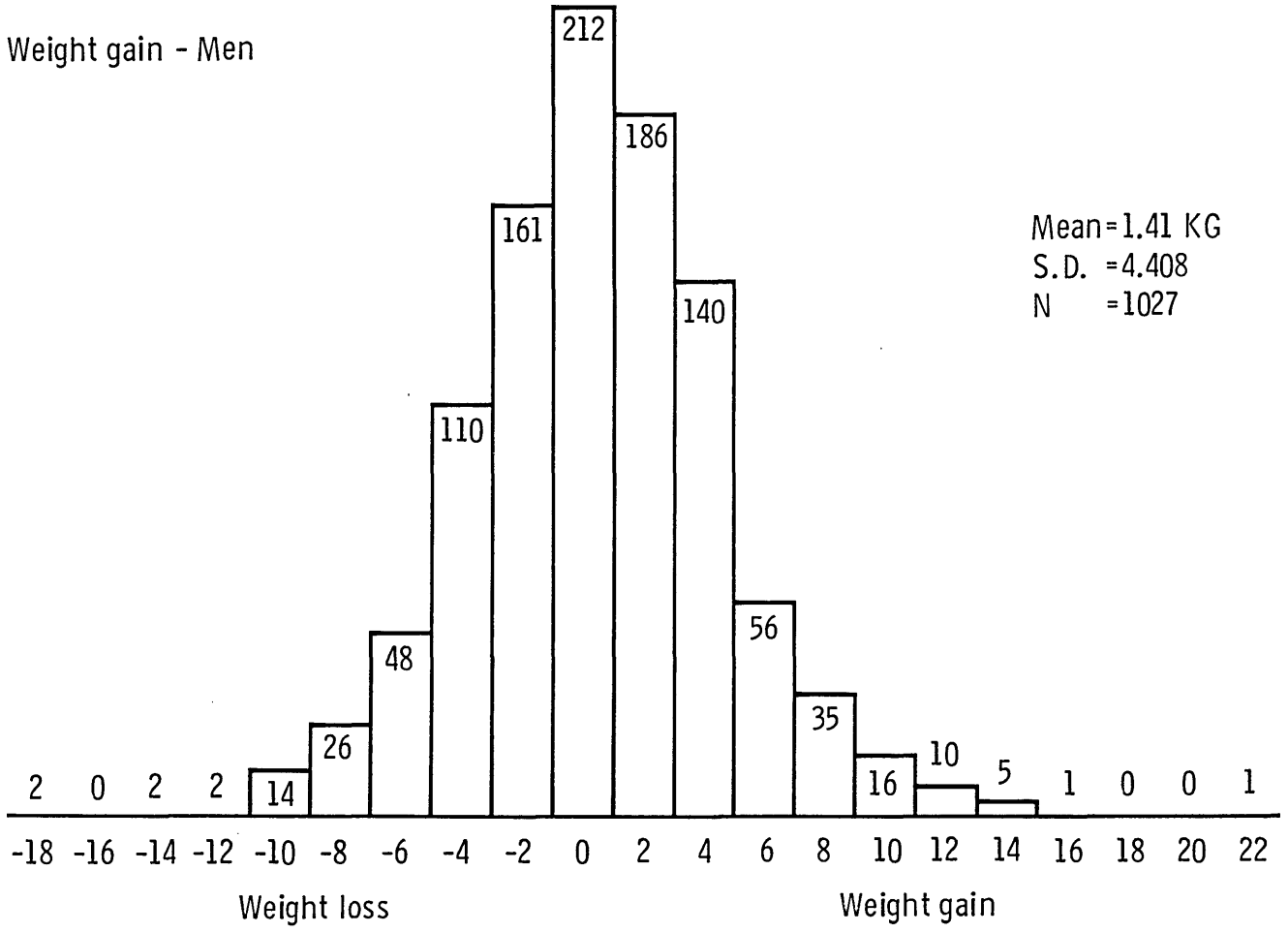
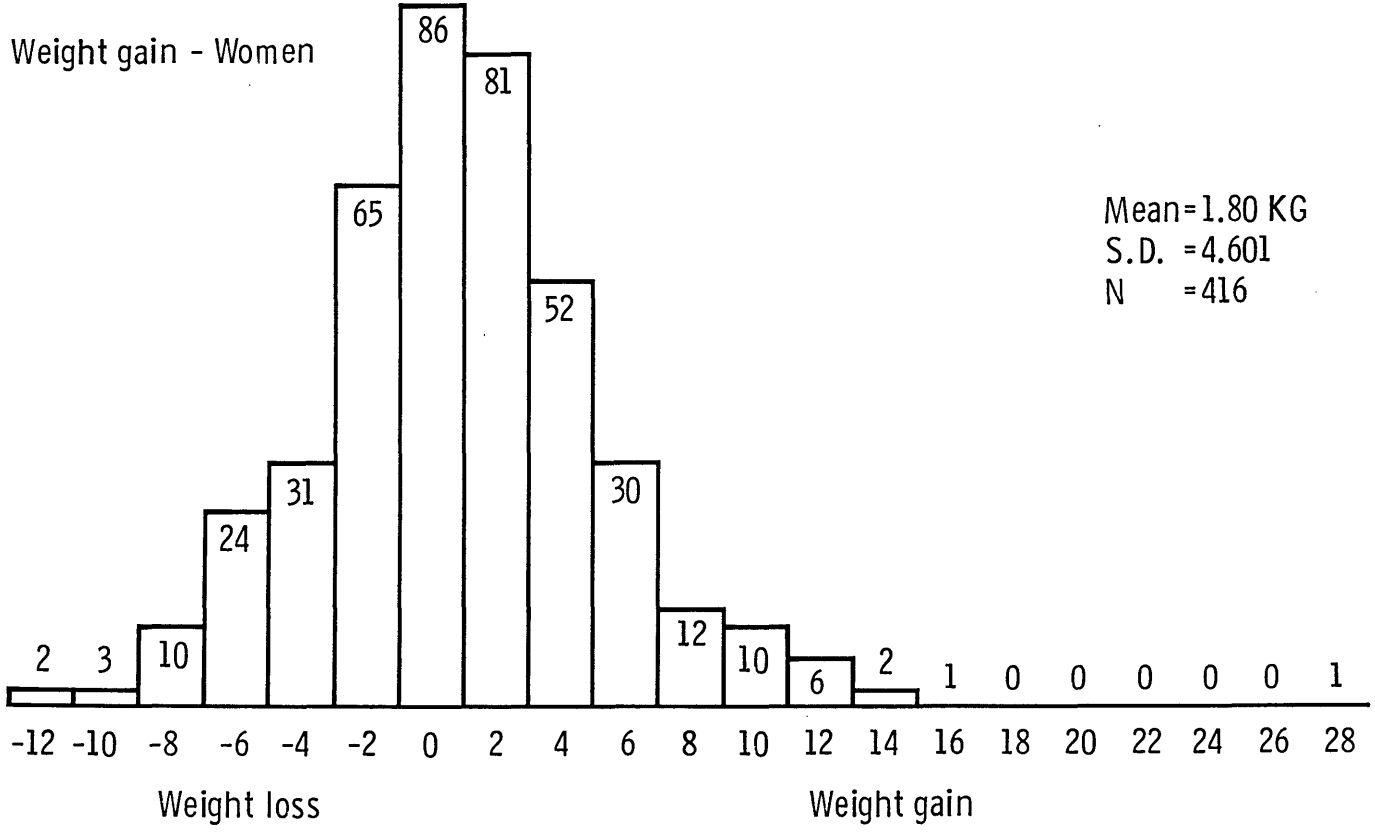

Weight gain - Men
Mean=1.41 KG
S.D. =4.408
N =1027
2 0 2 2 14 26 48 110 161 212 186 140 56 35 16 10 5 1 0 0 1
-18 -16 -14 -12 -10 -8 -6 -4 -2 0 2 4 6 8 10 12 14 16 18 20 22
Weight loss
Weight gain

Figure 8


Weight gain - Women
Mean=1.80 KG
S.D. =4.601
N =416
2 3 10 24 31 65 86 81 52 30 12 10 6 2 1 0 0 0 0 0 1
-12 -10 -8 -6 -4 -2 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Weight loss
Weight gain

possibility of coding errors. The differences between the two examinations for males and females are shown in the figures 7 and 8. The distributions around the mean for the two sexes are slightly skewed and range from 18.0 kilos weight loss to 22.4 kilos of weight gain for males and 12.0 and 28.2 kg respectively in the case of females.

Certain characteristics were found to be related to weight changes (Table 33). The mean differences given in this table do not take into account changes due to the 4 factors listed below in the table. The table shows that those who were fatter at entry tended to gain more weight over the follow up period. This was more pronounced in females than males. In both males and females age at entry was negatively associated with weight gain such that weight gain was less by a mean of 1.06 kg per decade (males) and 0.64 kg per decade (females). Stopping smoking was associated with around 2 kg weight gain. An increase alcohol consumption in males was also associated with weight gain as was a reduction in cigarette consumption. The changes in total skinfold thickness over time were also examined, however it was found that a consistent rise in mean skinfold thickness had occurred over the years since the beginning of the study. This is probably due to progressive weakening of the spring on the skinfold

calipers which lead to progressively less compression of the skinfolds over time and therefore a higher reading. Although it is possible to adjust for a steady change of this type such a tendency complicates interpretation of results and the changes between the two measurements have therefore been expressed in terms of weight changes. No systematic change in weight occurred over the duration of the entry examination (1972-78) or follow up suggesting that no consistent change in measurement over time was occurring. Minimal changes in height occurrred over the six year period (mean 1 mm fall in men and 3.5 mm fall in women) it was therefore unnecessary to express changes in obesity as changes in W/H^2.

Longitudinal relationships between weight change and change in cardiovascular risk factors.

In order to determine whether changes in weight between the two examinations were associated with changes in cardiovascular risk factors, multiple regression analyses were performed with the following as the dependent variable; factors VII and VIII, fibrinogen, cholesterol and systolic blood pressure. The independent variables in this series of multiple regression analyses were as follows; weight change, age at entry, smoking change, oral contraception and menopause (for females), initial level of variable under

examination, initial weight and height, the standards used in the assay of the coagulation factors, the three main occupational groups, day or night shift (for food processing workers only), initial skinfold thickness and social class. Fibrinolytic activity was not included in this analysis, both because it has not been consistently related to IHD in NPHS or other studies and because a progressive fall in fibrinolytic activity has taken place over the duration of the study for as yet unknown but presumably methodological reasons. The effects of aging within an individual have not been presented. The mean difference for the cohort between recruitment and the 6 year follow up may be biased by variations over time in measurements - e.g. observers may change their blood pressure measurement technique, standards for clotting factors change and other changes in laboratory methods may occur which may not be obvious but which may result in appreciable alteration in results. Differing lengths of follow up between individuals could allow an assessment of the aging effect, however in NPHS nearly all the participants followed up were seen between 5 - 7½ years - this is too small a range to allow useful estimates.

The longitudinal relationships of the five cardiovascular risk factors with weight change are shown in Table 34 expressed as % change from the entry value

Table 34

Longitudinal relationships with weight changes between entry and follow up in NPHS

		% change in baseline value per kg change in weight	Standardised Reg Coeff
VII	Male	0.90 (0.51, 1.29)***	0.142
	Female	0.82 (0.18, 1.48)**	0.124
VIII	Male	0.34 (-0.23, 0.93)	0.03
	Female	0.25 (-0.74, 1.25)	0.02
Fibrinogen	Male	0.11 (-0.22, 0.44)	0.01
	Female	0.21 (-0.27, 0.68)	0.05
Cholesterol	Male	0.86 (0.62, 1.09)***	0.236
	Female	0.46 (0.08, 0.84)*	0.126
Systolic BP	Male	0.57 (0.40, 0.74)***	0.195
	Female	0.36 (0.08, 0.63)**	0.120

Regression coefficients (95 % CI) for 1000 men and 400 women
*p<0.05, **p<0.01, ***p<0.001

of the variable per kg body weight change between the two examinations. Standardised regression coefficients. are also given to enable comparison between the relative effect of standard change in the variable in question on weight change expressed as standard deviation units of change in the variable per standard deviation unit of weight change. The change in factor VIII and fibrinogen with weight change is not significantly different from zero in both sexes. In the case of fibrinogen this differs from the cross-sectional data which shows a consistent association of fibrinogen with W/H^2. Changes in factor VII, cholesterol and systolic blood pressure are significantly associated with weight change in both sexes. Standardised regression coefficients tend to be larger for males than females in the case of these three variables. There is no association between the time elapsed between the two examinations (i.e. change in age) and the amount of weight gained.

Although comparison of the cross-sectional and logitudinal data is complicated by differences in measurement between the two examinations it does appear that the relationship between weight change and factor VII, cholesterol and systolic blood pressure is greater in the case of the longitudinal than the cross-sectional data. In the cross-sectional data the association has been expressed in terms of W/H^2. For a male of average

Table 35

W/H^2 and death in NPHS 1518 white men aged 40-65
Means of age-adjusted (to age 50) W/H^2

	Survivors	IHD	Cancer	Other (inc. CVD) non-IHD
Mean	25.45	26.3	25.1	25.3
SD	2.9	3.6	2.9	3.0
N	1402	54	42	18

height, one unit of W/H^2 3.0 kg and for females 2.5 kg. It can be seen that the change in factor VII, cholesterol and systolic blood pressure for a given change in obesity is somewhat greater in the case of the longitudinal data than the cross-sectional. The confidence limits however overlap for all but the cholesterol and systolic blood pressure in the case of the males only. Skinfold changes are not significantly associated with changes in any of the risk factors when allowance for weight change is made . The effect of weight gain appears the same at all ages with SBP in males a possible exception. ($p = 0.05$, stronger association at younger ages.)

Mortality and obesity

Mean W/H^2 in survivors, cases of fatal IHD, cancer deaths and other causes of death are given in Table 35 for white males aged 40-65. In view of the small number of women in the study the numbers of deaths are insufficient for statistical analysis. The mean W/H^2 of the fatal IHD cases is considerably higher than that for the survivors which is in turn slightly higher than that for cancer deaths.

There is little difference in the mean W/H^2 for other deaths. The distribution of the deaths in terms of tertiles of W/H^2 is shown in Table 36 for IHD deaths

Table 36

Distribution of age-adjusted W/H^2 by tertiles,

		Mean	Low	Middle	High	Total
Survivors,	aged 40-59	25.5	398	404	409	1211
	60-65	25.3	70	58	63	191
	total	25.5	468	462	472	1402
IHD deaths,	aged 40-59	26.7	9	12	15	36
	60-65	25.6	3	8	7	18
	total	26.3	12	20	22	54

Table 37

Distribution of age-adjusted W/H^2 by tertiles,

		Mean	Low	Middle	High	Total
Survivors,	aged 40-59	25.5	398	404	409	1211
	60-65	25.3	70	58	63	191
	total	25.5	468	462	472	1402
Cancer	aged 40-59	26.0	7	7	8	22
deaths,	60-65	24.2	10	8	2	20
	total	25.1	17	15	10	42

Table 38

Logistic regression of mortality and W/H^2

	Logistic regression coefficient (s.e.) p-value		Relative risk of 1 $kg\,m^{-2}$ W/H^2 increase at different W/H^2 values
	W/H^2	$(W/H^2 - 25)^2$	
IHD death:	0.119 (0.046) p=0.009	-	1.13 overall (1.03-1.26) 95% C.L.
	0.076 (0.050)	0.011 (0.007) p=0.13	20: 0.98 22: 1.02 24: 1.07 26: 1.11 28: 1.16 30: 1.21

Table 39

Logistic regression of mortality and W/H^2

	Logistic regression coefficient (s.e.) p-value		Relative risk of 1 $kg\,m^{-2}$ W/H^2 increase at different W/H^2 values
	W/H^2	$(W/H^2 - 25)^2$	
All deaths (n=114)	0.054 (0.034) p=0.11	-	1.06 overall
	0.037 (0.036)	0.007 (0.006) p=0.27	20: 0.98 22: 1.00 24: 1.03 26: 1.06 28: 1.09 30: 1.12

and survivors and Table 37 for cancer deaths and survivors. The W/H^2 is age adjusted to age 50 to remove the confounding effect of age on comparisons of W/H^2. It can be seen that amongst IHD deaths a consistently greater number are found in the upper two tertiles of W/H^2 than in the lower tertiles. The mean W/H^2 is somewhat higher amongst the fatal cases of IHD aged less than 60 compared with the older IHD deaths. In the case of cancer deaths the converse applies in males aged 60-65. Logistic regression of W/H^2 and IHD mortality taking age into account showed a statistically significant association ($p= 0.009$) (Table 38). Increasing W/H^2 by 1 kg m^{-2} would result in an increase in relative risk of fatal IHD of 1.13 overall. The increase in relative risk for a 1 kg m^{-2} increase in obesity at different values of W/H^2 is also given in the table. A similar analysis in the case of total mortality is shown in Table 39 which, as expected, does not reveal a significant association. The inclusion of a quadratic term $(W/H^2 - 25)^2$, where 25 is the approximate mean W/H^2 for males, does not show any significant quadratic relation between W/H^2 and mortality in either table.

For those 46 males who died of IHD and for whom data was available on other risk factors namely, cigarette smoking, blood pressure, serum cholesterol,

factor VII and fibrinogen, univariate and multivariate logistic regression analyses were performed also taking age and date of interview into account to determine whether the relation between W/H^2 and mortality was due to its association with other cardiovascular risk factors. These analyses showed that W/H^2 is independently associated ($p = 0.03$) with IHD death when the other variables were taken into account. The regression coefficient is only slightly reduced (from 0.126 to 0.106) in the multivariate compared with the univariate analysis. The 8 males on whom data was incomplete were slightly leaner (mean $W/H^2 = 25.8$) than the whole group of IHD deaths ($n = 54$), (mean $W/H^2 = 26.3$).

Restricting the analysis to those deaths occurring within 5 years of recruitment (24 IHD deaths in males) resulted in there being no significant univariate association between IHD death and W/H^2. The weighting for W/H^2 in multivariate logistic regression analysis of the 24 IHD deaths in males is 0.069 ($p = 0.3$).

Triglycerides were not associated with IHD mortality in either univariate or multivariate analysis. There is no relation between total skinfolds and death when W/H^2 was taken into account. Logistic regression analysis of mortality in relation to the four individual

skinfolds showed that when age and length of follow up are taken into account there is no significant relation between any of the four skinfolds and IHD mortality. Subscapular skinfold is the most closely related but the association did not reach conventional levels of significance (p=0.07).

Table 39b

Relation between individual skinfolds and fatal IHD, Logistic regression analysis

Skinfold	Estimated change in relative risk per mm change in skinfold thickness	t value	p value
Forearm	1.0185	0.18	0.9
Triceps	1.0605	1.21	0.2
Subscapular	1.0632	1.81	0.07
Suprailiac	0.9470	1.37	0.2

Comments on study design and interpretation of data

NPHS is based on the study of participants recruited through their workplace and the study population cannot therefore be said to be representative of the general population. It is well known that occupational groups are likely to contain less chronically ill, physically disabled and mentally disturbed individuals than random samples of the general population. The mortality of working populations tends to be lower than that of the general population - the 'healthy worker' effect. The NPHS study population also includes women and individuals of various ethnic groups (particularly black West Indians). The number of white males in the age group likely to produce cases of fatal IHD is only around 1500 although the total study population is around 3500. The relatively small size of the study and the possible selection biases operating as a consequence of the use of occupationally based groups of participants must be borne in mind when interpreting the results.

In addition to these selection biases NPHS, like every other study, is open to potential bias from the failure to recruit a proportion of individuals who were eligible (non response bias). The estimated response

rate of around 80% was in the range generally agreed as acceptable but any level of non response introduces some uncertainty as to how representative the results are of the study population as a whole. A further potential souce of bias arises during the follow up of a population since it is unlikely that repeat measurements will be obtained on all individuals.

In the case of the longitudinal data presented in this thesis, analyses were performed on data from 1027 males and 416 females. Individuals were recalled in the order in which they were recruited and the longitudinal data presented in this thesis are therefore derived largely from the employees at the food processing company at both Harlesden and Hayes who were recruited before the other two occupational groups. The response rate for the second interview and examination was 80% at the time that these analyses were undertaken. There are several potential reasons for failure to return for a second examination. Very few (3%) participants in this study have been totally lost to follow up in that no information at all is available about them, a further 7% died before their follow up appointment and are obviously not included amongst non respondents to follow up.

One of the reasons for failure to attend follow up is that individuals have moved to other parts of the country. Some of these individuals have been visited at home by a trained nursing sister involved with the study, others have been persuaded to attend Northwick Park Hospital. Out migrants from any study population represent a selected group which in this case may include individuals who have left work for health reasons and retired prematurely as well as healthy migrants who have left for family or economic reasons. Despite these caveats concerning the possible impact of various forms of bias on the interpretation and implications of the data reported in this thesis there are several reassuring features which suggest that although the population studied is not representative of the UK population as a whole nevertheless the findings are of relevance to the study of the role of obesity in cardiovascular disease and to the formulation of public health recommendations.

The mortality data from the study are of high quality with all participants having been tagged at the National Health Service Central Registry and all assessments of the cause of death having been performed by independent assessors blind to the laboratory results. Notifications are received on a regular 3 monthly basis are therefore up to date.

Those variables found to be associated with obesity cross-sectionally are also associated in the longitudinal data with the exception of plasma fibrinogen in both sexes which is associated with W/H^2 in the cross-sectional analysis but not in the longitudinal. The possible reasons for this are discussed later. Given the differences in the measurement of blood pressure between the first and second examinations and the change in the method used for the determination of serum cholesterol, the consistency of the associations in the two analysis is strong evidence of a true association.

The principal aim of the study was to determine prospectively the association between haemostatic variables and subsequent cardiovascular disease rather than to provide a population which could be said to be representative of the country (or the local community) as a whole. However it could be argued that a population had been selected in which the association between a given risk factor (in this case obesity) and the endpoint (fatal IHD), or between the various risk factors themselves, were atypical. Comparisons between the occupational groups recruited did not however suggest any differences between them in the associations between obesity on the one hand and haemostatic variables, cholesterol and blood pressure on the other. The associations between cholesterol, blood pressure and obesity were similar to those found in other studies (for discussion see later).

Some individuals were found to have evidence of pre-existing IHD at the initial examination (see Tables 31 and 32) and have been included in the follow up and in the mortality data. Under 20% of those who died of IHD (9 of 54) had evidence of previous IHD at entry to the study.

Patients who have clinical IHD may of course undergo changes in lifestyle and therapeutic interventions which may alter their risk profile. Nonetheless in view of the small numbers of cases of fatal IHD available for analysis I felt that it was undesirable to remove those with previous IHD from the analyses without a very strong a priori reason. Recently the British Regional Heart Study, which studied over 7000 men in 24 towns, showed that the differences in risk factors between patients who developed subsequent myocardial infarction or died suddenly and those who did not were of similar magnitude irrespective of whether they had a previous history of IHD. Only serum cholesterol was however a statistically significant risk factor in those who have pre-existing IHD at entry (Shaper et al 1985).

Previous history of IHD is itself a strong risk factor for subsequent events so that the proportional effect of other risk factors may be less in those patients. If this is so, by including prevalance cases

of IHD I may have slightly underestimated the potential contribution of obesity to subsequent IHD but the effect in this data set is likely to be minimal as the numbers are small.

The British Regional Heart Study also found that the differences in risk factors in those who had pre-existing IHD at entry and those who did not were small and of considerably lower magnitude than the difference between those who developed myocardial infarction and sudden death during the follow up and those who did not. Similarly, in NPHS the difference in W/H^2 between prevalence cases of MI and those without IHD at entry is smaller than that observed between the incidence cases and those who did not die of fatal IHD during follow up and is not statistically significant. This observation is also discussed later (p 184-185).

The follow up of the NPHS population is quite variable due to the long period of recruitment (1972-78) necessitated by the time consuming nature of the tests for the haemostatic variables which made it impossible to recruit more than six or so participants at any one time. At the time of the data analysis on which this thesis is based the mean length of follow up was around 7.75 years and varied from 5.75 to 11.75 years. Thus only a minority of participants had been followed up for more than 10 years. Since several studies have shown

that the effect of obesity on cardiovascualar risk may be more marked on prolonged follow up (Hubert et at 1983, Rabkin et al 1977) future anlayses may reveal a stronger association than that described here.

Chaper 4

Discussion

Measures of obesity - comparison with other studies

Comparison of obesity in NPHS participants with other studies is made difficult by differences in measurement between studies and the variety of indices of obesity used in the past. In addition NPHS is not a random sample of the general population but comprises three main occupational groups. It is likely that the massively obese and those with chronic disease leading to major weight loss are underepresented because such conditions would impair their likelihood of obtaining and continuing in employment. Some studies have recorded weights from participants wearing jackets and shoes (Metropolitan Life Insurance Company 1959, Kemsley 1952), these items of clothing may contribute around 6lbs. in weight. Nevertheless some comparisons can be made with previous studies in the U.K. Table 40 shows a comparison of results for males from several UK studies.

The participants in NPHS were considerably more obese than those in the 1930 National Survey (males only) and the participants in the 1943 National Survey (males and females) (Cathcart, Hughes and Chalmers 1935, Kemsley 1950).

Table 40

Mean values for the weight-height index (W/H^2) of men in different surveys undertaken in the UK during the last 50 years

Year of survey	Group	Age (years) 20–25	35–40	55–60
		W/H^2	W/H^2	W/H^2
1930	National	21.3	22.8	23.3
1943	National	21.8	22.7	24.6
1960	Birmingham	22.8	24.9	24.9
1965	Port Talbot	24.3	26.2	26.2
1969	Directors	-	25.6*	26.0*
1971	BP Employees	22.5	24.3+	25.4+
1974	Richmond	22.6"	24.9"	24.7"
1980	National	23.0	24.7	25.2

Weight in kg; height in metres

Adapted from DHSS/MRC 1976

* Middle age group, 35–44 years; upper age group, 55–64 years

\+ Age group, 30–39 years; upper age group, 50–59 years

" Lower age group, 15–29 years; middle, 30–49 years; upper, 50–65 years

Studies which have been undertaken since 1960 however show similar results to NPHS. The study undertaken in 1965 by Lowe et al (1968) on over 10,000 Port Talbot steel workers showed that they were somewhat more obese than the NPHS participants but the differences were quite small, for instance the steel workers aged 55-60 (all male) had a mean W/H^2 of 26.2 compared with 25.6 for the males aged 50-59 in NPHS. Differences of similar magnitude were observed throughout the age range. A sample of over 5,000 men employed at an electrical engineering works in Birmingham in 1960 (Lowe and McKeown 1962) yielded somewhat lower mean values for W/H^2 at all ages varying from 22.8 in males aged 20-25 to 24.9 in those aged 55-60. The NPHS results for males lie between the values from these two studies.

The NPHS participants were somewhat more obese overall than the participants in the study in the London Borough of Richmond (McLean Baird et al 1974) of individuals aged 15-64. In that study the mean W/H^2 was 24.3 for males and 23.9 for females compared with 25.1 and 24.4 respectively in NPHS participants. Amongst males both those aged under 30 and those over 50 seem more obese in NPHS than in the Richmond study (mean W/H^2 23.6 vs 22.6 and 25.5 vs 24.7 respectively), the difference is only marginal however in the middle aged

Table 41

Mean values for the weight-height index (W/H^2) of women in three surveys undertaken in the UK

Year of survey	Group	Young adult* age	Early middle+ age	Late middle"
		W/H^2	W/H^2	W/H^2
1943	National	20.7	22.5	23.6
1971	BP Employees	21.6	22.9	25.9
1974	Richmond	21.6	23.7	25.1
1980	National	22.7	23.9	25.4

Weight in kg; height in metres

* Adapted from DHSS/MRC 1976
+ Young, 20–25 or 20–30 years
+ Early middle age, 30–49 or 35–40 years
" Late middle age, 50–65 or 50–60 years

men. The response rate for the Richmond study was only 36% but a random sample of non respondents was visited at home and their weights and heights recorded. The male non respondents appeared to be of similar obesity to the respondents but amongst the female respondents the obese were somewhat over represented. The results from a study of over 10,000 (7,400 of whom were males) B.P. employees between 1964-1966 were very similar to those of male NPHS participants (Montegriffo 1968). A study of directors published in 1969 yielded somewhat higher levels of W/H^2 than NPHS, for instance in the age group 35-40 mean W/H^2 was 25.6 in the Directors study and 24.4 in NPHS (Richardson and Pincherle 1969) The distribution of W/H^2 in the Civil Servants study (Reid et al 1976), which comprised males aged 40-64, was very similar to males of the same age in NPHS.

In the case of women information is rather more scanty than for men (Table 41). NPHS females are considerably more obese than female participants in the 1943 National Survey (e.g. W/H^2 22.3 vs 20.7 for women aged <30, similar differences throughout the age range). Later studies, on B.P. employees and in Richmond, gave similar results to NPHS except that young women (<40) in NPHS were slightly more obese than young women in the other two studies. The evidence from studies in the UK suggests that after 1960 no consistent changes in

obesity have occurred in adults in the UK, although there may be some increase in obesity occurring in young women according to NPHS and the 1980 National survey (Office of Population Censuses and Surveys 1981). Compared to the first half of the century there has been a considerable increase in obesity in both males and females. Data from the USA show that Americans tend to be more obese than Europeans (Keys et al 1972). The NPHS results are very similar to those in 10,000 Israeli Civil Servants (Goldbourt and Medalie 1974).

The pre-war data show a steady rise in obesity with age in males until about age 60 but in post war studies obesity increases considerably with age until about 35-40 (Table 40) and then flattens off. In NPHS W/H^2 flattens off in the 40-49 age group compared with the rise at younger ages and reaches a peak at around 55 years. In females the increase in obesity with age continues to a somewhat later age in all the four major UK surveys (1943 National, BP Employees, Richmond and 1980 National) and in NPHS. Since these studies are cross sectional and not longitudinal there are difficulties in deciding whether the changes in obesity with age represent the effects of aging alone or result from differing levels of obesity in different birth cohorts. There is a dearth of data on large groups of individuals in the UK with measures of obesity recorded

on several occassions spread over long periods of time. Studies from other countries have indicated a tendency for increasing obesity in individuals with age. For instance a study in Goteborg, Sweden (Larsson 1978) which studied 718 men born in 1913 both in 1963 (50 years of age) and 1973 (60 years of age) showed that the men gained an average of 1.8 kg over the decade and that 7.7% gained more than 10 kg. The mean value for weight gain was normally distributed. In contrast a comparison of the 50 and 60 year old men from a cross sectional study in the same population showed no difference in obesity between the two age groups. Thus at least some of the flattening in mean levels of obesity with age may be due to older birth cohorts being less obese than younger. Another possible contributing factor could be a selective increase in mortality of obese individuals from middle age onwards. However as will be discussed later this is unlikely to account for much of the observed flattening with age.

The longitudinal data from NPHS show that both males and females tended to gain weight between the two examinations but those who were older tended to gain less weight than younger participants. This could account at least in part for the observed flattening of W/H^2 with increasing age in the cross-sectional data.

Relation of W/H^2 with skinfolds

There is a close relationship between W/H^2 and skinfolds overall but women have a greater total skinfold thickness for a given level of W/H^2 than men. Females tend to have a higher percentage of body fat than males.

Other large studies have generally measured one or two skinfolds only - frequently triceps and subscapular. Although they provide a more direct measure of body fat than W/H^2, skinfold thickness measurements suffer from the disadvantage of considerable observer variability even when precautions are taken to standardise measurement technique. For instance displacement of the site of measurement for triceps skinfold by 2.5 mm from the mid point can alter readings by as much as 25% (Ruiz et al 1971). Other surveys using several observers have recorded considerable between observer differences in measurement, e.g. the Ten State Study in the USA (Lohmann 1981) recorded observer differences of as much as 13 mm in triceps skinfold measurement in normal subjects. In NPHS, as well as the observer differences that were detected, there was a tendency for a steady change in total skinfold thickness over time which was probably due to instrument error. The calipers used in

the study have since been returned to the manufacturers for checking and it is possible that a progressive weakening of the caliper spring with continued use resulted in less pressure being applied to the skinfold and therefore a higher reading. The observer differences and constant changes over time can be taken into account by multiple regression analysis but their presence adds to the complexity of data analysis and interpretation.

In NPHS the relation between subscapular skinfold and W/H^2 was closer for all observers and in both sexes than for any of the other skinfolds. In particular the relationship was weaker for the limb skinfolds (forearm and triceps). Similar results have been reported from other studies (Carlsson 1978, Goldbourt and Medalie 1974). This may, in part at least, be due to the fact that a higher proportion of subcutaneous body fat is carried on the trunk than on the arms and that this proportion increases with increasing obesity. Women have a more even distribution of subcutaneous fat than men.

The relation between total skinfolds and W/H^2 in NPHS males is slightly concave upwards and tends to decrease with age. Amongst males about 53% of the total variance in total skinfolds is accounted for by W/H^2 and

about 64% amongst females. The partial correlation coefficient for skinfolds and W/H^2 is 0.75 in both sexes.

In the study of men in Goteborg (Carlsson 1978) there was a correlation of around 0.7-0.8 between body fat, as measured by total K40 determinations on the one hand and W/H^2 on the other, in three groups of men aged 30, 50 and 60. For the sum of subscapular and triceps skinfolds the correlation with body fat was very similar.

Although it has been suggested that skinfolds may give a more accurate estimate of body fat than W/H^2 (Durnin and Womersley 1974) the practical advantage of measuring skinfold thickness, at least in studies of cardiovascular risk in Western populations, seems equivocal as judged by NPHS and other studies. In fact in NPHS the association of obesity with cardiovasular mortality is particularly with W/H^2.

Other workers have found that, in females at least, body weight correlated somewhat more highly with body fat mass ($r = 0.90$) than with the sum of triceps and subscapular skinfolds ($r = 0.77$). Multiple regression analysis incorporating these two variables and buttock circumference showed that all three variables made

independent contributions to the prediction of body fat mass and that they accounted for between 80-90% of the variation in body fat mass in the age strata studied (44, 52, 56, 60 and 66 years of age). (Noppa et al 1979).

In children the correlation between triceps skinfold and weight adjusted for height increased from 0.5 at age five to nearly 0.7 at age 11 with some curvature in the relation. There was a closer relation for heavy than for light children (Morris and Chinn 1981).

The use of W/H^2 allows easier comparison with other studies and largely avoids the problem of observer variability whereas skinfold thickness gives information about the distribution of subcutaneous fat as well as being a measure of obesity. In general there seems to be no consistent advantage of one over the other in determining the association of cardiovascular risk factors with obesity and the simplicity of measurement of weight and height make W/H^2 a particularly valuable measurement for epidemiological studies.

The association of individual skinfolds with cardiovascular risk factors and mortality

Several studies have shown that fat laid down in adulthood tends to accumulate on the trunk rather than on the limbs (Vague 1956, Ashwell et al 1978). In NPHS this was particularly obvious for males but amongst the females the ratio of limb to trunk skinfolds increased moderately until early middle age (40-49), thereafter no consistent changes were observed. Moderate adult onset obesity is associated with fat cell hypertrophy rather than hyperplasia although hyperplasia may develop in adulthood if the fat deposition is sufficient (Hirsch and Batchelor 1976). Fat cell hypertrophy in the abdominal region has been associated with hyperlipidaemia (Bjorntorp and Sjostrom 1971, Kissebah et al 1982). The menopause has also been said to result in the deposition of more fat centrally (Edwards 1951).

In NPHS both triceps and suprailiac skinfolds were significantly greater in post than pre menopausal women when age was taken into account.

A recent report in which triceps and subscapular skinfolds were examined in relation to blood pressure in the data from the First U.S. Health and Nutrition Examination Survey (HANES), showed that subscapular skinfold was a better predictor of blood presure than

triceps (Blair et al 1984). However the authors did not determine whether either skinfold was significantly associated with blood pressure when W/H^2 was taken into account. The results from NPHS show that although in males both forearm and suprailiac skinfold thickness have independent associations with systolic blood pressure these are considerably weakened when W/H^2 is introduced into the multiple regression equation. Triceps skinfold has no independent association with blood pressure when the other skinfolds are taken into account. In the case of women the association is strongest with subscapular skinfold and is no longer significant when W/H^2 is included. In the case of serum cholesterol in males, forearm and subscapular skinfold thickness are independently associated but when W/H^2 is included in the multiple regression analysis the relationship is considerably weakened and is of borderline statistical significance. Overall the individual skinfolds contribute very little to the relation of the four cardiovascular risk factors (SBP, cholesterol, factor VII and fibrinogen) with obesity over and above W/H^2. Two possible exceptions are plasma fibrinogen in males (suprailiac alone) and factor VII in females (subscapular and suprailiac) for which skinfolds contribute somewhat more of the variance in the multiple regression analysis than W/H^2.

The data from NPHS suggests that central obesity is of greater importance than peripheral subcutaneous fat in determining cardiovascular risk factors in females. In males for 3 of the 4 risk factors found to be associated with skinfolds, both forearm skinfold (peripheral fat) and either subscapular and suprailiac (central fat) make independent contributions although the association is somewhat stronger with central fat. The independent contribution of forearm skinfold in males does not seem to be due to more accurate measurement of forearm skinfold compared with triceps since the correlations of both with W/H^2 are similar for all three observers. The independent contribution of forearm skinfold to cardiovascular risk factors in males is perhaps surprising in view of the observation that in males the ratio of central to peripheral skinfolds increases somewhat with age (at least up to age 40) suggesting that fat acquired in adult life is being laid down to a greater extent centrally than peripherally. Of the three risk factors significantly associated with forearm skinfold thickness only in the case of serum cholesterol is the relation significantly stronger in younger males. It is of course possible that populations differ in their relation between the distribution of body fat and cardiovascular risk factors. Much of the work in this area up to now has been in N. America and Scandinavia. Longitudinal

studies may help to illuminate the relative importance of cental and peripheral fat but they are likely to be complicated by difficulties in making reproducible measurements over long periods of time using several observers.

Recently, publications from Goteborg, Sweden have indicated that the ratio of waist to hip circumference was associated with an increased risk of ischaemic heart disease and stroke in men (Larsson et al 1984) and women (Lapidus et al 1984) after 13 and 12 years of follow up respectively. Triceps, subscapular and parathoracic were the three sites at which skinfold measurement was made in the Goteborg study. No association was found between IHD and individual skinfolds but the investigators did not measure suprailiac skinfold. In NPHS subscapular skinfold was the most closely related of the individual skinfolds to IHD mortality but the association was not statistically significant at conventional levels of significance.

Waist and hip circumference were not measured in NPHS, it is therefore impossible to compare the two studies directly. Assessment of the comparative predictive value of individual skinfolds and waist/hip ratio may be complicated by the possibility of greater observer error in the case of skinfold measurements.

Both NPHS and the Goteborg study suggest that centrally located fat is of particular relevance in the causation of IHD, the results of the Goteborg study emphasize the possible role of abdominal and suprailiac fat distribution.

Obesity and other personal characteristics

In affluent societies obesity is generally more common in people of lower socio-economic status (Gordon and Kannel 1975, Koskenvuo et al. 1981). In the UK previous studies have tended to be limited to either social classes III-V (Khosla and Lowe 1972) or social classes I and II (Richardson and Pincherle 1969, Waller and Brookes 1972). Some studies in Western populations have shown obesity to be more prevalent in upper social classes (Bullen et al 1963, Keys et al 1967, Keys and Brozek 1957) and others have shown no relationship (Jacobs and Gottenborg 1981, Kittel et al 1978). These discrepancies may have arisen because of differences in socio economic scales used, study populations and international or regional variations. There may be rural urban differences in obesity (Metzner et al 1977, Monello et al 1965) but these do not show a consistent pattern. There appears to be an interaction between social class, smoking and obesity in NPHS with male smokers in the upper social classes being more obese than non smokers; in the lower social classes the

difference between smokers and non smokers is reversed. This relationship does not appear to be due to daily number of cigarettes smoked since this is not related to weight in males. One possible explanation is that men in social classes I and II may be able to afford to smoke and eat more than they need whilst those in lower social classes may have to spend less on food if they smoke. The proportion of cigarette smokers is lower amongst higher social classes than lower social classes, this may reflect a better response to health warnings in the upper social classes. Many studies have shown that on average cigarette smokers are leaner than non smokers (Blitzer, Rimm and Giefer 1977, Higgins and Kjelsberg 1967, Jacobs and Gottenborg 1981, Khosla and Lowe 1972, Noppa and Bengtson 1980). In NPHS there is an inverse relationship between obesity and stated number of cigarettes smoked in women only. This raises the possibility that some women use cigarettes as a method of controlling obesity and clinically it is not uncommon to find that concern about possible weight gain is given by some women as a reason for not stopping smoking. Interestingly however the difference in W/H^2 between female never smokers and ex-smokers is minimal whereas in males there is an appreciable difference (24.7 vs 25.8). Possibly this indicates that female ex-smokers were only light smokers when they did smoke cigarettes. In the Framingham study in both sexes ex-smokers were

lighter than never smokers and current cigarette smokers were lighter still. In Framingham the relationship in both sexes between stated number of cigarettes smoked and weight was non linear with the leanest category being those who smoked 11-19 cigarettes per day, the heaviest smokers (40+/day) weighed more than all the other smoking categories. Those men who quit smoking during the follow up of the Framingham study population gained about 4 lbs on average. In NPHS amongst male cigarette smokers those who smoked 11-20 cigarettes a day were leanest, the mean W/H^2 for this group was similar to that of those who had never smoked. The average weight gain over time in those who stop smoking has generally been found to be higher than in continuing smokers and in those who have never smoked (Blitzer, Rimm and Giefer 1977, Bosse, Garvey and Costa 1980, Noppa and Bengtsson 1980). There have been three main hypotheses to explain this observation, firstly smoking may act as an appetite suppressant, secondly smoking stimulates the resting metabolic rate and thirdly after giving up smoking the amount of food eaten is increased as a substitute for smoking. In the longitudinal data those who stop smoking between the two examinations gain a mean of around 2 kilos. This compares quite closely with the difference between current and ex-smokers in the cross sectional data and with the results of the Framingham study. Interestingly, in males there is a

statistically significant relation between change in cigarettes smoked between the two examinations and weight change suggesting a direct dose response effect of cigarette consumption on weight which is not evident in the cross sectional data.

A recent publication suggests that the baseline activity of adipose tissue lipoprotein lipase is related to the amount of weight gain following smoking cessation and that this may be the mechanism of the gain in weight (Carney and Goldberg 1984). Lipoprotein lipase in adipose tissue is a key enzyme in the regulation of uptake and storage of triglyceride fatty acid by adipocytes. The level of lipoprotein lipase in adipose tissue increased in obese subjects after weight loss and fell to lower levels when weight was regained (Scwartz and Brunzell 1978). The rise in activity of this enzyme following weight loss may represent a compensatory attempt to maintain a predetermined mass of adipose tissue. In the case of cigarette smokers who stop smoking, although those with the highest pre-smoking cessation levels of lipoprotein lipase in adipose tissue have the biggest weight gain, no evidence is currently available on changes in this enzyme following cessation.

There are several possible explanations for the lack of an overall relation between cigarette smoking

and obesity in the cross sectional data on male participants in NPHS. It is possible that the leaner smokers may have been under-represented amongst the participants due to a poorer response rate, alternatively it may reflect different smoking patterns in the NPHS male population than in other studies. The largest occupational group in NPHS were workers in a food processing factory who are not permitted to smoke whilst working. It is possible that the male smokers in this group tend to smoke mainly in the evenings whilst in pubs or other social situations whilst the women may smoke predominantly at meal breaks. Differences in smoking patterns could account for varying effects (or lack of them) of smoking on weight. In NPHS current cigarette smokers did have a slightly lower mean subscapular and suprailiac thickness than never smokers and ex-smokers, this may suggest a somewhat different distribution of body fat in smokers but the effect is small.

There is rather sparse and contradictory data about the relation between alcohol consumption and obesity. In NPHS those women who consume alcohol are more obese than those who were teetotalers but there was no apparent relation with stated amount consumed. This may reflect the inadequacy of alcohol consumption data or alternatively may indicate that alcohol itself is not

responsible for the weight difference but is merely an indicator of some other aspect of life style which is responsible. In the longitudinal data however there is an association between increase in alcohol consumption and weight gain between the two examinations amongst males.

Oral contraceptives are well documented as causing increases in weight (Spellacy, Buhi and Birk 1972). In NPHS only forearm skinfold thickness is significantly greater in women on oral contraceptives. However NPHS was not designed to investigate the effects of oral contraceptives on weight, in order to do this repeated measurements over time in women on contraceptives and those not taking oral contraceptives would have been necessary.

Postmenopausal women have greater mean triceps and suprailiac skinfold thickness than premenopausal women when age and other factors were taken into account although there is no significant difference in W/H^2. Menopausal status has been shown to affect serum cholesterol, factor VII, fibrinogen, levels of these variables being 6-10% higher in postmenopausal than premenopausal women when age is taken into account (Meade et al 1983). Characteristics of the menopause other than the decline in oestrogen production may be

responsible since exogenous oestrogens tend to result in rises in weight, factor VII and fibrinogen levels. The rise in gonadotrophins during and after the menopause is one possible explanation although there appears to be no firm evidence of any link of gonadotrophins with lipid metabolism and blood coagulation.

Obesity and blood pressure

Many studies have demonstrated a relationship between obesity and hypertension (US Department of Health Education and Welfare 1979, Chiang, Perlman & Epstein 1969). The relationship is found in both sexes and in both children and adults (Voors, Webber and Berenson 1977). In addition to the association in cross sectional studies, longitudinal studies have shown that those who are obese at the onset of the study were more likely to develop hypertension later than participants who were not over weight (Kannel et al 1967, Tyroler, Heyden and Hames 1975, Paffenbarger, Thorne and Wing 1968).

After reviewing studies comparing direct intra arterial and indirect methods of determining blood pressure, Chiang, Perlman and Epstein (1969) concluded that the discrepancy is minor in most cases and that it often inconsistently related to obesity, in any event it is insufficient to account for the overall relation between

obesity and blood pressure. A more recent study (Maxwell et al 1982) however apparently showed that the regular sized cuff (12 x 23 cm) resulted in the greatest bias in blood pressure readings in 1240 obese patients compared with a large cuff (15 x 33 cm) and a thigh cuff (18 x 36 cm). For instance, for a person with an arm circumference of 40 cm there was a mean 7.5 mm Hg difference in diastolic pressure between thigh cuff and the regular cuff and about 3.5 mm Hg between the large and the regular cuff. However it was not clear from this paper whether the cuffs had been applied in random order - failure to do so might have exaggerated the difference if the regular cuff had consistently been used before two larger cuffs since repeated measurements of blood pressure tend to result in the later readings being somewhat lower than the earlier readings - possibly as a result of the patient being more relaxed. In addition measurements in this paper were not performed by random zero sphygmonometer and therefore could have been open to bias since those performing the measurements must presumably have known the hypothesis that they were testing.

In NPHS arm circumference is only partly responsible for the relation between W/H^2 and blood pressure. During the second (follow up) measurement (on average 6 years after recruitment) there is a small

independent association of arm circumference with blood pressure when W/H^2 is taken into account. At follow up two cuff sizes were used depending on arm size and although this may have served to reduce the relation between blood pressure and obesity due to arm circumference it did not abolish it. At recruitment only one size cuff (23 cm bladder) was used and this could have resulted in some of the association found in the recruitment examination results between obesity and blood pressure being due to spuriously high readings in those with fat arms. However the association of systolic blood pressure and W/H^2 is quite similar in both examinations,this suggests that any such bias must have been of small magnitude.

The association between increasing obesity and age seems to occur widely in Westernized populations. In non Western populations however there is frequently no relation and no rise in blood pressure occurs with age (Sever et al 1980, Mann et al 1964, Whyte 1963). However this may not necessarily imply that obesity is a major determinant of age related changes in blood pressure since other factors including salt consumption could be relevant. In NPHS age is a stonger determinant of blood blood pressure in both sexes in the cross sectional data than indices of obesity. The relation between obesity and hypertension may have been slightly

underestimated in NPHS because some hypertensives were receiving antihypertensive treatment. NPHS is complicated by the differences in blood pressure measuring technique between the two examinations and because many participants were not examined by the same observer on both occasions. Although it can be shown by multivariate analysis using interaction terms for different observers that the effect of observer differences in measurement does not account for the relationship of blood pressure with weight changes between the examinations, nevertheless the exact magnitude of the effects observed comparing initial with follow up data must be open to some conjecture because of these complicating factors.

Despite the difficulties of comparing the longitudinal and cross sectional data it does appear that weight changes between the two examinations have a greater effect on blood pressure than the cross sectional data suggest. Initial weight had no significant effect on changes in blood pressure between the two examinations when the weight change was taken into account. This is in agreement with other studies including Framingham (Ashley and Kannel 1974). In the Framingham data changes in relative weight explained about 4.6% of the variance of systolic blood pressure in males and 2.7% in females, in NPHS the % is somewhat

smaller for both sexes (3.8% and 1.4% respectively). The Framingham estimates were based on six measurements each two years apart and may therefore represent a more accurate assessment than the NPHS results but in any event the two studies show quite similar results.

Older participants of both sexes tended to gain less weight between the two examinations than younger participants. A similar pattern was evident in the cross sectional data for males but not for females. There is a tendency in males for the effect of weight gain on systolic blood pressure to be somewhat greater at younger ages.

There are several possible explanations for the apparently greater importance of weight change within individuals on blood pressure than differences between individuals in the cross sectional data. One is that other factors, both genetic and environmental, may determine differences between individuals but these are kept absolutely constant (genetic) and relatively constant (environment) within individuals. Secondly weight changes in an individual generally represent changes in body fat whereas differences in W/H^2 between individuals do not entirely reflect differences in body fat. There is a stronger relation between change in body weight and blood pressure change than with change

in skinfold thickness. However the measurement of skinfold thickness in NPHS is complicated by evidence of progressive changes in skinfold thickness over time, perhaps due to changes in sensitivity of the calipers. In addition since an increasing proportion of body fat may be deposited internally with advancing age changes in skinfold thickness may not reflect changes in body fat with age sufficiently accurately. The Goteborg study which measured changes in systolic blood pressure and body weight between 1963 and 1973 in men aged 50 in 1963 found that the regression coefficient was 0.88 mm Hg/Kg change in body weight (Carlson 1978) which is quite similar to the findings of NPHS.

There are several possible mechanisms for the association between weight change and blood pressure. One is that there is an underlying confounding association with salt consumption. Dahl for instance suggested that an increased intake of sodium along with increased caloric intake produces hypertension in the obese (Dahl, Silver and Christie 1958). However recent randomised controlled trials in humans of salt restriction have produced differing results. Two recent studies of patients with 'mild' (MacGregor et al 1982) or 'mild to moderate' (Beard et al 1982) hypertension showed an apparently beneficial effect. The former was a randomised double-blind crossover study on 19 patients

who were advised not to add salt to their diet and then supplemented with 'Slow Sodium' (Ciba) or identical placebo which showed a difference between the fourth week of the supplemented and placebo periods of 7 mm Hg in mean supine blood pressure in favour of the placebo group. The mean 24 hour urinary sodium was 162 mmol in the fourth week of the supplemented period and 86 mmol in the fourth week of the placebo period. The latter study was a randomised trial of a no added sodium diet in 90 patients on medication. The mean urinary sodium excretion was 37.0 mmol/24 hour in the diet group and 161.0 mmol/24 hour in the control group. Both groups had falls in blood pressure but the diet group finished with 14 of 45 off medication and, 37 of 45 having either stopped or reduced the dose, compared with no reduction in treatment in 30 of 45 in the control group. The diet group also lost a mean of 2.1 kg, but there was no association between individual weight loss and outcome. It was not clear whether the weight loss represented a reduction in adipose tissue or fluid loss.

Long term salt restriction over a period of 2 years was shown in another study (Morgan et al 1978) to result in a reduction of diastolic presure by a mean of 7 mm Hg, a result similar to that in patients treated with antihypertensives. In an untreated control group there was a mean rise of 1.8 mm Hg. The mean urinary sodium

excretion over 24 hours fell to 157 mmol/l compared with 191 mmol/l before therapy. The sodium restriction was therefore very modest and one third of patients failed to provided a urine specimen. No changes in weight were mentioned. Neither of the last two studies were analysed on an intention to treat basis and patients who failed to complete the study were therefore excluded from analysis.

A study of 18 patients with a mean blood pressure of 144/93 who restricted their sodium intake for eight weeks in a double blind randomised crossover trial of Slow Sodium and placebo tablets failed to show any difference between the treatment and placebo periods in blood pressure (Watt et al 1983). The study had a 99% power to detect a difference of 5 mm Hg mean arterial pressure between the two periods. These patients were recruited from a single general practice and comprised those whose diastolic blood pressure was within the range 90-104 mm Hg based on the mean of six casual blood presure readings. Mean urinary sodium excretion over 24 hours was 143 mmol during the period on sodium supplementation and 87 mmol during the period on placebo. A further study in the same practice (Watt, Tudor Hart and Foy 1983) showed that in offspring whose parents were both in the top third of the distribution of blood pressure for their age group (high/high) there

was no difference in 24 hour urinary electrolyte excretion or plasma renin activity compared with offspring whose parents were both in the lowest third of the blood pressure distribution (low/low). There was no overall difference in mean weight in the offspring of high/high and low/low parents (mean weight 60.7 kg and 59.6 kg respectively). Results for W/H^2 were not given in this paper.

It seems likely that the response of blood pressure to salt loading and restriction may depend on the group selected for intervention and tests for identifying salt sensitive individuals accurately within the population have not yet been developed. There is however evidence that the effect of salt restriction and weight reduction are probably due to separate mechanisms. For instance 25 obese patients placed on a 12 week reducing diet in which salt intake was either medium (120 mmol) or low (40 mmol) showed that weight loss was the same in the two groups, that mean blood pressure fell equally in both groups and that the fall was correlated with weight loss (Tuck et al 1981). Reisin et al (1978) also showed, in obese patients randomly allocated to a weight reducing diet or a control group, with a sodium intake which was uncontrolled and equivalent in the two groups that the weight reduction group showed a greater fall in blood pressure.

Two studies suggest that reduction in dietary fat might lead to falls in blood pressure independently of weight loss. Puska et al in North Karelia, Finland (1983) in a randomised controlled trial compared a low fat (23% of energy) high polyunsaturated/saturated ratio (1:0) diet with two other groups, one a reduced salt intake (192 mmol to 77 mmol/day) and another which continued on their normal diets. The low fat group showed a fall in blood pressure over the 6 week intervention period, the other two groups did not. Both the low fat and the low salt group lost a little weight (mean 0.7 kg and 0.9 kg respectively). A further study of 59 patients suggested a blood pressure lowering effect (of 5-6 mm Hg systolic pressure) of a vegetarian diet which appeard independent of sodium and potassium intake (Rouse et al 1983). There were no significant falls in weight during the periods on vegetarian diet.

There is thus evidence for independent effects of weight reduction and reduction in fat intake on blood pressure.

It has been shown that plasma renin activity and aldosterone fall with weight loss (Tuck et al 1981) at different levels of salt intake. The fall in plasma renin activity was correlated with the degree of weight loss but that of plasma aldosterone was not. In NPHS

plasma renin activity was found, if anything, to correlate inversely with blood pressure (Meade et al 1983) and there was no relation between plasma renin activity and obesity.

It has been shown that overeating of protein, carbohydrate and fat causes an increase in the deiodination of thyroxine to triiodothyronine (T_3) and a corresponding increase in serum T_3 (Danforth et al 1979). It is possible that this observation could be relevant to the development of hypertension in obesity since T_3 may increase B adrenergic receptor number (at least in rats!) and may therefore increase sensitivity to pressor mechanisms.

During fasting there is a decrease in sympathetic activity (Landsberg and Young 1978) and it is possible that the catecholamine response to overfeeding could cause sodium retention. However the activity of the adrenergic nervous system has not been shown to be different in obese hypertensive individuals compared with lean hypertensives although weight reduction may lead to a reduction in circulating noradrenaline levels (Messerli 1982). There may of course be individuals who are particularly susceptible to a change in catecholamine metabolism with weight change.

Hyperinsulinaemia, which is commonly found in obese individuals, may affect sodium handling by the kidney probably by enhancing the tubular reabsorption of sodium (De Fronzo et al 1975). Although there is a relative insulin resistance at a tissue level in obese patients nevertheless organs differ in their sensitivity and it is possible that adipose tissue and renal tubular calls (Howard et al 1979) could remain sensitive in the face of the insulin resistance of muscle and liver.

Plasma and total blood volumes tend to expand in obese patients and cardiac output rises (Messerli et al 1981). Hypertension alone is associated with a contraction of intravascular volume and there is an inverse association between peripheral resistance and intravascular volume (Julius et al 1971, Tarazi et al 1968). The effects of obesity and hypertension on intravascular volume tend to be in opposite directions and may in some patients offset each other. The blood supply to adipose tissue tends to be relatively poor compared with lean tissue, furthermore the perfusion per unit of fat tissue tends to decrease with increasing obesity. It seems that there may be a discrepancy between the increase in cardiac output in obesity and the perfusion of adipose tissue. This chronic high output state may, together with volume expansion, eventually lead to a rise in peripheral resistance and

arterial pressure. The exact mechanism for the association between raised blood pressure and obesity is however still open to speculation.

Obesity and lipids

The marked rise in serum cholesterol with age which tends to flatten off in males over aged 40 has been well documented (Tyroler et al 1975, Johnson 1967). This pattern is also seen in the data from NPHS. In women however the rise occurs throughout the age range studied. Many cross sectional studies have shown a modest association between serum cholesterol and obesity (Kahn et al 1969, Kannel et al 1962) and it has also been shown that when individuals change weight their cholesterol levels tend to parallel weight changes. In males weight loss has been shown to result in a decreased ratio of low density lipoprotein cholesterol (LDLC) to high density lipoprotein cholesterol (HDLC) in males. Inconsistent results have been achieved in females (Lewis et al 1976, Thompson et al 1979, Contaldo et al 1980, Dobrea et al 1981, Brownell and Stunkard 1981). There may be differences in the lipoprotein response to active weight loss and stable reduced weight. A recent study found that LDLC was reduced and HDLC raised in obese women during stable reduced weight

loss (Friedman et al 1982). Total cholesterol was unchanged from the baseline measurements in this study which was however on only 15 women. In NPHS the association of serum cholesterol with obesity is somewhat lower for females than males in both the cross sectional and the longitudinal data (weight change) but the difference is minimal in the case of the cross sectional data and is not statistically significant in either case. The relation between obesity and serum cholesterol is somewhat stonger in younger compared with older men in the cross sectional data but there is no evidence that the response of cholesterol to weight change was more pronounced in younger males in the longitudinal data. This may suggest cohort differences in the association between obesity and serum cholesterol, alternatively the observation may be due to the greater range of W/H^2 at entry in the younger males. The Framingham offspring study (Garrison et al 1980) found that, amongst males, LDLC was most closely related to obesity in the youngest (20-29 years) age group. The converse was found in females in whom the relation was modest except in the oldest (40-49 years) age group. This study also noted a paucity of lean males in the 40-49 age group and suggested that this might be an explanation for the weak relationship in that group. (Only 2.6% had a relative weight of below 100% based on the Metropolitan Life Insurance Co. data.) Findings

from the Framingham Heart Study cohort, who were all over 50 years of age at the time of the relevant measurements, showed that 4 of the 6 age specific correlations in males between relative weight and LDLC were not significantly different form zero (Kannel, Gordon and Castelli 1979). Similar data for HDLC were reported from the Collaborative Lipid Research Clinics (Glueck, Taylor and Jacobs 1979). Amongst adolescents in Bogalusa only the most obese boys (upper 15% of the distribution) appeared to have elevated LDLC (Frerichs, et al 1978).

Although age has a more powerful effect overall on serum cholesterol than obesity, nevertheless those in the fattest quartile of NPHS males aged 30-39 years have a serum cholesterol similar to the leanest two quartiles in the 40-49 age group. The effect of obesity in the younger age groups is therefore quite substantial. The lack of any apparent effect of age on the association between serum cholesterol and obesity in women may be due to the confounding effect of menopause which results in an elevation of serum cholesterol in middle aged women (Meade et al, 1983).

The association between serum triglycerides and obesity has been well documented (Olefsy, Reaven and Farquhar 1974). Several mechanisms may be involved in

this association, for example the rate of free fatty acid mobilization is a determinant of the amount of substrate presented to the liver for plasma triglyceride synthesis. Hydrolysis of fat cell triglyceride to yield free fatty acids is in part under the control of insulin levels. Adipose tissue lipoprotein lipase is the major enzyme responsible for hydrolysis of triglycerides circulating in chylomicrons or very low density lipoproteins to fatty acids which are taken up by fat cells for storage as adipose tissue triglycerides. Levels of fat cell lipoprotein lipase will therefore affect circulating plasma triglyceride and the activity of this enzyme has been shown to be elevated in obese patients (Schwartz and Brunzell 1978). The elevation remains following weight loss, and may become even greater. It may therefore indicate an underlying metabolic abnormality of importance in the aetiology of obesity and account for the difficulty in maintaining a reduced weight that obese individuals tend to experience. Olefsky, Farquhar and Reaven (1974) proposed than in non-diabetic patients insulin resistance was a major determinant of insulin secretion and that insulin levels in turn were a major factor determining hepatic triglyceride synthesis and thus plasma triglyceride levels. Insulin resistance is related to fat cell size which is known to be elevated in adult onset obesity (Sjostrom 1980).

There has been some controversy as to whether plasma triglyceride level is related to IHD incidence or mortality. Two studies found an apparent relationship (Carlsson and Bottiger 1972, Pelkonen et al 1977). Recent studies suggest however that there is no independent association of IHD with triglycerides (Wilhemssen, Wedel and Tibblin 1973, Gordon et al, 1977). In a comprehensive review Hulley et al (1980) examined the results of 27 studies which showed an association between serum triglyceride and coronary disease and found that only 8 had taken the range of known risk factors into account. When adjustment for several risk factors was undertaken only 2 showed a residual independent association between IHD and triglycerides. They pointed out that earlier studies had failed to take into account the importance of HDLC and found in their own results from the Western Collaborative Group Study that when this was done there was no remaining association between IHD and triglyceride. In NPHS there was no evidence of an association between triglyceride and IHD mortality.

The results from NPHS were on non-fasting blood samples, and this may have resulted in somewhat higher levels of triglycerides than would have been observed on fasting samples. However there is a surprisingly high correlation between fasting and non-fasting triglyceride

levels (r = 0.7) which suggests that although the use of non-fasting samples may have decreased the strength of association somewhat the effect was not sufficient to seriously interfere with the interpretation of results (North and Meade unpublished observations). From an epidemiological perspective there are considerable advantages in being able to use non-fasting samples since it is generally easier to persuade large numbers of individuals to attend for examination if it involves comparatively little disruption of their routine. In addition in many ways the non-fasting state is likely to be more represtative of long-term exposure than fasting levels since individuals spend little of their lives undergoing morning fasts!

Although there is a paucity of epidemiological data on cardiovascular risk factors in women compared with the wealth of data on men, the Framingham study showed that the risk factors and their inter-relationships were essentially similar in the two sexes although there was a univariate association between triglyceride and coronary heart disease incidence in females which was not present in males, this however disappeared when HDLC levels were taken into account (Gordon et al 1977). In addition diabetes appeared a risk factor for females only both in univariate and multivariate analysis. Relative weight was a risk factor for females in univariate analysis only.

In the Framingham data the association between relative weight and low density lipoprotein cholesterol, triglyceride and systolic blood pressure was similar in males and females. In NPHS total cholesterol was measured and no direct measurements of HDL-C and LDL-C are available but the associations between W/H^2 on the one hand and lipids and blood pressure on the other are generally similar in the two sexes although somewhat stronger for males. Mean triglycerides are lower in females than males in both NPHS and the Framingham study, this may reflect the lower values of W/H^2 and relative weight respectively for females compared with males in the two studies although the difference in triglycerides appears somewhat larger than would be expected on the basis of differences in obesity alone.

Haemostatic variables

Amongst the haemostatic variables measured there is good evidence that factor VII, factor VIII and fibrinogen are related to ischaemic heart disease and that the relationship may be causal (Meade et al 1980).

Males in NPHS who developed fatal IHD had higher levels of factor VII_c, fibrinogen and factor $VIII_c$ than those who did not. The independent association of factor VII_c and fibrinogen with cardiovascular death appeared at least as strong as that between serum

cholesterol and cardiovascular death. A clustering of high levels of two of the three clotting factors was present in 63% of those who died of cardiovascular disease compared with 23% of those who survived. There was no evidence of association with death from cancer. Exclusion of those with a pre-existing history of cardiovascular disease did not affect the difference between those who died and the survivors.

Several studies have shown that factor VII_c levels vary in parallel with plasma lipids. Vegetarians have lower levels of factor VII_c and lipids than non-vegetarians (Haines et al 1980). Blacks have lower levels of factor VII_c and cholesterol than whites (Meade et al 1978). Factor VII_c and cholesterol levels are higher in post than pre-menopausal women even when age differences are allowed for (Meade et al 1983). Use of oral contraceptives (Meade et al 1977) results in raised VII_c and cholesterol levels and patients with hyperlipidaemia (Constantino et al 1977, Simpson et al 1983) also tend to have elevated factor VII_c levels. Reduction of plasma lipids in hyperlipidaemic patients is associated with a fall in factor VII_c levels (Simpson et al 1983). In NPHS there is a fairly weak but statistically highly significant correlation (r=0.23) between serum cholesterol and factor VII_c (Meade et al 1980).

The association of factor VII_c and lipids does not seem to be due to an artefact of the assay system since factor VII_c levels are not raised by the addition of lipoproteins to plasma in vitro.

High factor VII levels could influence the risk of IHD in several ways. Factor VII exists in a less active single chain form and as a more active double chain form (Silverberg, Nemerson and Zur 1977). The factor VII clotting assay (VII_c) uses plasma which has been collected directly into citrate and tested either fresh or after snap freezing and storage in liquid nitrogen. The factor VII_c assay probably measures factor VII protein in the proportion of single and double chain VII (the double chain variant being denoted by αVII_a) which existed at the moment of venepuncture. The factor VII activity of both the sample and the standard against which it is assayed will depend upon the proportion of αVII_a, i.e. as the proportion of αVII_a increases the level of factor VII_c will apparently increase. Factor VII measured by a tritiated factor X method (in which all factor VII is first converted to αVII_a) is not associated with cholesterol. This suggests that the association between factor VII_c and cholesterol is due to an increasing proportion of factor VII circulating as αVII_a in patients with high cholesterol levels (Miller et al Brit J Haematol in the press). Kallikrein and other

proteases are able to convert single chain VII to αVII_a (Seligsohn et al 1979). The kallikrein system is activated in hyperlipidaemia as indicated by depletion of prekallikrein and kallikrein inhibitors (Carvalho et al 1978). Conversion of prekallikrein to kallikrein occurs following adsorbtion of the contact factors on to a negatively charged surface. It is possible that lipoprotein particles, which are negatively charged, may provide sufficient surface for activation of the contact system. Whilst the reactions of the contact system may be too slow to affect the rate of thrombin production during coagulation (Altman and Hemker 1967) it is possible that an increased proportion of αVII_a may increase the rate of thrombin production and thus render the haemostatic system more sensitive to pro-coagulatory stimuli.

In NPHS males the similar convex relation of both cholesterol and factor VII_c to W/H^2 (and their closer association with W/H^2 at younger ages) is added evidence that there is a close parallel between the two. However the association between factor VII_c and obesity persists when serum cholesterol and triglyceride levels are taken into account.

In contrast to factor VII, there is no association between factor V and fatal myocardial infarction in NPHS

and its epidemiological features do not suggest any major association with cardiovascular risk. It has not been measured at the follow up examination.

High fibrinogen levels may exert an adverse effect on cardiovascular risk by increasing plasma viscosity, alternatively they may operate through the role of fibrinogen in the coagulation system. In addition fibrin may have a role in the production of atheroma (Smith et al 1979). The lack of any association between weight change and fibrinogen in the longitudinal data suggest that fibrinogen may not be directly related to obesity. Their association in the cross sectional data might represent a common association with a third, as yet unknown, confounding factor or may indicate that fibrinogen is an indicator of metabolic factors which predispose to obesity. Plasma fibrinogen concentrations are higher in smokers than non-smokers and are reduced by alcohol consumption (Meade et al 1979) but these associations do not of course account for the relation with W/H^2 in the cross sectional data. A recent study of dietary determinants of lipids, blood pressure and fibrinogen on 117 middle aged men who completed 7 day weighed dietary records showed that there was no significant association between fibrinogen and dietary fat intake but an inverse association was found between cereal fibre intake and fibrinogen (Fehilly et al 1982).

Factor $VIII_C$ is not related to obesity and also differs from factor VII and fibrinogen in that it is not produced in the liver. Factor VIII tends to be raised by adrenergic stimuli, exercise and cigarette smoking (Cohen et al 1968, Ingram 1961).

Fibrinolytic activity has not been shown to be consistently associated with cardiovascular risk unlike the three preceeding haemostatic variables. In the cross sectional data it was consistently inversely related to obesity but the pronounced fall in fibrinolytic activity which has occurred since the later part of the recruitment for as yet unkown reasons, has made comparisons between cross sectional and longitudinal changes impossible. There is no consensus about the most appropriate method of measuring fibrinolytic activity and the dilute blood clot lysis time is undoubtedly a crude method which however has the advantage of being methodologically simple and reflects the balance between activators and inhibitors of fibrinolysis. In practice it does mainly reflect activators of fibrinolysis although inhibitors are also present. Whole blood dilute clot lysis time and euglobulin lysis time are quite closely correlated (Flute 1964), the latter method being independent of inhibitors. There was no significant difference in fibrinolytic activity between those in NPHS who died of

myocardial infarction and those who survived (Meade et al 1980). In other respects there are some suggestions, from what is known about the epidemiology of fibrinolytic activity, that it could be of some relevance in the aetiology of vascular disease. Fibrinolytic activity falls with age, is reduced in smokers (Meade et al 1979), elevated somewhat in those who consume alcohol compared with non drinkers, it also falls in the immediate aftermath of myocardial infarction (Haines et al 1983). However some associations are in the opposite direction to what might be expected, for example it is lower in blacks than whites despite a lower IHD mortality in blacks, it is elevated in women taking oral contraceptives and increases in lower social class men (Meade et al 1980).

These apparently paradoxical effects may reflect compensatory mechanisms which react to situations in which individuals are at increased (or decreased) risk of thrombotic events. If this is so then those individuals who fail to react adequately with increased activity in such situations could be at increased risk. Because of the complexity of the fibrinolytic system a simple measurement such as that used in NPHS could reflect an increased risk of thrombotic events in some circumstances and in others a reaction to increased risk.

Several other studies have shown a similar, inverse relationship between fibrinolytic activity and obesity (Szczeklik et al 1980, Shaper et al 1966). It is possible that because of the crude method of measurement used for fibrinolytic activity its contribution to cardiovascular risk may have been underestimated in NPHS data. If this is so then its inverse association with obesity may be of relevance to the relation of obesity with cardiovascular mortality.

Longitudinal relationships of weight change with haemostatic variables and other cardiovascular risk factors

There are difficulties in determining the exact magnitude of the longitudinal changes in cardiovascular risk factors between the two examinations. In the case of the coagulation factors, different standards have been used in the assay on the two occasions. Although conversion factors have been calculated to allow expression of results in terms of one standard it is obviously difficult to determine with absolute confidence how much of the changes between examinations are due to changes in population characteristics and how much due to differing potencies of standard since the two factors are confounded.

Similarly the differences in the method used to measure serum cholesterol which changed in 1976 make exact comparison difficult but at least in the case of cholesterol some data is available for the later method at both recruitment and follow up examination and the two methods were taken into account in the multiple regression analaysis. In the case of blood pressure a standard cuff and sphygmomonometer were used at recruitment compared with standard and oversize cuffs with a random zero sphygmomonometer at follow up. In addition individuals were, in many instances, measured by different observers on the two occasions. Whilst it is possible to make some allowance for the observer differences using interaction terms in the multiple regression analysis it is impossible to take into account any difference between the sphygmomonometer without performing direct comparisons between them on the same individuals at the same point in time. Nevertheless since the particular aim of the analysis of the longitudinal data is to determine the contribution of weight change to changes in cardiovascular risk factors, the differences in the methods used between the two examinations, whilst affecting the absolute amount of the change of the variable measured should not affect the contribution of weight unless of course those who were measured on say, a particular coagulation factor standard gained or lost weight at a different rate to

those measured on another standard. There is however no evidence of any such tendency in NPHS data. The general similarity of the longitudinal and cross sectional results (with the exception of fibrinogen) is further evidence that the estimates of the effects of weight change are reasonably accurate.

The mean change in weight over the 6 year follow up is quite similar to the mean weight change of 1.4 kg in a study of Swedish women aged 38-60 years who were measured in 1968-9 and again in 1974-5 (Noppa, 1980).

The Swedish study also showed that older women gained less weight than younger women, a similar observation was noted in both sexes in NPHS. In NPHS, just as in the Framingham study, (Ashley and Kannel, 1974) the changes in serum cholesterol and blood pressure with weight change are somewhat greater in males than females. Weight changes have a somewhat greater effect on serum cholesterol than systolic blood pressure in both studies but in NPHS the difference is very small. In NPHS and Framingham the change in weight was the important determinant of change in risk factors and the initial weight did not affect the change. This has important repercussions for public health since it implies that if individuals could be prevented from gaining weight, particularly relatively young

individuals who tend to gain more than older people, then a worth while reduction in the rise in cardiovascular risk that occurs with ageing could be achieved. In practical terms this may be more achievable than widespread weight reduction in the population. Health education should place more emphasis on regular weighing with the aim of preventing a rise in weight and reversing any small elevations as they occur.

Obesity and mortality

The association of W/H^2 and mortality in NPHS males is statistically significant both in the univariate and the multivariate analysis which takes into account other risk factors. The univariate analysis showed that cholesterol, fibrinogen and factor VII were associated with fatal IHD as reported previously (Meade et al 1980). This suggests that obesity had an effect on mortality which is mediated only partially through the risk factors measured in this study. Of the 54 male participants who suffered fatal IHD, 8 had incomplete data because of an insufficient volume of blood collected, and were therefore excluded from multivariate analysis. It is possible that the unavoidable exclusion of these participants from the multivariate analysis may have resulted in an underestimate of the contribution of obesity to fatal IHD through its effect on the cardiovascular risk factors measured in NPHS if there

had been a particularly strong relation between obesity and cardiovascular risk factors amongst those eight individuals. This seems unlikely because the mean W/H^2 of these 8 individuals in question was actually somewhat lower than that of the whole group of 54 fatal IHD cases.

The adverse affect of obesity may be due to its negative association with High Density Lipoprotein cholesterol (HDL-C) which was not measured in the NPHS population (Berchtgold et al 1981, Rhoads et al 1976, Avogaro et al 1978).

In NPHS previously identified hypertensives were more obese than normotensives. There is however no association between blood pressure and mortality in the NPHS population. One possible explanation is because the hypertensives in this population have relatively well controlled blood pressures. However treatment for hypertension is thought to be mainly of benefit in preventing stroke and congestive cardiac failure. The effects of treating hypertension on the prevention of myocardial infarction have been equivocal (WHO/ISH Mild Hypertension Liaison Committee 1982.)

The varying results of studies of obesity and cardiovascular mortality may be due to the opposing

effects of cigarette smoking on cardiovascular mortality and obesity. In NPHS males there is no significant overall relation of obesity and cigarette smoking, upper social class smokers tend to be fatter and lower social smokers thinner than non smokers. This may account for the clear association of obesity and IHD mortality in NPHS males. A further possible explanation is that NPHS involves a working population in whom those with chronic disease, in which mortality is likely to be associated with underweight are probably under-represented.

Obesity tends to have a more marked influence on cardiovascular mortality on long term follow up (>5 years) than in the short term (Garrow 1981). This pattern is also seen in NPHS where there is no significant relation between obesity and mortality within 5 years of recruitment (although there were only 24 male deaths due to IHD in this period). When all IHD deaths in males are included however there is a strong association with obesity. It may be of particular importance as a risk factor in young men in whom the absolute risk of myocardial infarction is small so that many years have to pass before sufficient cases occur. Several studies have indeed shown that the cardiovasular risk conferred by obesity seems apparent only in younger males. For instance in the Manitoba study (Rabkin et al 1977) only in those men under 40 was there an increase

risk of coronary heart disease with obesity when they were followed up for 16 years. In the Pooling Project (1978) the association with obesity was only in those age <50. In NPHS the excess risk appeared somewhat greater at younger ages although the numbers in any one age group were small and the relation with age was not statisitically significant.

Obesity may be a better predictor of IHD mortality than the laboratory measures of cardiovascular risk in long follow up because it is less variable. An alternative explanation is that the association of obesity with IHD mortality is via another mechanism which is independent of those variables measured in NPHS. The measurement of individual skinfolds gives somewhat poorer prediction of IHD mortality compared with W/H^2.A recent report has suggested that the ratio of waist to hip measurement may be an independent predictor of coronary mortality at least in males (Larsson et al 1984). These measurements are not available in NPHS.

The lack of any difference in W/H^2 in these participants with a previous myocardial infarction at the entry examination is not surprising given that many patients are likely to be advised to lose weight following a major coronary event. An alternative

explanation is that obese patients with myocardial infarction are less likely to survive than leaner patients. However in studies of survival following myocardial infarction obesity has not been mentioned as a prognostic factor (Norris, Brandt and Lee 1969, Pohjola, Siltanen and Romo 1980, Luria et al 1979). Nevertheless weight and height are rarely measured in the acutely ill patient on admission to coronary care unit and therefore it is possible that if obese patients have a higher early mortality following myocardial infarction than lean patients this could have been missed in many studies.

There is no significant association between total mortality and obesity amongst the NPHS males because the slightly lower mean W/H^2 in those who die from cancer and other causes partly counterbalances the greater obesity of those who die of IHD. The lower mean W/H^2 of the fatal cancer cases seems to occur particularly in those aged 60 and over at recruitment although the total numbers are small. Several epidemiological studies have found that there is excess mortality amongst persons of below average weight, including the Framingham Study and the Chicago People's Gas Company Study (Sorlie, Gordon and Kannel 1980, Dyer et al 1975), which suggested that the lowest mortality occurred in those who exceeded their 'ideal weight' by 25-35%. Even when all those

with definite clinical evidence of lethal disease were excluded the excess mortality in those with below average weight persisted. It was suggested that this might be due to subclinical disease. Those who lost weight without deliberately dieting had a higher than average mortality if there was a medical explanation for their weight loss (Gordon and Kannel 1973). There is considerable debate about the nadir of the U shaped curve relating W/H^2 to total mortality. The US Life Insurance studies have found the minimum mortality at well below average weight for height (Society of Actuaries 1959). However those who were accepted for policies are not representative of the general population in that those with chronic disease leading to weight loss would tend to be excluded. More recent Life Insurance data from the USA (Society of Actuaries 1979) confirms that the lowest mortality is in those below average weight although there may be a slight increase in those greater than 20% below average weight.

In Framingham the mortality in the second 12 years of the 24 year follow up showed a greater tendency to increase with relative weight than mortality in the first 12 years of follow up, but this pattern did not extend to those of less than 90% of median weight for their age and sex in whom a somewhat higher mortality persisted (Hubert et al 1983). This observation could

have been due to cigarette smoking. A re-analysis of the American Cancer Society data (originally published by Lew and Garfinkel in 1979) for the recent (1983) report of the Royal College of Physicians - 'Obesity', shows that mortality rises in both smokers and non-smokers (although at a higher level in smokers) above a W/H^2 of about 24. The mortality in the leanest group of non smokers (W/H^2 <20 in both sexes) was slighly higher than that for those with a W/H^2 between 20-24, but was around the average for the complete study population.

The association between obesity and IHD mortality is insufficient to account for the flatening of W/H^2 with age which is seen in NPHS and other studies.

Despite the risk associated with obesity in NPHS males there is no doubt that in an obese smoker the priority should be given to smoking cessation since the average weight gain following stopping smoking will only confer around 6% increase in the risk of fatal IHD compared with around twofold for 20 cigarettes/day or more (Royal College of Physicians 1983).

NPHS data relates mainly to males and although the number of women included is too small to yield sufficient cases of fatal IHD for analysis the association between cardiovasular risk factors in the

two sexes is broadly similar. The American Cancer Society and the Framingham studies have suggested a similar association between obesity and cardiovascular mortality in the two sexes although the death rate amongst females for cardiovascular disease is of course considerably lower than amongst males.

There are several factors which could result in obesity predisposing to fatal cardiovascular disease. One possibility is that obese individuals are less likely to take exercise than lean individuals.

The limitations of the various methods for recording physical activity in a free living situation have been reviewed by Garrow (1978) who concluded that none of the available techniques was able to determine reliably whether a low activity level was of aetiological importance in obesity. Many studies used predicted energy expenditures for given tasks but it is known that there is considerable intra and inter individual variation in the energy costs of particular tasks. It is also possible that observation may result in alteration of activity levels.

Some studies have not found any significant differences between the lean and the obese in physical activity (Maxfield and Konishi 1966, McCarthy 1966) and

others have shown an apparently lower level in the obese (Bloom and Eidek 1967, Bullen, Reed and Mayer 1964, Morris and Stunkard 1957). However it is possible that this reflects the greater energy expenditure required for exercise in the obese or the stigma of obesity which discourages participation in sports and other forms of physical exertion.

Nevertheless several studies suggested that exercise may have a protective effect on cardiovascular disease. Mild physical exercise on a regular basis over 2 months has been shown to have beneficial effect on serum lipoproteins (increased HDL subfraction two) and arachidonic acid metabolites (decreased serum thromboxane and increased plasma 6 Keto prostaglandin F 1 α concentration) (Rauramaa et al 1984). Work activity in longshoremen was inversely associated with coronary heart disease mortality (Paffenbarger and Hale 1975). Male members of Kibbutzim in Israel with sedentary jobs had a 2-4 fold higher risk of IHD (both total and fatal), (Brenner et al 1974) than those with non sedentary jobs. In a study of 18,000 male civil servants in the UK, those who reported vigorous exercise during a two day sample period were less likely to suffer fatal coronary heart disease subsequently than those who did not (but there was no relation with total physical activity) (Chave et al 1978). The Framingham

study (Kannel and McNamara 1967) showed a threefold higher incidence of fatal myocardial infarction in the least active compared with the most active. Physical activity, both total energy expenditure and peak exertion as in strenuous sports, appeared to be protective in Harvard graduates independently of obesity (Paffenberger, Wing and Hyde 1978) .

In summary, it appears that although exercise may be protective against coronary disease, particularly fatal myocardial infarction, it does not seem to operate via reduction of obesity. The role of lack of exercise in the genesis of obesity is still open to debate.

It is also possible that obesity could be associated with fatal IHD because of dietary differences between the obese and non obese. However the relation of obesity with fatal IHD does not seem to be due to excessive food consumption, in fact several case-control or prospective studies have shown that those who develop ischaemic heart disease consume a lower energy intake than those who do not (Keen, Thomas and Jarrett 1982). This observation has been noted in a case control study from Canada (Little et al 1965), a case control study of Hawaiian Japanese (Bassett et al 1969) and similar but not statistically significant trends were seen in prospective studies in Israeli civil servants (Medalie

et al 1973) and Japanese-Americans (Rhoads et al 1978). In a retrospective analysis of data from 337 healthy middle-aged males in London who underwent a seven day individual weighed dietary record between 1956-1966 and were followed until 1976, Morris, Marr and Clayton (1977) found that those with a high energy intake had a lower rate of ischaemic heart disease and independently, those with a high cereal fibre intake also had a lower rate.

Implications for public health policy

Prevention of obesity or effective weight reduction in those already obese could play a worthwhile part in the prevention of IHD. Much attention has been given to weight reduction in the popular press and a variety of dietary approaches have been advocated. The sheer variety of dietary regimes suggests however that attainment of sustained weight loss is difficult in many cases. Comparatively little attention has been paid however to the possibility of preventing the weight gain which tends to occur in early adult life until middle age. If the average increase of between 2-3 kg/m^2 in W/H^2 which tends to occur in males and females with age could be prevented, a considerable reduction in fatal IHD should follow. Prevention of weight gain is of course more difficult to evaluate than weight reduction because long term follow up of whole populations would

be necessary to determine the effectiveness of preventive programmes. Nevertheless I believe that strategies for the prevention of weight gain aimed at increasing exercise and improving diet should be developed and monitored. These might include comparison of the effectiveness of interventions in school children, through familes and use of mass media. Some general recommendations for the population have been made which are aimed at preventing obesity, for instance The Royal College of Physicians (1983) recommended improved labelling of foods to indicate energy, fat and sugar content in a wide range of manufactured foods and mentioned the responsibility of catering organisations involved in the provision of meals at factory canteens, schools and large institutions such as hospitals to provide a range of dishes which contain less fat and sugar than those currently served.

The adoption by Health Districts of a Food and Health Policy which involves a wide range of health service staff could be of considerable importance in changing public eating habits. For example recently a Working Party of Brent Health District (in which I was involved) produced a policy for Food and Health whose recommendations included; the acceptance of dietary guidelines by the Health Authority aimed at reducing fat

and sugar intake and increasing cereal fibre intake, greater information for hospital in-patients about the health aspects of food and, of particular relevance, it also recommended that primary health care staff should play a more active role in health promotion. (Report of an ad hoc Working Group on Food and Health 1983).

In the recent report of the Royal College of General Practitioners on Health and Prevention in Primary Care (1981), the prevention of obesity has not been given prominence. General practitioners, health visitors and district nurses need to be made more aware of the relevance of obesity to health and their potential role in prevention. Considering the public health importance of obesity it is a relatively under researched area. I hope that the conclusions of this thesis will reinforce the need for more action in this important area of preventive medicine.

Conclusions

This thesis has demonstrated that four cardiovascular risk factors; blood pressure, serum cholesterol, plasma fibrinogen and factor VII, are related in both sexes to W/H^2 in cross-sectional data. Analysis of longitudinal data has shown that weight

changes over a 6 year period are significantly associated with changes in three of the variables: blood pressure, serum cholesterol and factor VII.

The data on skinfold thickness lend support to the suggestion that centrally located subcutaneous fat is a more powerful determinant of cardiovascular risk factors than peripheral fat with the proviso that, in males, forearm skinfold thickness is independently but weakly associated with blood pressure, cholesterol and factor VII after taking into account associations with other skinfolds.

Obesity is a risk factor for fatal IHD amongst males such that, on average, a change in W/H^2 of 1 kg/m^2 results in a change of risk of 13%. Despite the association between W/H^2 and other cardiovascular risk factors its association with fatal IHD persists after taking these into account. The relation between obesity and fatal IHD is manifested after prolonged (greater than 5 years) follow up. There is no significant association between total mortality and obesity because the positive association with fatal IHD is at least partly counterbalanced by a tendency for patients dying of cancer to have somewhat lower levels of W/H^2 at entry to the study.

Of the two measurements of obesity, W/H^2 was more closely related to fatal IHD than either total or individual skinfolds perhaps because of the observer variability in the measurement of skinfolds.

The reduction of obesity should be afforded more prominence in public health programmes aimed at preventing ischaemic heart disease.

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