Familial and Non-Familial Factors Associated with Obesity

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Abstract

The work of my thesis is based on the MIDSPAN Family Study, which included a survey of the parent generation in 1972-6 and the offspring generation in 1996. The main aim was to investigate familial and non-familial factors associated with changes in body mass index (BMI) between the two generations and to identify the characteristics of susceptible subgroups.

The study populations come from a highly deprived area with high mortality and cancer incidence rates. In the parent population, BMI was positively associated with cardiovascular mortality and negatively associated with respiratory mortality. Only breast cancer and lung cancer incidences were associated with BMI. Lung cancer incidence was negatively associated with high BMI. The observed association was not the result of confounding effect of smoking or sub-clinical illness. The negative association between lung cancer incidence and BMI was found in other cohort screened at the same time as the parents cohort. This finding encourages further research explaining this observation at the biological level.

The first finding was that the prevalence of obesity (BMI>30kg/m^2) has doubled in sons while a slight increase in the prevalence of obesity was found in daughters with almost no change in mean BMI or the prevalence of obesity and overweight combined (BMI>25kg/m2). Comparison of BMI distributions in parents and offspring showed an anchoring of the lower parts of the BMI distributions and skewing in the top parts. To a certain extent this observation was found in all social class and smoking subgroups.

Parental obesity was the strongest factor associated with offspring BMI and obesity prevalence. The offspring of obese parents were more than four times as likely to be obese than the offspring of lean parents. Physical activity, smoking status and dietary intakes were the important environmental determinants of high BMI. However, the effect of these factors was not the same in men and women or in different social class

groups. Further, the correlates of high BMI were different in offspring with and without family predisposition to high BMI.

Familial susceptibility is an important factor associated with offspring obesity. The offspring of obese parents are at highest risk of becoming obese themselves. However, the effect of familial susceptibility depends on environmental and behavioural factors. This conclusion was based on findings from studying exceptions (obese offspring with obese parents and obese offspring with normal weight parents) and differences between groups of offspring (obese and normal weight offspring of obese parents and obese and normal weight offspring of normal weight parents) offspring groups. In the presence of family susceptibility, obese offspring were less likely to be smokers, to be in the manual social class and were less physically active than normal weight offspring. In the absence of family susceptibility, obese offspring were more likely to be former smokers, to be in the manual social class, were less physically active and reported high intakes of energy-dense foods than normal weight offspring. On the other hand, obese offspring with family susceptibility were more likely to be smokers, in the manual social class, physically active and had high food intakes compared to obese offspring without family susceptibility. Normal weight offspring with obese parents were more likely to be smokers, in the manual social and to report high food intakes.

The findings of this study are consistent with gene-environment interaction in the development of obesity and stress the fact that offspring with family susceptibility are more affected by differences in environmental and lifestyle factors. Individuals with familial susceptibility to obesity are at higher risk of becoming obese if they are former smokers, in the manual social class and physically inactive. They are less likely to become obese if they are current smokers or have manual father. The findings encourage further research to investigate the genetic and patho-physiological basis of these findings. Furthermore, these findings raise the possibility of intervention programmes targeted at high risk groups.

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Author's declaration

I declare the contents of this thesis to be all my work except where acknowledged on the previous page

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CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION

Definition

Obesity is described as "an excess of fat storage in the body adipose tissue", whereas overweight is defined as "an excess of body weight relative to height" (World Health Organisation 1998). Weight gain occurs first by increase in the size of fat cells in the body and later by increase in their number, to the extent that health may be affected significantly (Bray 1992). According to the World Health Organisation's (World Health Organisation 1998) classification—which is based primarily on the association between body mass index (BMI) and mortality— a person with a BMI (the weight in kilograms divided by the height in meters squared) of 30kg/m^2 or more is considered obese and a person with a BMI between 25 and 29.9 is considered overweight (Table 1-1). Some researchers may classify BMI based on the 85th percentile of the study population (Megnien et al. 1999). However, using percentile cut-offs will minimise the estimated risk associated with obesity because the cut-off points will increase as a population gains weight.

Obesity measures

Generally, BMI indicates general obesity and total fat storage. BMI is widely used to estimate the prevalence of obesity and allows comparison between and within groups or populations. It allows the identification of individuals or groups at risk of morbidity or mortality and hence permits the identification of priorities for intervention at individual and population level (Kopelman 2000).

The use of BMI to define obesity is based on the assumption that an individual with a BMI of 30kg/m^2 or more has an excess of fat mass in his/her body with no distinction between muscle or fat weight (Shaper, Wannamethee, & Walker 1997). BMI may not correspond to the same degree of fatness across different populations (Steering Committee 2000).

Furthermore, BMI is considered an inappropriate basis for measuring obesity in children and adolescents. Although some studies recommend the use of BMI in these cases, WHO defines overweight children as those exceeding the median weight-for-height plus two standard deviations (Gurney & Gorstein 1988). Recently, a new definition of overweight and obesity in childhood based on pooled international data for BMI, linked to the adult obesity cut-off point of 30kg/m^2, has been proposed (Cole et al. 2000). The use of recommended cut-off points allows international comparisons of prevalence of obesity (Cole, Bellizzi, Flegal, & Dietz 2000).

Abdominal (central or regional) obesity is a specific form of obesity. It is estimated using a waist to hip ratio (WHR), which is highly correlated with visceral adipose tissue (Björntorp 1992), to identify individuals at increased risk of obesity-related diseases (Table 1-1). Recently, waist circumference has been used to estimate intra-abdominal fat mass and total body fat (Table 1-1) (Pounder et al. 1998). It is thought that changes in WHR may result from changes in hip circumference and result in increased or decreased risk estimation, especially in females with large hip circumferences. Waist circumference may reflect abdominal obesity and associated risk (Han et al. 1996;Han et al. 1997;Han et al. 1995).

BMI and waist circumference are highly correlated with each other and it is difficult to separate the effects that each may have on health (Lean, Han, & Morrison 1995). Seidell pointed out that variation in BMI may be due to lean mass or fat mass but not fat distribution, whereas variation in waist circumference reflects both total and regional fatness (Seidell et al. 2001). Furthermore, BMI and waist circumference seem equivalent as risk factors for chronic disease.

Table 1-1: Definition of waist circumference and body mass index categories

BMI cut-offs		
Normal	<25 kg/m^2	
Overweight	25-29.9 kg/m^2	
Obese	≥30 kg/m^2	
Waist circumference cut-offs	**Men**	**Women**
Increased risk	≥94 cm	≥80 cm
Substantially increased risk	≥102 cm	≥88 cm

The Epidemiology of obesity

Obesity is recognised as a major public health problem world-wide. Intensive documentation of the patterns and trends of obesity in different populations has been reported. This has helped to identify populations at high risk of obesity and its complications, to predict the size of the obesity problem in the future and to help in the evaluation of intervention strategies (Gill, Antipatis, & James 1999).

Comparison of obesity prevalence data from different countries establishes several important points. First, countries in the first stages of economic transition have higher proportions of obese people in the wealthiest sector while underweight is more prevalent in the poor sector. In later stages the proportion of overweight people increases in the poor sector. A similar pattern exists in urban and rural areas. Urban populations have a higher prevalence of obesity compared to rural populations. However, the prevalence of obesity in rural areas has started to increase as rural populations have started to import the energy-dense, high fat diets and to adopt more sedentary lifestyles. Finally, women tend be obese, whereas men tend to be overweight. This pattern has started to change, however, and the prevalence of obesity is becoming similar in men and women.

The global epidemic of obesity

In the last three decades, the prevalence of obesity has been more common in developed countries and in the rich people in developing countries. Obesity is becoming a common world-wide phenomenon, however, and reaching epidemic levels in developing countries (Table 1-2). Evidence from several studies indicates that obesity is a major cause of morbidity, mortality and impaired life quality.

The obesity epidemic in the US has been well documented (Flegal et al. 2002;Flegal & Troiano 2000;Freedman et al. 2002;Mokdad et al. 2001;Ogden et al. 2002). The first report of trends in the US was in 1988 when Flegal studied trends in obesity or overweight between 1960 and 1980. According to the National Health and Nutrition

Examination Survey (NHANES) 67% of men and 62% of women were overweight or obese, of which 28% of men and 34% of women were obese. This trend affected the whole population, including children (Flegal & Troiano 2000;Ogden, Flegal, Carroll, & Johnson 2002).

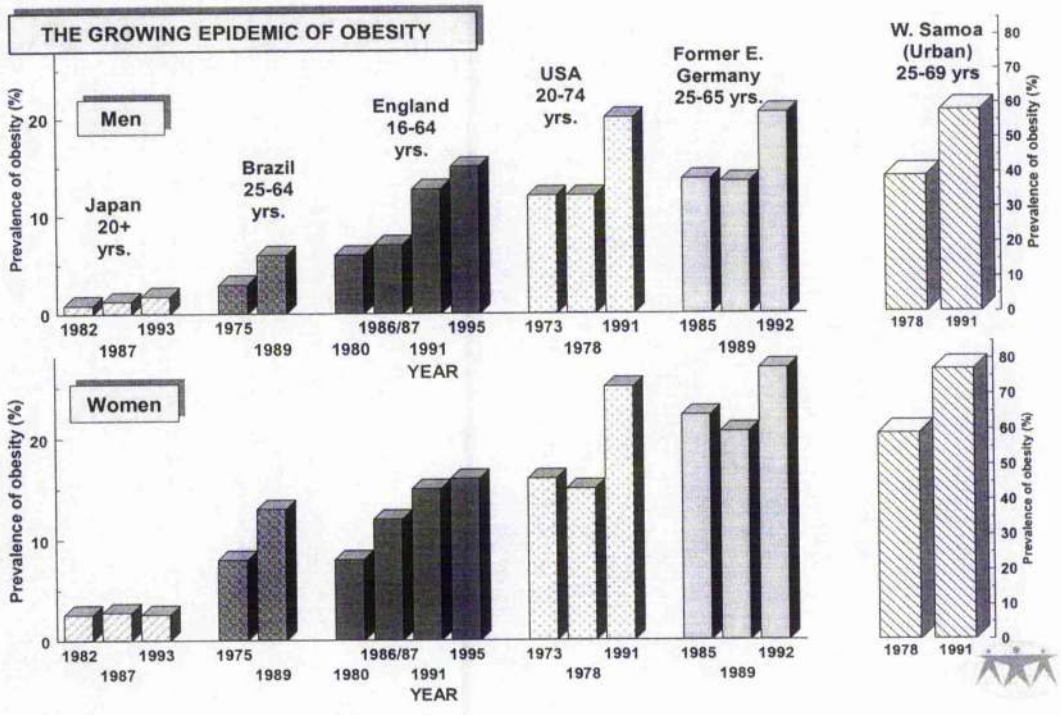
The obesity epidemic has also affected the European countries. Obesity prevalence ranges from 10-20% in men and from 10-25% in women. Obesity rates are highest in southern and eastern European countries.

Dutch studies reported an increase in obesity prevalence between 1976 and 1997 in men from 4.9% to 8.5% and in women from 6.2% to 9.3% (Visscher, Kromhout, & Seidell 2002). In Belgium, obesity prevalence increased from 9.2 to 14.5% in men between 1977 and 1992 (Stam-Moraga et al. 1998). A similar pattern was found in developing countries.

Even Mediterranean countries, which are famous for their healthy diet, have witnessed an increase in obesity prevalence. In France, one study reported a slight increase in obesity prevalence, between 1980 and 1991, especially in women (Maillard et al. 1999). Other French studies using three cross sectional surveys, have reported increases in obesity prevalence in men but not in women (Marques-Vidal et al. 2002). In Spain, obesity prevalence increased in men (7.6 v 12.2%) and women (8.9 v 12.1%) between 1987 and 1997, when both men and women had a similar prevalence (Gutierrez-Fisac et al. 2000;Gutierrez-Fisac, Regidor, & Rodriguez 1996).

The picture in developing countries is more striking. These countries face the problem of underweight due to malnutrition in addition to the problem of overweight and obesity because of changing lifestyle and habits. In Brazil for instance, obesity increased from 3.1 to 5.9% in women and from 8.2 to 13.3% in men between 1975 and 1989 (Monteiro et al. 1995).

Table 1-2: The growing epidemic of obesity world-wide.



Adopted from the IOTF.

Obesity epidemic in the UK

In Britain, the prevalence of obesity in adults doubled over a 20 year period, between 1980 and 1991 (Prentice & Jebb 1995), In England the prevalence of obesity in adult approximately trebled between 1982 and 2001. Data from the Health Survey for England has shown that the prevalence of obesity has increased from 6% and 8% in men and women respectively to 21% and 23.5%. A higher prevalence of obesity was found in some ethnic groups, particularly Black Caribbean and Pakistani women (The National Audit Office 2001).

In Scotland, mean BMI increased by 1kg/m^2 between 1984-6 and 1995, and from 26kg/m^2 in the Scottish Heart Health Study (SHHS) to 27kg/m^2 in the Scottish Health Survey. The prevalence of obesity for those aged 40 to 59 years, defined as BMI greater than 30 kg/m^2 for men and 28.6 kg/m^2 for women, increased from 12 to

22% in men and from 21 to 28% in women over the last ten years (The Scottish Office: Scotland's Health 1995).

It is hard to compare the prevalences of overweight and obesity in children because of the different and complicated definitions used. An international Reference standard was proposed in 2001 to use BMI to monitor trends in overweight and obesity in young people. A large increase was found in the prevalence of overweight and a slight increase in prevalence of obesity in children between 4 and 11 years of age (Chinn & Rona 2001). The prevalences of overweight and obesity were higher among girls compared to boys and among Scottish children compared to English children.

Obesity co-morbidity

Obesity is a chronic disease, with an International Classification of Diseases code (178) that involves genetic predisposition, hormonal and behavioural aspects. The major complications include multiple morbidity, reduced quality of life, discrimination and early mortality (Table 1-3).

Table 1-3: Medical consequences of overweight and obesity

Physical	**Metabolic**	**Social**
Tiredness	Hypertension	Isolation
Breathlessness	NIDDM	Agoraphobia
Varicose veins	Hepatic steatosis	Unemployment
Back pain	Hyperlipidemia	Family/marital stress
oedema/ cellulites	Hypercoagulation	Discrimination
Sweating/ intertrigo	IHD and stroke	
Stress incontinence		
Anaesthetic/ surgical	**Endocrine**	**Psychological**
Sleep apnoea	Hirsutism	Low self-esteem
Chest infections	Oligomenorrhea/ infertility	Self-deception
Wound dehiscence	Metromenorrhagia	Cognitive disturbance
Hernia	Oestrogen-dependent	Distorted body image
Venous thrombosis	Cancers: breast, uterus, prostate	Depression

Adopted from (Lean 2000)

Coronary heart disease usually refers to angina pectoris, myocardial infarction, and sudden death. The published literature emphasises the role of obesity in the development of coronary heart disease. Weight gain affects all elements of CHD, including dyslipidemia (borderline-high cholesterol concentration, high triglyceride and LDL-cholesterol concentrations, and low HDL-cholesterol concentration),

hypertension, insulin-resistant glucose intolerance, left ventricular hypertrophy, hyperuricemia and elevated fibrinogen (Kannel, Agostino, & Cobb 1996;Lean 2000). Cross-sectional and longitudinal studies have shown a relationship between abdominal obesity and CHD (Pi-Sunyer 2000).

The British Regional Heart Study was based on 7735 men aged 40-59 years at screening between 1978-1980. From this cohort, it was estimated that each increase in 1 BMI from 20.0-21.9 onwards was associated with an approximately 10% increase in the rate of coronary events and a 10% increase in a combined end point, including stroke, heart attack or diabetes (Shaper, Wannamethee, & Walker 1997).

Many cross-sectional and longitudinal studies have found that diabetes mellitus, impaired glucose tolerance and insulin resistance are strongly associated with obesity. The suggested explanation is that excess body fat causes increase in insulin resistance, which in turn predisposes to diabetes (Björntorp 1992). However, other proteins also appear to have a role in mediating this relationship. Leptin and resistin are thought to link obesity to diabetes (McTernan et al. 2002;Senior 2001a;Senior 2001b;Steppan et al. 2001).

On the other hand, weight loss results in an improvement in glucose levels and insulin sensitivity in diabetic patients. These results were achieved regardless of the method used for weight loss, either caloric restriction, dieting, or surgery (Scheen 2003;Sjostrom et al. 2000).

While some obese people develop diabetes quickly, others may be obese for years without developing diabetes (Felber, Acheson, & Tappy 1992). This variation might depend on genetic predisposition to obesity or diabetes or both (Pi-Sunyer 2000). Studies based in twins, family and ethnicity have shown a strong genetic basis for both obesity and diabetes (Lindsay et al. 2001). These findings were confirmed in studies of populations with high prevalences of obesity and diabetes such as the Pima Indians (Knowler et al. 1991; Hanson et al 1998).

Hypertension is associated with both general and abdominal obesity. Although large proportions of hypertensive individuals are obese, not all hypertensives are obese and vice versa. The association between obesity and hypertension becomes apparent when an obese person with high blood pressure loses weight; his /her blood pressure is reduced to the accepted normal range (The Trials of Hypertension Prevention Collaborative Research Group 1997).

For many years it has been known that both systolic and diastolic blood pressures and BMI are correlated between and within parents and offspring to varying extents. The relative contributions of genes and environment to the familial aggregation of blood pressure and BMI have been estimated in many studies (Harrap et al. 2000;Cui, Hopper, & Harrap 2002;Rice & Province 1994). The Victorian Family Heart Study, for example, a study of healthy adult families, including monozygotic and dizygotic twins, has estimated that genetic factors accounted for 41%, 46% and 42% of the variation in SBP, DBP and BMI respectively. Family environmental factors shared during cohabitation accounted for 13%, 19% and 35% of adult variance in the same phenotypes (Harrap, Stebbing, Hopper, Hoang, & Giles 2000).

Obesity pathogenesis

During famine conditions, the human body has developed the ability to store fat for the period of energy deprivation. However, these days, we are surrounded by energy-rich, unlimited and easily available food, and hence our bodies accumulate excess energy for no useful purpose.

Regulation of energy balance

Human obesity usually results from a very small positive energy balance over many years. This positive energy balance may be due to over-consumption or reduction in energy output. A small over-consumption on a daily basis is hard to notice and not easily controlled. Similar reasoning applies to energy output. Several studies showed that physical inactivity is the main cause of the observed obesity epidemic world-wide.

The complex molecular mechanisms by which ingestion behaviour, energy expenditure and dynamic energy storage in adipose tissue are regulated and matched remain largely unknown. Two signalling mechanisms, including brain insulin and leptin protein pathways, are thought to match energy intake and expenditure. The responsiveness of these systems to insulin and leptin decrease in obesity. These changes make the right matching of intake and expenditure even more unlikely as obesity begin to develop (Campfield & Smith 1999).

The regulation of food intake involves the central nervous system (CNS), and hormonal and neurochemical signals relating to brain and metabolic states (McMinn, Baskin, & Schwartz 2000). One hypothesis postulates that food intake is controlled by the interaction of five classes of signal. They are the hypothalamic neuropeptides, brain insulin, leptin, metabolic signals including transient decline in blood glucose concentration and ascending and descending neural inputs (Campfield & Smith 1999).

Energy output on the other hand includes resting metabolic rate, dietary and cold-induced thermogenesis and the energy cost of voluntary physical activity. Resting metabolic rate regulation is a product of energy intake, energy balance, hormonal and autonomic neural activity. Resting metabolic rate decreases when an individual reduces caloric intake and shifts into a state of negative energy balance. The regulatory adaptation appropriately reduces obligatory energy expenditure when energy intake is reduced. This adaptation requires falling concentrations of both circulating insulin and leptin. However, this same adaptation causes a deceleration of weight loss following voluntary calorie restriction and contributes to the difficulty of maintaining weight loss, once achieved, over time (Bogardus 1986; Campfield 1999).

Leptin

Leptin is a peptide protein product of the adipose specific *ob* gene (Auwerx & Staels 1998). Its main effect is thought to be to inhibit the synthesis and release of the hypothalamic neuropeptide Y, which increases food intake, decreases thermogenesis, and increases levels of insulin and corticosteroid in the plasma, but leptin may have other targets and pathways inside and outside the brain. A particularly important effect may be to suppress ingestion of fat without affecting carbohydrate ingestion (Sørensen & Echwald 1996).

Adipose tissue leptin and plasma leptin levels have been found to be closely correlated with the size of adipose tissue deposit (Zimmet et al. 1996), which suggests that obesity is not caused by a deficiency in leptin production. These findings gave rise to the leptin resistance hypothesis, which argues that obesity is the result of inadequate leptin signalling for a given leptin concentration (Auwerx & Staels 1998). Caro and his colleagues have compared the leptin level in CSF to leptin level in serum in obese and lean individuals. They found higher levels of leptin in obese individuals in both serum and CSF compared to lean individuals. The leptin CSF/serum ratio was 4.3 fold higher in lean than in obese individuals. These results

suggest that leptin enters the brain by saturable transport system, and that the capacity of leptin transport is lower in obese individuals (Caro et al. 1996).

Leptin expression and action is influenced by insulin, other candidate effectors include melanocyte-stimulating hormone and receptor, glucagon-like peptide-1, corticotropin- releasing hormone and melanin concentrating hormone (Auwerx & Staels 1998).

Resistin is another protein that is secreted from fat cells (Steppan et al 2001). High levels of resistin were found in individuals with genetic and diet-induced obesity (Berger 2001;Senior 2001b;Steppan et al 2001).

Genetics of obesity

Obesity is a multifactorial disease in which environmental and genetic factors interact. In the Human Obesity Gene Map, the authors reviewed evidence from rodent and human obesity cases caused by single-gene mutations, Mendelian disorders exhibiting obesity as a clinical feature, quantitative trait loci (QTL) uncovered in human genome-wide scans and in cross-breeding experiments in various animal models, and association and linkage studies with candidate genes and other markers (Chagnon et al. 2000).

Rare cases were reported to be the result of single gene mutation. Forty-seven human cases of obesity were reported in the 2000 update of human obesity gene map (Pérusse et al. 2001). These cases are characterised by severe obesity with childhood onset (Clement, Boutin, & Froguel 2002). These cases were caused by mutations in the melanocortin receptor 4 gene (MC4R), pro-opiomelanocortine gene (POMC) (Hinney et al. 1999), leptin gene (LEP) (Strobel et al. 1998), uncoupling protein3 (UCP3) and domain D4 receptor (DRD4) genes (Nothen et al. 1994). All these obesity genes encode proteins that are involved in the leptin axis and its hypothalamic targets (Clement, Boutin, & Froguel 2002).

1.2 STUDY AIMS AND RESEARCH QUESTIONS

Obesity is an increasing problem world-wide. Although many studies have investigated the associations of obesity with environmental, behavioural and familial factors (as shown in later chapters), the mechanism by which these factors combine is not clear. Most studies refer to changes in environmental factors as the major driving factors causing the global increase in obesity.

The central hypothesis of this thesis is:

While changes in BMI and in the prevalence of obesity are the result of environmental factors, population subgroups with familial susceptibility to obesity are more vulnerable to the effects of environmental factors.

The general goal of this thesis is to study familial and non-familial factors associated with obesity in a population in the West of Scotland using data from parent and offspring generations. The understanding of the roles of familial and non-familial factors in obesity development will help in planning effective and specific prevention and intervention programs as well as enhance further specific research on the aetiology and prevention of obesity.

The three general aims of the thesis are:

1- to investigate the factors associated with obesity-related morbidity and mortality in the general population of Renfrew and Paisley. Morbidity analyses included all cancer and cancer specific incidences. The analyses focused on understanding the patterns of relationship between obesity and outcomes, confounding factors, length of the follow-up period, exclusion criteria and identification of high-risk groups.

2- to describe and explain changes in the prevalences of obesity and mean BMI between the parent and offspring generations, including an analyses of similarities and differences in correlates of obesity in both generations.

3- to investigate the role of familial susceptibility in offspring obesity. This section focuses on the heritability of BMI and estimates the risk of becoming obese in offspring with obese relatives. It also describes the characteristics of offspring with contrasting family susceptibility.

Each chapter has a list of specific aims and a review of relevant literature.

CHAPTER 2

METHODS

2.1 INTRODUCTION

This thesis is based on data from the MIDSPAN Family Study, a two-generation study based on offspring aged 30-59 in 1996 whose parents, aged 45-64, took part in a cardiorespiratory screening survey in 1972-6 in two towns in the west of Scotland.

The first part of this chapter provides a detailed description of the study populations, sampling processes, response rates and measurements. The second part provides a review of the statistical methods used in the study. In each chapter there will be a description of the populations subsets used and the specific statistical methods used in that chapter.

2.2 STUDY DESIGN

The MIDSPAN Family Study comprises two cross-sectional studies: The Renfrew and Paisley population and the Family Study population. Data from the Collaborative Occupational Study were also used to check the consistency of some results found for the Renfrew and Paisley population with other populations. Descriptions of each population follow below.

Renfrew and Paisley Study

Sampling

Renfrew and Paisley are two towns 10 miles west of Glasgow with high level of socio-economic deprivation. A door-to-door census of all households was carried out in 1972 to 1976. Everyone aged 45-64 years resident in the two towns was invited to attend screening examination (Hawthorne et al. 1995). 15406 men and women participated in the survey with a 78% response rate.

All participants were re-invited to attend a second screening survey between 1977-79. More than 50% (8531) of the original attendants attended the second screening where similar measurements were collected.

Measurements

On the screening day, an extensive questionnaire completed by the subject was checked by experienced interviewers. This questionnaire included information about age, gender, marital status, smoking, occupation and cardiorespiratory symptoms.

Smoking was classified in terms of the average numbers of cigarettes smoked per day using the categories: never smoked; 1-14; 15-24; 25-34; and 35 or more. Former smokers were classified as ex-smokers of five years or more. Pipe or cigar smokers only were classified separately.

Respiratory and cardiovascular symptoms were assessed using the Medical Research Council bronchi questionnaire and the Rose chest questionnaire respectively.

Social class was determined by occupation, according to the Registrar General's Classification, except for housewives and retired women whose husbands' or fathers' occupations were used.

At the screening examination, blood pressure was recorded using the London School of Hygiene sphygomo-manometer and a cuff of 12 x 22 cm (Rose, Holland, & Crowley 1964). Forced expiratory volume in one second (FEV1) was measured using a Garthur Vitalograph. Measurements of height and weight were made for subjects in indoor clothing and without shoes. Height was measured to the nearest cm and weight was measured to the nearest kg.

Plasma cholesterol concentration was measured (using non-fasting blood sample) by the method of Annan and Isherwood. Glucose was measured (using whole blood) by the measurement of oxygen consumption.

Participants in the Renfrew and Paisley study were flagged at the National Health Service Central Registry in Edinburgh, and notifications of deaths have been received for 25-year follow-up. Causes of death were coded to ICD-9 (International Classification of Diseases, ninth edition).

Family Study

Sampling

Selection of adult offspring was based on information collected from their parents who took part in the Renfrew and Paisley study. Table 2-1 shows the process of selecting offspring eligible to participate in the Family Study 1996.

The original Renfrew and Paisley study population included 4064 married couples. In 1996, addresses were available for 3445 couples (including the death certificate informant when both parents had died). 2841 responded with information on the

names, dates of birth and addresses of natural offspring. 4829 offspring aged 30-59 years were identified from 2365 couples with children. 3202 offspring from 1767 families lived locally, within 30 miles, and formed the eligible population for this study. 1040 sons and 1298 daughters offspring from 1477 families participated (Upton et al. 2000).

Fieldwork took place between 4th March and 12th December 1996. It was based at a temporary community clinic established at the YMCA in Paisley to survey those living in Renfrew and Paisley towns. An additional clinic was established, in the grounds of Gartnavel Hospital for three weeks, to survey offspring who lived in Greater Glasgow.

All 3202 eligible offspring were invited by post to complete a cardiorespiratory questionnaire at home and to bring it with them when they attended an examination at the community clinic.

Out of the 3202 offspring aged 30-59 who were living locally, 2342 attended the cardiorespiratory examination. Of these 2342, 2338 completed the examination and the survey questionnaire. The individual response rate was 73% (2338/3202). The family response rate, defined as the number of families where at least one offspring attended, was 84% (1477/1767).

Measurements

A semi-structured questionnaire was piloted using patient volunteers at Blantyre Health Centre in the west of Scotland. The questionnaire included the following information

Personal: Gender, age, marital status, education, occupation, housing tenure, car ownership, smoking habit, exposure to passive smoking, reported physical activity, and the Yarnell Food Frequency questionnaire (Yarnell et al. 1983), which had previously been adopted for the use in Scotland (Bolton-Smith et al. 1991;Bolton-Smith, Brown, & Tunstall-Pedoe 1991) (See Chapter 7).

Medical history: Medical history, medication, family history, cardiovascular and respiratory symptoms (including identical questions to the 1972-6 survey), and the Rose chest pain questionnaire in addition to the European Community Respiratory Health Questionnaire.

Women only: Women were asked about menstruation, pregnancy, the use of contraception and hormone replacement therapy (HRT).

Early life: All offspring were requested to ask their mothers about their birth weight, place of birth, infant feeding and whether they were admitted to hospital with respiratory illness in their first two years of life.

Family data: Parents, number of siblings, childhood circumferences, health beliefs and behavioural changes, vehicle access, accommodation, parental smoking and parental occupation.

Participants were also asked to provide details of their parents names, dates of birth and the addresses where they would have been living between 1972 and 1976. This information was used to check the link between parents and offspring were correct. Of five individuals who attended the clinic but who were not included in the study population, one was excluded because of a linkage error and four because they did not complete the questionnaire.

Cardiorespiratory examination

Participants were asked to bring their completed questionnaires with them to the clinic. The clinic was staffed by six research nurses who rotated between measurement stations. Questionnaire answers were first checked for completeness (station 1); and after written informed consent, measurements were made in the following order: blood pressure, height, sitting height, weight and spirometry (station 2); an electrocardiogram (ECG) and waist-to- hip circumference (station 3); and a 66 ml non-fasting venous blood sample.

Blood pressure

Blood pressure and pulse were recorded using a Dinamap 8100 instrument with a cuff applied to the left arm in the sitting position. After 5 minutes timed rest with a stop-watch, three readings were taken and the mean of the last two was used. The Dinamap cuff-size indicator was used to find the appropriate cuff. A daily static calibration check of the Dinamap against an Accuson test gauge at approximately 200, 150, 100 and 50 mm mercury pressure were made. There was no calibration drift during the study.

Height

Standing height was measured in stockinged feet in the Frankfort plane using a Holtein standiometer. A single measurement was made after participants inhaled and stretched to reach their maximum height. Measurements were recorded to the nearest mm. Sitting height was measured using the same stadiometer with the subject sitting on a stool of known height. The calibration of the stadiometer was checked daily using a 1800mm metal rod prepared by the Clinical Physics Department at the Western Infirmary to British Standards.

Weight

Weight was measured to the nearest 0.1kg using Seca digital scales in stockinged feet wearing indoor clothes. Participants were asked to empty their pockets before measurement. The calibration of the scales daily using five 15-kg standard weights was made. There was no calibration drift during the study.

Waist/ hip circumferences

Waist and hip circumferences were measured using a Wessex self-tensioning tape. Waist circumference was measured unclothed. Prior to measurement, the lower costal margin and the iliac crest were located, and the skin was marked with ink in

the mid-axillary line. The mid-point between the iliac crest and costal margin were located with a ruler and marked with ink before measuring the circumference through these points. Measurements were made during gentle expiration. The goal of measurement was two readings within 1 cm of each other. Hip circumference was measured over indoor clothes. Measurements were made at the widest point of the hips, with the tape horizontal, aiming to record two measurements within 1 cm of each other.

Blood samples

66 ml of non-fasting venous blood were collected using the Vacutainer system. Participants were seated on a chair that could be reclined if they fainted. The sample was distributed between specimen tubes for subsequent analysis (electrolytes; Gamma GT; urate; total and HDL cholesterol; cotinine; Vitamin A, C and E; Haematocrit; white blood count; Viscosity; Fibrinogen; Factors VII and VIII; Activated protein C resistance; Von Willebrand factor; fibrin D-dimer and plasminogen activator inhibitor activity).

The clinic was equipped with two Heracus centrifuges which were used to prepare aliquots of citrated plasma for the coagulation analysis, and aliquots of serum or plasma for saving at –70° C. The clinic was equipped with a –40° C freezer for immediate storage.

The following samples (serum, plasma (EDTA and Litium heparin) and four DNA aliquots are stored in the Laboratories of the Western Infirmary hospital.

Collaborative Occupational Study

Sampling

The cohort for this study was recruited from 27 workplaces throughout the central belt of Scotland between 1970-73. 6022 men and 1006 women took part in the survey, including 3766 men aged 35-64 at the time of screening (Davey Smith et al. 1998).

Notification of death is received from the office of the General Registrar for Scotland.

Measurements

Participants completed a self-administered questionnaire, which included socio-demographic data; health status measures and health related behaviours. However, it differed from the questionnaire used in Renfrew and Paisley study, as it included more detailed questions about lifestyle and early life. At a temporary centre, participants had height and weight check, respiratory function test, 6 lead ECG, blood pressure and chest x-ray. The examinations used were similar to those used in the Renfrew and Paisley study. Cholesterol, triglycerides and phenotyping of lipoproteins were measured using fasting blood plasma samples (Davey Smith et al 1998).

2.3 STATISTICAL ANALYSES

In this thesis, a variety of statistical methods have been used to analyse the data available from the study populations. Data analysis was held using SPSS-9 for windows, STATA-6 (StataCorp 1999) and Ml-wiN1.10 (Goldstein et al. 1998;Rasbash et al. 2000) softwares. In each chapter of the thesis, there is a specific description of the statistical method used. The following is a brief description of the main tests used.

Descriptive statistics

Simple presentation of data included percentages of categorical variables and means (standard deviation or standard error) for continuous variables.

The Chi-square test was used to detect significant associations between two categorical variables. The test compares the observed values to the expected value, which is calculated from the distribution of the variables in the whole sample.

The t-test was used to compare normally distributed continuous data from two independent samples. The test compares the difference between the sample means with the standard error of this difference.

Regression analyses

In regression analysis we fitted a predictive model to our data and used the model to predict values of the dependent variable from one or more independent variables. Simple regression seeks to predict an outcome from a single predictor whereas multiple regression seeks to predict an outcome from several predictors. Multiple regression was used first to study the effect on the outcome of simultaneous changes in several predictors and to identify the predictors having the most influence on the outcome. The type of regression was determined by the outcome variable, with linear regression being used for continuous variables and logistic regression for binary

variables. A description of the assumption and theory behind each statistical method used follow below.

Linear regression

In this type of regression the model fitted to predict a continuous outcome is based on summarising the data with a straight line. The straight line is fitted using the least squares method. The least squares method is a way to finding the line that best fit the data (i.e. finding the line that goes across as many of the data points as possible). This line is found by ascertaining that the line results in the least amount of difference between the observed data points and the line.

Simple linear regression is based on this equation:

$$Y = \beta_0 + \beta_1 X_i + \varepsilon_i$$

Where Y is the predicted outcome, β_0 the intercept of the line, β_1 the slope of the line, ε the residuals which are the difference between the predicted and observed values of Y for the i^{th} subject.

In multiple regression, a similar equation is derived in which each predictor variable has its coefficient, and the outcome variable is predicted from a combination of all the variables multiplied by their coefficients plus a residual term.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n X_n + \varepsilon_i$$

Y is the outcome variable, β_1 is the coefficient of the first predictor (X_1), β_n is the coefficient of the nth predictor (X_n), ε is the residual term.

$\mathbf{R^2}$ measure represents the amount of variance in the outcome explained by the model relative to how much variation there was to explain in the first place.

Logistic regression

Logistic regression is a multiple regression but with an outcome variable that is a categorical dichotomy and predictor variables that are continuous or categorical.

Logistic regression predicts the probability of Y occurring given known value of X_1.

$$P(Y) = \frac{1}{1 + e^{-(\beta_0 + \beta_1 X_1 + \varepsilon_i)}}$$

In which P(Y) is the probability of Y occurring, e is the base of natural logarithms and the other coefficients form a linear combination similar to the simple regression.

Logistic regression equation expresses the linear regression equation in logarithmic terms and thus overcomes the problem of violating the assumption of linearity.

Cox's proportional hazards regression analysis

Survival analysis is concerned with measuring the risk of occurrence of an outcome event as a function of time and also concerned with the comparison of survival curves for different combinations of risk factors.

Cox's regression modelling is a semi-parametric approach. No particular type of distribution is assumed for survival time, but a strong assumption is made that the effects of the different variables on survival are constant over time and are additive in a particular scale.

The term proportional hazards arises from the fact that the relative risk of failure or hazard ratio at time ***t*** for any two subjects ***j*** and ***k*** is given by the ratio of their hazard functions. The hazard function represents the risk of dying in very short time interval after a given time, which can be interpreted as the risk of dying at time ***t***.

In Cox's regression the dependent variable is the hazard at the given time, if there are several independent variables of interest x_1 to x_p, the hazard function at time ***t*** will be

Hazard function: $h_i = h_{0i} \exp(\sum_{j=1}^{p} b_j x_j)$

P= independent variable, h_{0t}=baseline hazard function.

Hazard ratio: $\frac{h_{it}}{h_{kt}} = \exp\left[\sum_{j=1}^{p} b_j\left(x_{ij} - x_{kj}\right)\right]$

Multilevel modelling

Multilevel modelling is used for data with hierarchical structure. For example, offspring are grouped within families and families are grouped geographically (Ecob 1996;Golstein 1991).

Multilevel modelling was used to estimate covariance between spouses, between siblings, between parents and their offspring, in addition to variation between spouses and variation between offspring.

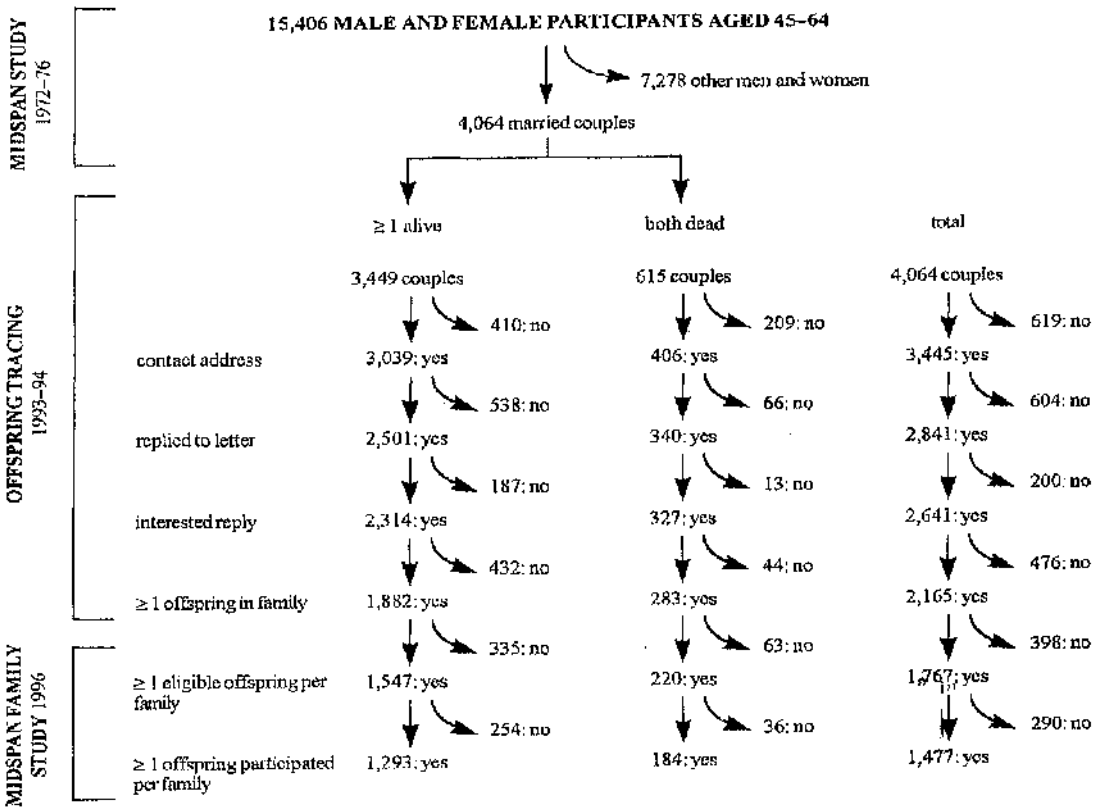
Estimates were based on the following model:

$$\log BMI_{ij} = \beta_{0ij} father_{ij} + \beta_{1ij} mother_{ij} + \beta_{2ij} son_{ij} + \beta_{3ij} daughter_{ij} + u_j + e_{ij}$$

u_j: is the random component between families

e_{ij}: is the random compartment between individuals.

Table 2-1: Selection of 1767 eligible families from 4064 married couples who participated in the original Renfrew and Paisley Study in 1972-6



CHAPTER 3

CHARACTERISTICS OF MIDSPAN FAMILY STUDY

3.1 INTRODUCTION

MIDSPAN Family Study is a two generation cardio-respiratory study. The Renfrew and Paisley study involved screening 78% of the general population of two towns in the West of Scotland. The offspring of married couples, who participated in the original study, were traced between 1993 to 1994. Some 20 years later, offspring aged between 30 to 59 and living locally were invited to take part (Chapter Two).

Given the complicated nature of the sampling process for the study populations, it is difficult to assess the representativeness of the offspring study population, and thus, the generalisability of the research findings.

Figure 3-1 shows a flow diagram indicating the sampling process. 78% of the Renfrew and Paisley general population have taken part in the survey leaving 22% non-participants. Out of 5014 offspring, for 4064 couples, 3202 aged 30 to 59 offspring were eligible to take part in 1996. 2338 offspring have participated in the Family Study in 1996, for 1477 parents.

The aim of this chapter is to put the study populations in context by comparing participants and non-participants at different stages, and by comparison with other Scottish and UK studies carried out at the same times. In this chapter we attempt to answer the following questions:

i. **How did participants in the original Renfrew and Paisley study compare with non-participants?**
ii. **How did participants in the original Renfrew and Paisley study compare with participants in similar epidemiological studies carried out in the UK at the same time?**
iii. **How do the parents of offspring who participated in the family study compare with other married couples who participated in the Renfrew and Paisley Study but who did not have offspring participating in the offspring study?**
iv. **How do offspring who participated in the Family Study compare with offspring who did not participate?**

v. **How do offspring who participate compare with offspring who had left the area and were not invited to participate?**

vi. **How do offspring who participated in the study compare with participants of the Scottish Health Survey, carried out at the same time?**

3.2 CHARACTERISTICS OF STUDY POPULATION

i How did participants in the original Renfrew and Paisley study compare with non-participants?

The participants were representative of the local general population because of the high response rate in the Renfrew and Paisley study (78%). There is not any information available about the non-participants. However, in unpublished work, by Professor Hole, a comparison between the expected death rate based on the Scottish population with the observed death rate in the Renfrew and Paisley population was done. Results showed that participants in the Renfrew and Paisley study have a lower death rate than that for the local general population. These results might be due to the following factors: first, people with health problems were not interested in taking part in the survey because they knew that they had a health problem and they were consulting their local GP. Second, the people who took part in the study were more interested in their health and they may have subsequently been more likely to take on board the health messages which have become more common over the years and that have altered their lifestyle to a degree. Finally, there were differential response rates by sector corresponding to the socio-economic profile of the sectors (Hole 2003).

ii How did participants in the original Renfrew and Paisley study compare with participants in similar epidemiological studies carried out in the UK at the same time?

The characteristics of participants in the Renfrew and Paisley study were compared to other British studies conducted at the same time (Hawthorne, Watt, Hart, Smith, & Gillis 1995). In summary, men in Renfrew and Paisley were shorter, had higher blood pressure, a higher proportion of current smokers, lower FEV1, higher level of reported angina, breathlessness and chronic bronchitis than men in other UK studies. There were no UK studies of women for comparison. In comparison with men in Renfrew and Paisley Study, women were shorter, had higher serum cholesterol, fewer current and former smokers, lower FEV1 and higher level of reported breathlessness.

iii How do the parents of offspring who participated in the family study compare with other married couples who participated in the Renfrew and Paisley Study but who did not have offspring participating in the offspring study?

Compared to the other married couples who participated in the original Renfrew and Paisley study, but who did not have offspring who participated in 1996, parents of offspring who participated in 1996 were less likely to be current smokers and more likely to be in the non-manual social class. There were no differences between offspring parents and their married peers in other classical cardiovascular risk factors and symptoms, nor in anthropometric variables (Table 3-2 & Table 3-3).

iv How do offspring who participated in the Family Study compare with offspring who did not participate?

The only information available for offspring who did not participate in the study in 1996 comprises their personal age, sex and parental BMI and social class. Overall, there was no difference between participating and non-participating offspring (Table 3-4 and Table 3-5). Response rate was similar across paternal, maternal and mid-parental BMI categories.

v How do offspring who participate compare with offspring who had left the area and were not invited to participate?

About half the non-participating (51%) offspring are no longer living locally in the study area. Men who migrated from the study area were younger (43.4±7.8) than offspring who participated in the Family Study (44.3±6.3) and those who didn't participate and were living locally (44.7±6.6). There was no age difference between the three groups in women (Table 3-5). Offspring who no longer live locally were not different from those who participated in the Family Study. However, they had higher prevalence of obese mothers compared to offspring who didn't participate in the Family Study (16% v 14%). This difference was minor compared to participating offspring (16% v 15%)

vi How do offspring who participated in the study compare with participants of the Scottish Health Survey, carried out at the same time?

The Scottish Health Survey (SHS) is a cross-sectional survey of the general population of Scotland conducted within 12 months of the Family Study (The Scottish Office: Scotland's Health 1995). Approximately 90% of Family Study population were aged 35-54, so comparison between the two surveys was restricted to this age group.

In the Family Study, there were more non-manual and fewer manual men and women compared to the SHS. This is due to the higher proportion of men and women in class I/II in Family Study, the lower proportion of men in class IV/V (10% v 16%) and the lower proportion of women in class III manual (7% v 21%) compared to SHS (Table 3-6).

Participants in the Family Study were more likely to be never smokers and less likely to be current smokers. The prevalences of current smokers in Family Study men were lower than that in SHS (23% v 29 in 34-44 group and 26% v 34% in 45-54 group). Similar results were found in women (26% v 34 in 34-44 group and 24% v 37% in 45-54 group).

There were fewer differences in weight, height and BMI between the Family Study and the SHS populations. Family Study women, aged 45-54 years, had lower BMI compared to SHS women, but there was no difference in weight or height. However, there were slight differences in men's height, in men aged 45-54 years, and BMI in men aged 34-44 years. There was no significant difference in obesity prevalence (BMI $\geq$30kg/m^2) between the two surveys.

Compared to SHS, systolic blood pressure was lower in Family Study men and women. Diastolic blood pressure was higher in Family Study men. Total serum cholesterol was lower in Family Study men and women, and HDL-cholesterol was lower in women only.

3.3 DISCUSSION

The original Paisley and Renfrew general population study comprised a 78% participation rate from men and women aged 45-64 living in two Scottish towns in 1972-6 characterised by high levels of socio-economic deprivation, cancer incidence and all cause mortality.

Men and women included as the parent generation are a sub-set of the Renfrew and Paisley population, defined by parenthood, contactability, willingness to provide information about their offspring and the availability and participation of offspring living locally in a subsequent, large cardio-respiratory survey. Despite these many possible sources of bias, the parents appear representative of men and women in the original general population survey with respect to mean BMI, blood pressure, serum cholesterol and social class. They only differ in the proportion of current smokers, which was lower in the parents of the Family Study.

Adults participating in Family Study are not representative of the general Scottish adult population. Participating offspring seem to have better health profile compared to the SHS population 1995. Family Study men and women are more likely to be never smoker, less likely to be in the manual class, and had a lower blood pressure, serum cholesterol and BMI than SHS participants.

On the other hand, participating offspring appear to be representative of all offspring identified for couples who took part in the Renfrew and Paisley survey. There was no significant difference between participants and non-participants in their age, father's social class and parent obesity. Participating offspring were representative of families whose offspring were eligible to participate in the Family Study, with response rate of 84%.

In addition, although Family Study population is different from the SHS population, the Family Study has a reasonably large number, which increases the findings credibility.

3.4 SUMMARY

The Renfrew and Paisley study population is representative of the general population in the West of Scotland and has a different profile compared to other UK populations. Parents of offspring in the Family Study were not different from couples who did not have participating offspring, with the exceptions that the former group were less likely to be smokers and more likely to be in the non-manual social class.

Offspring in the Family Study were not typical of the Scottish adult population. However, they were representative of families in the Renfrew and Paisley study population and the sample size was reasonably large.

The study population is unusual, but may be of value in describing and explaining the role of familial and non-familial factors affecting BMI and obesity within a particular population

Figure 3-1: Study populations selection

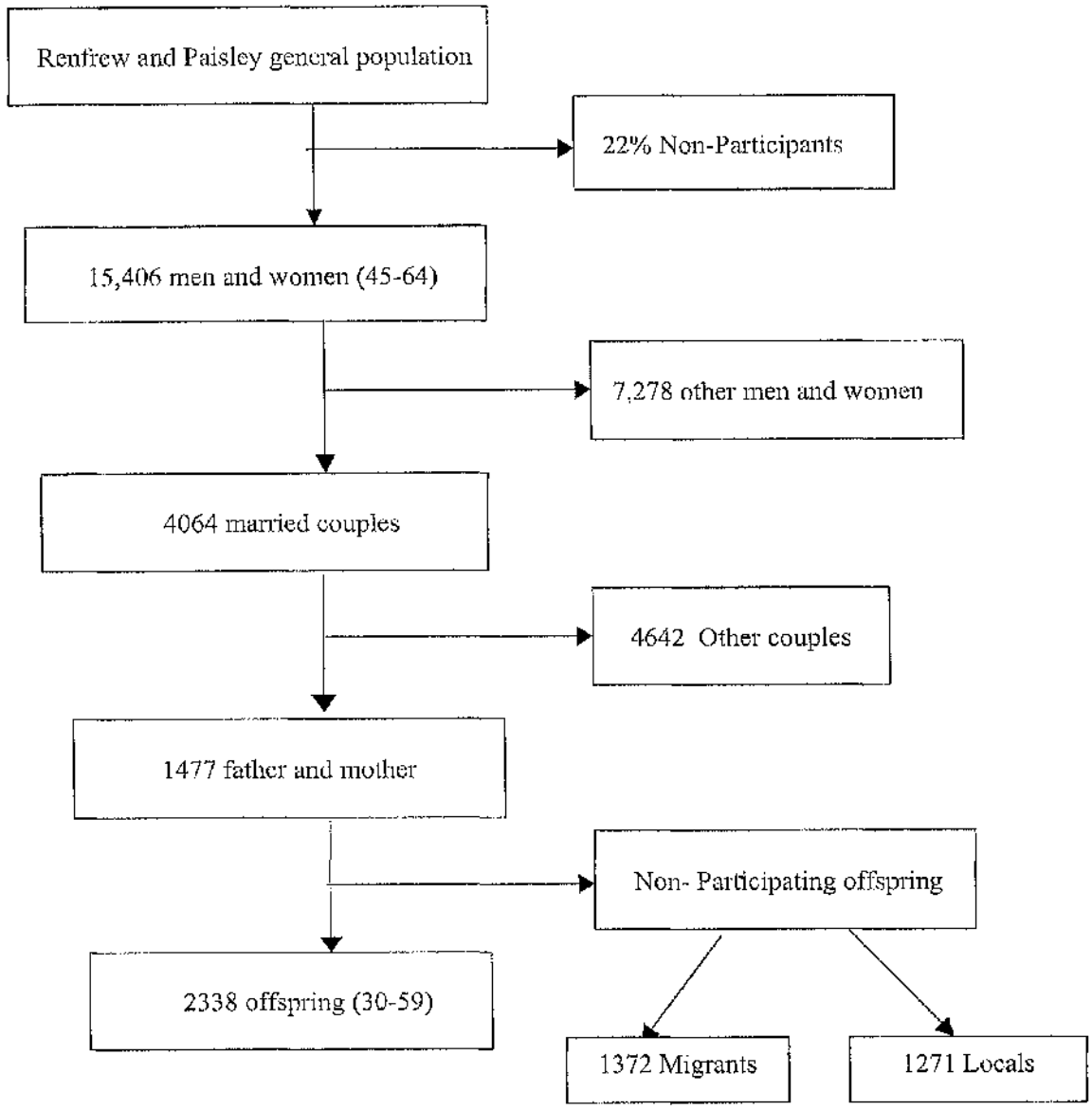


Table 3-1: Age standardised[1] summaries of variables in male parental population

% (N)	Fathers	Non-study married	Test[2]
	1477	4779	
Mean Age (years)	54.9	53.8	
Never smoker	21.1	17.7	9.33
			0.0023
Former smoker	26.2	24.3	2.21
			0.14
Current smoker	52.8	57.9	13.75
			0.0002
Manual social class	66.6	68.9	3.51
			0.061
Stroke	1.3	1.2	0.41
			0.52
Height (m)	1.70±0.065	1.70±0.067	0.31
			0.58
Weight[3] (kg)	74.9±11.12	74±11.26	2.52
			0.11
BMI (kg/m^2)	26.0±3.27	25.8±3.38	2.20
			0.14
SBP (mmHg)	148.3±23.64	148.4±22.68	0.23
			0.63
DBP (mmHg)	86.1±13.23	85.9±13.18	0.26
			0.61
Cholesterol (mmol/l)	5.9±0.96	5.9±0.95	0.22
			0.64

[1] Standardisation to age distribution in total male parental population

[2] F-test from logistic regression model for dichotomous variables and linear regression for continuous variables.

[3] Weight, BMI, SBP and DBP were log transformed for statistical testing.

Table 3-2: Age standardised[1] summaries of variables in female parental population

% (N)	Mothers	Non-study married	Test[2]
	1477	4642	
Mean Age (years)	52.78	53.96	
Never smoker	49.1	44.2	7.56
			0.006
Former smoker	7.4	7.3	0.64
			0.42
Current smoker	43.5	48.5	9.96
			0.0016
Manual social class	57.0	59.5	3.74
			0.053
Stroke	1.1	1.3	0.75
			0.03
Height (m)	1.58±0.056	1.58±0.060	0.06
			0.81
Weight[3] (kg)	64.8±11.14	64.1±11.43	3.45
			0.063
BMI (kg/m^2)	26.1±4.34	25.8±4.51	3.21
			0.073
SBP (mmHg)	150.5±25.0	150.5±25.4	0.00
			0.97
DBP (mmHg)	84.9±13.4	85.4±13.5	1.73
			0.19
Cholesterol (mmol/l)	6.4±1.12	6.4±1.09	1.44
			0.23

[1] Standardisation to age distribution in total male parental population

[2] F-test from logistic regression model, testing for a difference between subgroups allowing for age as a categorical variable in 5-year bands.

[3] Weight, BMI, SBP and DBP were log transformed for statistical testing.

Table 3-3: Characteristics of all identified offspring

		Participants	Non-participants	Response rate	*p*-value
N		2342	2672		
Sex	M	1041	1431	42.1	<0.001
	F	1301	1240	51.2	
Age (mean ± SD)	M	44.3±6.3	44.0±7.2		0.317
	F	44.7±6.2	44.7±7.1		0.959
Father BMI categories	<25	857	1050	44.9	0.149
	25-29.9	1217	1327	47.8	
	>30	265	294	47.4	
Mother BMI categories	<25	1040	1238	45.7	0.331
	25-29.9	942	1023	47.9	
	>30	357	407	46.7	
Fathers social class	MN	722	880	45.0	0.114
	M	1600	1769	47.5	
Mid-parental BMI categories					
<25	NM	319	411	43.7	0.91
	M	555	654	45.9	
25-29.9	NM	348	416	45.5	0.069
	M	895	953	48.4	
>30	NM	55	53	50.9	0.436
	M	145	167	46.5	

Table 3-4: Characteristics of the 5014 offspring identified for couples living in Renfrew/Paisley cities

		Participants	Non-Participants	
		2342	Locals	Migrants
% (N)		2342	1271	1372
Sex	M	44.4	35.1	35.9
		(1041)	(676)	(739)
	F	55.6	46.9	46.1
		(1301)	(595)	(633)
Age (mean± SD)	M	44.3±6.3	44.7±6.6	43.4±7.8
	F	44.7±6.2	44.7±6.4	44.6±7.7
Father BMI categories	<25	36.6	39.7	39.0
		(857)	(504)	(535)
	25-29.9	52.0	50.1	49.5
		(1217)	(637)	(678)
	≥30	11.3	10.2	11.5
		(265)	(130)	(158)
Mother BMI categories	<25	44.5	49.3	43.9
		(1040)	(626)	(601)
	25-29.9	40.3	36.6	39.7
		(942)	(465)	(543)
	≥30	15.3	14.1	16.4
		(357)	(179)	(225)
Mid-parental BMI	Mean	26.0+2.9	25.8+2.9	26.0+2.9
Mid-parental BMI categories				
	<25	37.3	41.4	38.9
		(880)	(526)	(532)
	25-29.9	53.7	50.6	52.4
		(1256)	(643)	(718)
	≥30	8.6	8.0	8.7
		(201)	(101)	(119)
Fathers social class	NM	31.1	36.1	30.8
		(722)	(456)	(418)
	M	68.9	63.9	69.0
		(1600)	(806)	(940)

Table 3-5: Comparison of characteristics of men participating in offspring 1996 survey and SHS 1995

		Offspring 1996		SHS 1995			
	% (N)	35-44	45-54	35-44	45-54	P* value	P# value
Smoking	Never	51(426)	40(494)	47(581)	33(750)	0.14	**0.017**
	Former	19(426)	23(494)	17(851)	24(750)	0.28	0.65
	Current	23(426)	26(494)	29(851)	34(750)	**0.032**	**0.0027**
Anthropometry	Height	175.8+0.32	174.4±0.28	175.1±0.23	173.5±0.24	0.089	**0.014**
	Weight	81.1±0.66	82.0±0.62	82.2±0.45	82.4±0.50	0.18	0.59
	BMI	26.2±0.19	26.9±0.19	26.8±0.14	27.3±0.15	**0.014**	0.11
	% Obesity	15.5	20.6	18.9	21.9	0.13	0.60
Blood pressure	SBP(mmHg)	128±0.66	133±0.72	130+0.47	134±0.68	**0.021**	0.60
	DBP(mmHg)	77±0.53	81±0.48	74±0.40	80±0.45	**<0.001**	**0.024**
Cholesterol	Total	5.3±0.05	5.5±0.04	5.9+0.04	6.1+0.04	**<0.001**	**<0.001**
	HDL	1.3±0.02	1.3±0.02	1.3±0.01	1.3±0.01	0.18	0.95

		35-54 years	35-54 years	P value
Social class	I/II	47 (920)	41(1552)	**0.0024**
	III NM	12(920)	11(1552)	0.52
	III M	31(920)	32(1552)	0.64
	IV/V	10(920)	16(1552)	**<0.001**

P* value: test between offspring population and SHS population in the age range of 35-44.

P# value: test between offspring population and SHS population in the age range of 45-54.

Table 3-6: Comparison of characteristics of women participating in offspring 1996 survey and SHS 1995

		Offspring 1996		SHS 1995			
	% (N)	35-44	45-54	35-44	45-54	P* value	P# value
Smoking	Never	58(517)	53(632)	50(870)	42(776)	**0.0045**	**<0.001**
	Former	16(517)	23(632)	16(870)	21(776)	0.87	0.34
	Current	26(517)	24(632)	34(870)	37(776)	**0.0029**	**<0.001**
Anthropometry	Height	161.6±0.25	161.1±0.024	161.5±0.20	160.6±0.23	0.71	0.17
	Weight	66.8±0.58	67.4±0.51	67.3±0.46	68.5±0.49	0.54	0.13
	BMI	25.6±0.21	26.0±020	25.8±0.17	26.6±0.19	0.47	**0.032**
	% Obesity	19.0	17.1	17.0	20.8	0.37	0.083
Blood pressure	SBP(mmHg)	120±0.57	127±0.65	121±0.50	129±0.73	0.058	**0.017**
	DBP(mmHg)	70±0.42	72±0.40	69±0.39	72±0.47	0.14	0.76
Cholesterol	Total	4.6±0.04	5.4±0.04	5.4±0.04	6.1±0.04	**<0.001**	**<0.001**
	HDL	1.5±0.02	1.5±0.02	1.6±0.01	1.6±0.01	**<0.001**	**<0.001**

		35-54 years	35-54 years	P value
Social class	I/II	40(1149)	27(2197)	**<0.001**
	III NM	38(1149)	39(2197)	0.69
	III M	7(1149)	21(2197)	**<0.001**
	IV/V	15(1149)	13(2197)	0.16

P* value: test between offspring population and SHS population in the age range of 35-44.

P# value: test between offspring population and SHS population in the age range of 45-54.

CHAPTER 4

CORRELATES OF OBESITY IN THE RENFREW AND PAISLEY GENERAL POPULATION, 1972-76

4.1 INTRODUCTION

This chapter reviews the literature concerning the correlates of obesity, followed by a brief description of the statistical methods used, results and discussion.

4.2 BACKGROUND

Obesity occurs when energy intake exceeds energy expenditure over a period of time. This imbalance may be due to higher energy intake than required, a lower level of energy expenditure or a combination of both. The excess is stored in the body in the form of fat in adipose tissue (World Health Organisation 1998). However, this excess in fat storage is the result of complex interactions between genetic, environmental, behavioural and cultural factors. Some of these factors will be discussed in this section.

Age

Observational studies have suggested that there are critical periods during early life associated with persistent obesity during adulthood. These stages include gestation and early infancy (Ravelli et al. 1999), the period of adiposity rebound that occurs between 5-7 years of age, and adolescence (Dietz 1994). A follow up study found that the prevalence of obesity was high among young men who were exposed to famine *in utero* in the first two trimesters of pregnancy. In contrast, the prevalence of obesity in those who were exposed to famine in the last trimester of pregnancy was low (Dietz 1994). One explanation is that fetus adapt to the famine condition by permanently changing its physiology and metabolism (Barker 1995;Waterland & Garza 1999).

The period of adiposity rebound is the time at which the BMI for a child begins to increase and starts at the age of 5 years. Some cohorts have found that those who start the period of adiposity rebound before the age of 5 years have significantly higher BMI in adolescence and adulthood. Finally, long term studies suggested that the risk of both the onset and persistence of obesity appear greater for females than for males (Dietz 1994).

Obesity also becomes more prevalent with increasing age (Felber, Acheson, & Tappy 1992;Lean 2000). It increases in men until the age of 50 and in women up to the age of 65, although this varies between different populations. This increase is due to the slowdown of the resting metabolic rate (RMR), which is probably related to an age-

related reduction in muscle mass (Bosy-Westphal et al. 2003;Piers et al. 1998;Visser et al. 1995), and to a decrease of physical activity while still maintaining the same level of caloric intake as in younger ages (Grundy 1998).

Sex

In general, after puberty, women have a higher prevalence of obesity than men, to ensure their reproductive capacity (World Health Organisation 1998). On average, adipose tissue in a young adult accounts for approximately 15% of body weight in males and about 27% in females (Grundy 1998). This is explained by the ability of the male's body to utilise energy in protein synthesis, while the female's body tends to change excess energy into fat storage (World Health Organisation 1998)

Males and females also differ with respect to the location of fat deposition. Men tend to have more abdominal fat forming the "android" pattern of fat distribution. Women tend to have more gluteal fat (larger hip circumferences) forming the "gynoid" pattern of fat distribution.

Smoking

The link between smoking and weight gain is not clear in smokers, but becomes more obvious after smoking cessation (Flegal et al. 1995). Williamson et al studied changes in body weight to changes in smoking status in adults who were weighed in 1971-75 and then weighed again in 1982-84. In this cohort the mean weight gain due to cessation of smoking was 2.8kg in men and 3.8kg in women. They found that major weight gain (>13kg) occurred in 9.8% of men and in 13.4% of women who quit smoking (Williamson et al. 1991). Results from other cohort, the Royal College of General Practitioners Oral Contraception Study, conducted over a 26-year period, reported a 13.5% increase in obesity prevalence among women who stopped smoking (Owen-Smith 1999). Based on a review of literature, Froom et al has indicated that the risk of weight gain is highest during the first 2 years following smoking cessation and declines thereafter. Further, this review pointed out that the degree of weight gain might be attenuated by several factors including physical exercise, older age, higher baseline BMI and lower rates of smoking (Froom et al. 1998).

Cross-sectional studies have reported a U-shaped relationship between smoking status and body weight. That is, non-smokers and heavy smokers have the heaviest body weight, while moderate smokers weighed the least. The U-shaped relation was observed to be true for males. However, some studies showed that female heavy smokers have the least body weight (Klesges & Klesges 1993). These relationships are thought to be explained by the ability of smoking to induce an acute rise in metabolic rate and to reduce food intake through its effect on the sympathetic nervous system. Thus, smoking cessation would return sympathetic activity and catecholamine levels to normal, thus facilitating more efficient energy storage and weight gain.

Social class

Studies show that higher social class is negatively correlated with obesity in developed countries but positively related with obesity in the developing countries (Rice et al. 1997). Once the national income increases in the developing countries, the positive relationship between social class and obesity is slowly replaced by the negative correlation as seen in developed countries. However, individuals in different social class groups may have different patterns of dietary intake and physical activity. There is a difference between males and females in the relation between obesity and social class. Among women, obesity is associated with a lower social class; and among men, obesity is associated with higher social class (Sawaya et al. 1996;Wardle & Griffith 2001). Obesity is considered as one of the wealth indicators in some cultures and obesity in women is a symbol of motherhood and dignity in other cultures (Grundy 1998).

Education, in some communities, is often used as proxy for social class, and is consequently associated with obesity. Generally, those with high levels of education are wealthy, or wealthy individuals have a high level of education. In developed countries, body weight is inversely associated with individual's level of education. This relationship was supported in many studies for females. However, it was debatable, in some studies, for males. In Spain, the prevalence of obesity associated with less than third level education increased in women and decreased in men (Gutiérrez-Fisac et al. 2002).

One of the potential explanations is the attitude of educated females to their body image and body weight. However, a recent study in adult British participants showed that men and women in higher social class had higher levels of perceived overweight, monitored their weight more closely and were more likely to be trying to lose weight (Wardle 2001).

The aim of this chapter is to describe the distribution of BMI and obesity prevalence in Renfrew and Paisley general population and study the associations between obesity and some correlates including age, smoking and social class.

4.3 METHOD

Renfrew and Paisley survey

A population cohort from two towns, in the west of Scotland was screened between 1972 and 1976 (Hawthorne et al 1995;Watt et al. 1995). Men and women aged between 45 and 64 living in Renfrew and Paisley were identified and invited to take part in a cardiovascular screening survey. Participants completed a questionnaire, which was checked by trained nurses, when they attended the screening clinics. Physical measurements including height, weight, blood pressure and blood samples were collected for each participant. The response rate was 78%.

Statistical analysis

Age was recoded into four groups: 45-49, 50-54, 55-59 and 60-64 years to study the distribution of obesity and BMI.

Social class was defined according to the Registrar General's classification (General Register Office Classification of Occupation 1966) based on occupation at the time of screening. Retired participants were classified according to their last full time occupation. Women were given their own occupation except housewives who were given their husband's or father's occupation. Social class was recoded into manual group (which included class III-M, IV and V) and non-manual (which included class I, II and III-NM).

Three categories of smoking habit were defined: never smoker, current smoker and former smoker. To be able to compare our results with other studies, the number of smoked cigarettes was recoded into light smoker (<15 cigarettes per day), moderate (15-24 cigarettes/day) and heavy smoker (>24 cigarettes/ day) and was also used as continuous variable.

BMI (calculated by dividing weight by height squared) was divided into four groups according to the WHO criteria: underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥30.0 kg/m^2). Obese group was

further recoded into obesity class I (30-34.9 kg/m^2), class II (35-39.9 kg/m^2) and class III-morbid obesity ($\geq$40 kg/m^2).

Age-adjusted rates are quoted using the Scottish population structure for the year 1996 to provide (direct) standardisation.

First, univariate analysis was used to identify factors associated with BMI, and then a multivariate model was used to adjust for the effect of different factors. Chi-square test was used for categorical variables; independent t-test was used to compare the means of two continuous variables.

Logistic regression was used to calculate the Odds ratios using obesity as binary variable (obese: BMI$\geq$30kg/m^2 and non-obese: BMI<30kg/m^2) and linear regression was used to identify factors associated with BMI as continuous variable. Age (in years) was included in the model as a continuous variable, social class as a categorical variable using the non-manual as a reference group and finally smoking status as a categorical variable using never smokers as reference group.

4.4 RESULTS

Characteristics of the Renfrew and Paisley population

15406 subjects, comprising 78% of the Renfrew and Paisley population, took part in 1972-6 survey, 45.8% (7052) men and 54.2% (8354) women (Table 4-1).

Men and women had different smoking habits. Only 19% of men were never smokers, one quarter of them were former smokers and 57% were current smokers. On the other hand, 46% of women were never smokers, 8% former smokers and 46% current smoker (Table 4-1).

Renfrew and Paisley towns are highly deprived areas. 69% of men were in the manual social class compared to 31% in the non-manual social class. The difference between social class groups was less for women (Table 4-1).

Smoking was more prevalent in the manual social class (Table 4-2). The proportions of smoking groups were similar in manual and non-manual, however manual groups have more current smokers, and less former and never smokers compared to those in the non-manual group (Figure 4-1).

Prevalence of obesity and overweight

The mean BMI ($\pm$SD) for the Renfrew and Paisley population was 25.8$\pm$4.0. There was no difference between mean BMI in men and women.

The prevalence of obesity (BMI $\geq$30kg/m^2) in Renfrew and Paisley population was 13% (Table 4-3). Obesity was more prevalent in women (15% in women v 11% in men) while overweight (BMI 25-29.9 kg/m^2) was more prevalent in men (49% in men v 37% in women). More than 2% of women were underweight (BMI<18.5kg/m^2) compared to less than 1% of men. 0.2% of men but 0.8% of women were morbidly obese (BMI$\geq$40kg/m^2) (Table 4-4).

Obesity prevalence by age group

Men had a different obesity distribution across age groups compared to women (Table 4-5). For men, obesity prevalence increased with age until 50-54 years, then decreased in older age groups (Figure 4-2). A similar pattern was found for the mean BMI distribution across age groups (Figure 4-3). On the other hand, obesity prevalence and mean BMI increased linearly with age in women (Figure 4-2 and Figure 4-3).

Obesity prevalence by smoking status

Men and women who never smoked had the highest mean BMI and obesity prevalence while current smokers had the lowest (Table 4-6). In men, never smokers and former smokers had similar BMI and obesity prevalence. Women had higher obesity prevalence than men in all smoking groups (Figure 4-4). Although current smoking women had higher obesity prevalence than men, the mean BMI was significantly lower.

The relationship between intensity of smoking and obesity was examined using the number of cigarettes smoked per day. The mean BMI was lowest for light and moderate smokers in both men and women (Table 4-7). On the other hand, heavy smokers (>25 cigarettes per day) had higher BMI. This U-shaped patterns (high BMI in never and heavy smokers) was found in both men and women (Figure 4-5).

Obesity prevalence by social class

The prevalence of obesity and mean BMI were higher in manual women than in non-manual women (Table 4-8). Although manual men have higher prevalence of obesity, the mean BMI was similar for both manual and non-manual men. Women had a higher prevalence of obesity in both manual and non-manual groups (18% v 11%) compared to men (11% v 9%) and higher mean BMI in the manual group (Table 4-8 and Figure 4-6). By contrast, non-manual men had higher mean BMI than non-manual women presumably due to more overweight men (47% manual and 52% non-manual) compared to women (39% manual and 35% non-manual).

Regression analysis results

As BMI is a continuous variable, linear regression was used to study the association between BMI (the dependent variable) and age (in years), social class and smoking groups as independent variables. The risk of obesity was estimated using logistic regression using obesity as a binary variable (obese: BMI ≥30 and non-obese: BMI<30).

Results from linear regression revealed that BMI was positively associated with age in women ($p<0.001$) and negatively associated with age in men. Including age squared in the model shows that there is slight increase BMI in men at younger ages and then BMI starts to decrease with age (Figure 4-7). Overall, there was not a significant association between BMI and age in men, but there was for women (Table 4-9).

Adjusting for age and social class, smoking status was associated with BMI in men and women. For men, there was no significant association between BMI or obesity for former smokers compared to those who had never smoked, although former smokers showed a 10% lower risk of becoming obese (Table 4-10). Current smokers have a lower BMI compared to never smokers. Light and moderate smokers have a lower obesity risk compared to heavy smokers (≥25 cigarettes per day), former and never smokers (Table 4-10).

In women a different pattern was found between BMI and smoking groups. Former and current smokers were negatively associated with BMI (Table 4-9). The risk of obesity was low in light and moderate smokers and former smokers compared to never smokers, while heavy smoking women had relatively higher obesity risk than the other groups (Table 4-10).

Adjusting for age and smoking status, BMI was not associated with social class in men while manual women had significantly higher mean BMI compared to non-manual women. On the other hand, obesity was significantly associated with social class in men and women. 38% of manual men and 74% of manual women were more likely to be obese compared to non-manual men and women respectively (Table

4-10). Overall age, smoking status and social class explained only 5% and 7% of BMI variation in men and women..

4.5 DISCUSSION

The west of Scotland has a poor health record compared to other parts of Scotland, United Kingdom and other European countries (West et al. 1994). Participants in the Renfrew and Paisley survey were representative of the general population in the west of Scotland, with a participation rate of 78% (Chapter Three).

The definition of obesity used in the 1970's and 1980's was different from the one used in this study. Obesity used to be defined as a relative weight, measured by BMI (W/H^2), which was 120% of the desirable weight derived from the Metropolitan Life Insurance table (MRC 1976). The cut-off points for desirable weight varied for men and women and for different body frames. Recently, obesity has been defined using the WHO criteria (World Health Organisation 1998).

Generally obesity prevalence and mean BMI in the Renfrew and Paisley population were lower than that reported in the British Regional Heart Study (BRHS). Mean BMI in men was 26.4kg/m^2 in the BRHS (Shape et al 1985) and in the MONICA Study, mean BMI in men was 25.8 kg/m^2 and 26.1 kg/m^2 in women (The WHO MONICA Project 1988). One possible explanation for this difference is that MONICA and BRHS took place 5 to 10 years later than the Renfrew and Paisley study.

In this study, obesity prevalence and mean BMI increased with age in women and in early ages in men. The Medical Research Council (MRC) reviewed studies conducted in the period 1930 to 1975. The prevalence of overweight, above the desirable weight, increased with age, particularly in women. Men reached the highest level of overweight at an earlier age, with no increase after the age of 50 (MRC). However, in studies conducted in the period 1980 to 1990, reviewed by West et al, mean BMI increased with age in both men and women (West et al 1994).

The proportion of current male smokers in the Renfrew and Paisley population was lower than in the MONICA population but higher than the BRHS population (57%, 62% and 53% respectively). The MONICA population had less former smokers and more never smokers than the Renfrew and Paisley population. On the other hand,

the Renfrew and Paisley population had more current smokers and fewer women who had never smoked than the MONICA study.

The prevalence of obesity and mean BMI found in the Renfrew and Paisley population might be lower because of the higher proportion of current smokers compared to other populations studied at that time. This is supported by the finding that current male and females smokers had the lowest obesity prevalence and mean BMI.

Contrary to what was reported previously, heavy smoking men and women were the heaviest among current smokers; this observation has been reported in men but not in women (Klesges & Klesges 1993) where heavy smoking women were reported to be lighter than other current smoking women.

Several studies have reported a higher prevalence of obesity in the lower social class, particularly in women (Silverston 1969). Men had a lower prevalence of obesity than women, but the greatest obesity prevalence was in lower social class young men, aged between 20 and 39 (Department of Health and Social Security Medical Research Council 1976).

Studies conducted at the same time as the Renfrew and Paisley survey were focusing on coronary heart disease risk factors, and obesity was one of these factors. Descriptions of factors associated with obesity were not discussed in detail and this makes the comparison between our results and other results difficult. However, this chapter provides a description of the size of the obesity problem in the Renfrew and Paisley population and the factors associated with obesity.

4.6 SUMMARY

The prevalence of obesity in the Renfrew and Paisley population was similar to that reported in other studies conducted in the 1970's and 1980's. Obesity prevalence and mean BMI increased with age in women, and only in younger men. Lower obesity prevalence was found in light and moderate smokers and those in non-manual social classes in both men and women. Never and former smokers have higher obesity prevalence.

Table 4-1: Characteristics of Renfrew and Paisley population (number, %)

		Male	Female	Total
		7052	8354	15406
Age groups	45-49	1817	2035	3852
		25.8%	24.4%	25.0%
	50-54	1980	2302	4282
		28.1%	27.6%	27.8%
	55-59	1681	2042	3723
		23.8%	24.4%	24.2%
	60-64	1574	1975	3549
		22.3%	23.6%	23.0%
Smoking habit	Never smoker	1325	3833	5158
		18.8%	45.9%	33.5%
	Former smoker	1735	623	2358
		24.6%	7.5%	15.3%
	Current <14/day	839	1566	2405
		11.9%	18.7%	15.6%
	Current 15-24/day	2058	2018	4076
		29.2%	24.2%	26.5%
	Current >25/day	1095	314	1409
		15.5%	3.8%	9.1%
Social class	Non-manual	2167	3433	5600
		31.0%	42.9%	37.4%
	Manual	4816	4571	9387
		69.0%	57.1%	62.6%

Table 4-2: Distribution of smoking groups by social class

		Non manual	Manual
Smoking habits	Never smoker	2138	2839
		38.2%	30.2%
	Former smoker	941	1387
		16.8%	14.8%
	Current smoker	2521	5161
		45.0%	55.0%

Figure 4-1: Distribution of smoking groups by social class in men and women

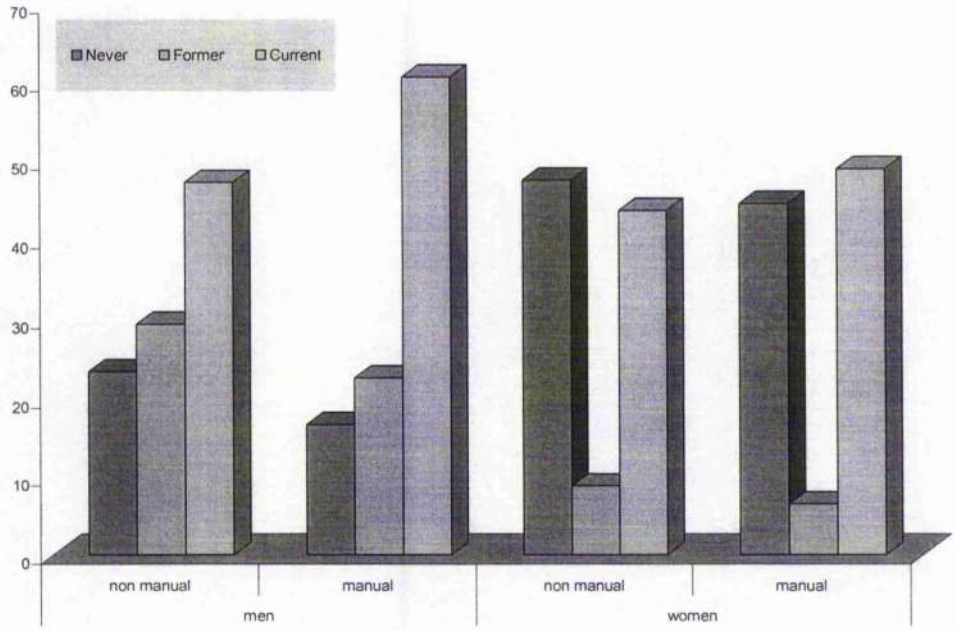


Table 4-3: Prevalence of obesity and overweight by sex (number, %)

		Male	Female	Total
		7049	8342	15391
Mean BMI		25.87+3.40	25.77+4.48	25.8+4.02
Obesity groups	<18.5	53	190	243
		.8%	2.3%	1.6%
	18.5-24.9	2813	3830	6643
		39.9%	45.9%	43.2%
	25-29.9	3430	3064	6494
		48.7%	36.7%	42.2%
	≥30	753	1258	2011
		10.7%	15.1%	13.1%

Table 4-4: Prevalence of morbid obesity by sex (number, %)

	Male	Female	Total
	7049	8342	15391
30-34.9	687	944	1631
	9.7%	11.3%	10.6%
35-39.9	55	244	299
	.8%	2.9%	1.9%
≥40	11	70	81
	.2%	.8%	.5%

Table 4-5: Prevalence of obesity (BMI >30kg/m^2) in different age groups by sex (number, %)

		Male		Female	
Age groups	45-49	179		247	
		9.9 %		12.1%	
	50-54	238		292	
		12.0%		12.7%	
	55-59	170		332	
		10.1%		16.3%	
	60-64	166		387	
		10.6%		19.3%	
		Mean	**SD**	**Mean**	**SD**
Age groups	45-49	25.85	3.34	25.25	4.13
	50-54	26.00	3.46	25.46	4.23
	55-59	25.82	3.37	25.87	4.60
	60-64	25.77	3.41	26.55	4.87

Figure 4-2: Distribution of obesity prevalence in men and women by age groups

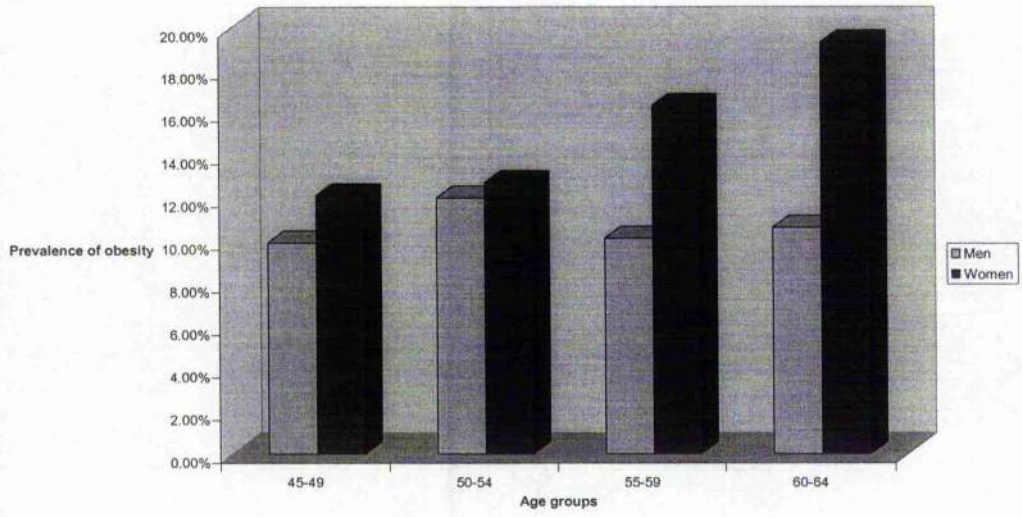


Figure 4-3: BMI distribution in men and women by age groups

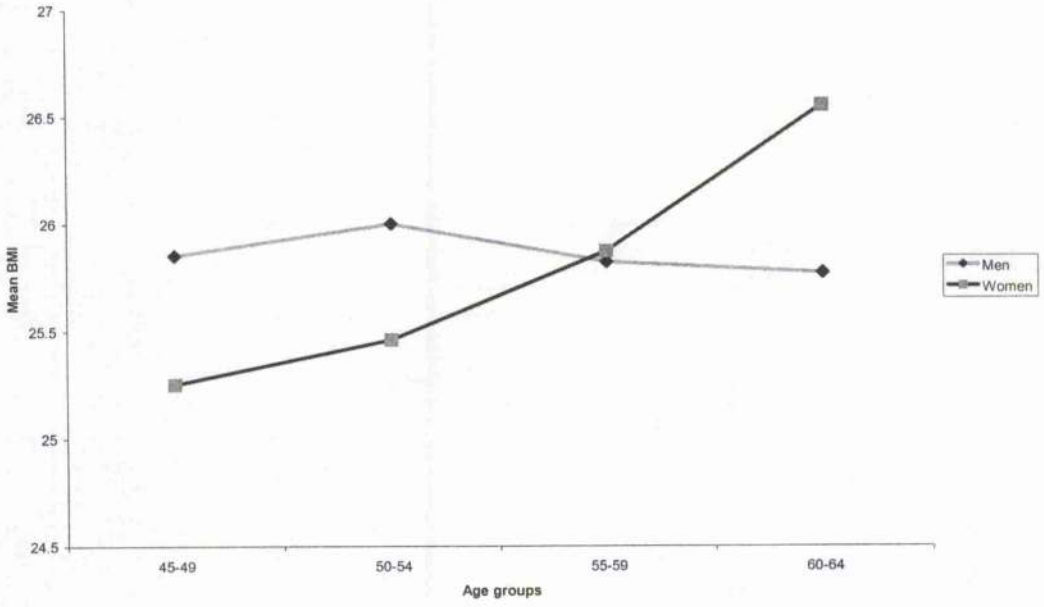


Table 4-6: Prevalence of obesity (BMI >30kg/m^2) in different smoking groups by sex (number, %)

		Male		Female	
Smoking habits	Never smoker	193		745	
		14.6%		19.5%	
	Former smoker	236		90	
		13.6%		14.4%	
	Current smoker	324		423	
		8.1%		10.9%	
		Mean	**SD**	**Mean**	**SD**
Smoking habits	Never smoker	26.71	3.33	26.76	4.55
	Former smoker	26.68	3.16	25.88	4.10
	Current smoker	25.24	3.38	24.77	4.25

Figure 4-4: Distribution of obesity (BMI >30kg/m^2) prevalence in men and women by smoking groups (number, %)

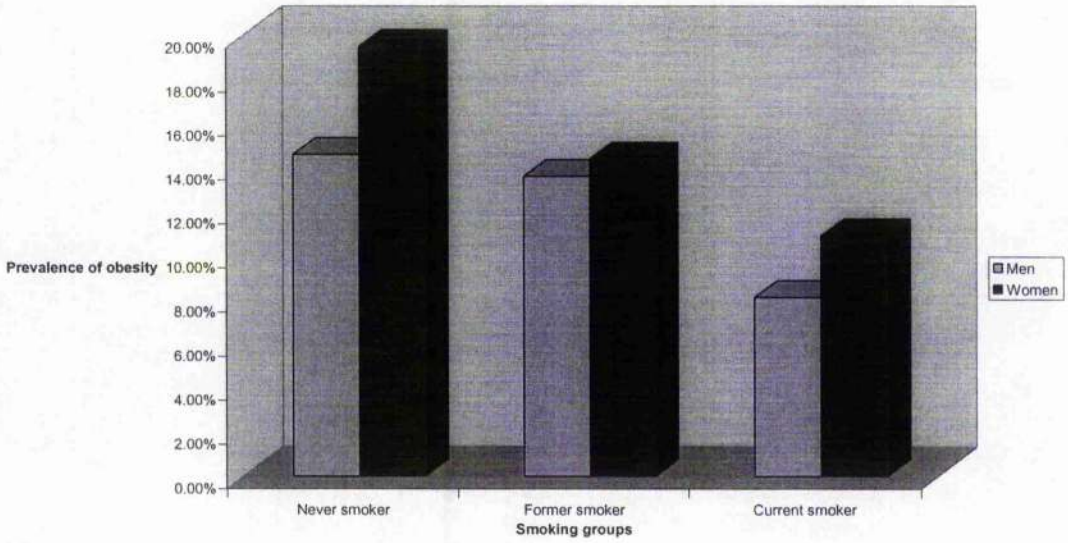


Table 4-7: BMI distribution in men and women by number of cigarettes per day

Smoking habit	Men	Women	Total
Never smoker	26.7+3.33	26.8+4.55	26.8+4.27
Former smoker	26.7+3.16	25.9+4.10	26.5+3.45
Current smoker <15/day	25.1+3.46	24.8+4.19	24.9+3.95
Current smoker 15-24/day	25.0+3.33	24.7+4.25	24.8+3.82
Current smoker >24/day	25.7+3.37	25.1+4.48	25.6+3.65

Figure 4-5: BMI distribution in men and women by number of cigarettes per day

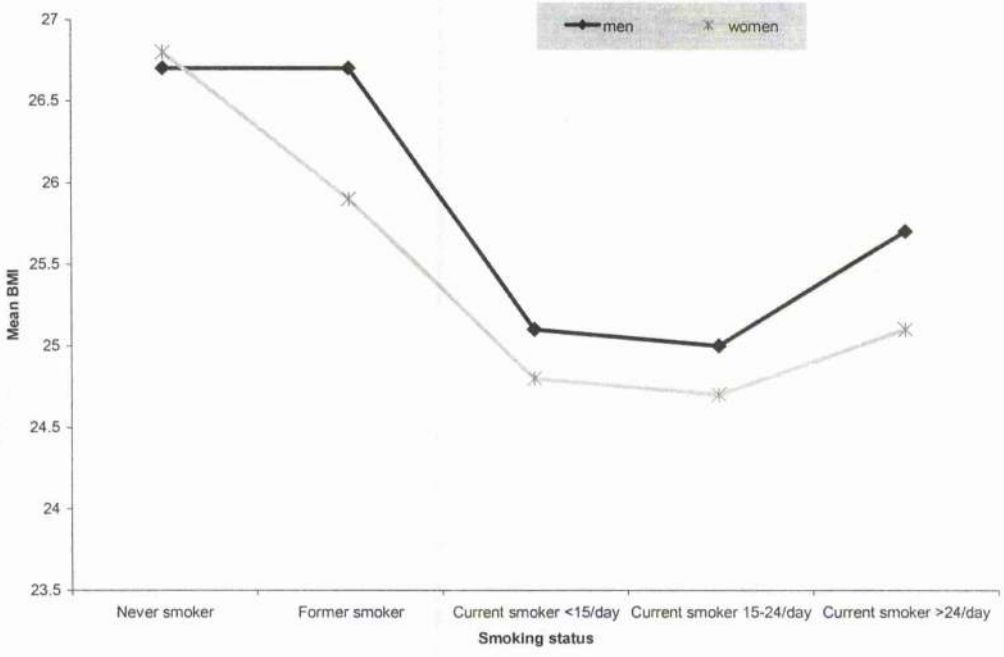


Table 4-8: Prevalence of obesity in social class groups by sex (number, %)

		Male		Female	
Social class	Non manual	201		384	
		9.3%		11.2%	
	Manual	546		820	
		11.3%		18.0%	
		Mean	**SD**	**Mean**	**SD**
Social class	Non manual	25.94	3.19	25.14	4.03
	Manual	25.84	3.48	26.26	4.72

Figure 4-6: Distribution of obesity or overweight prevalence in men and women by social class

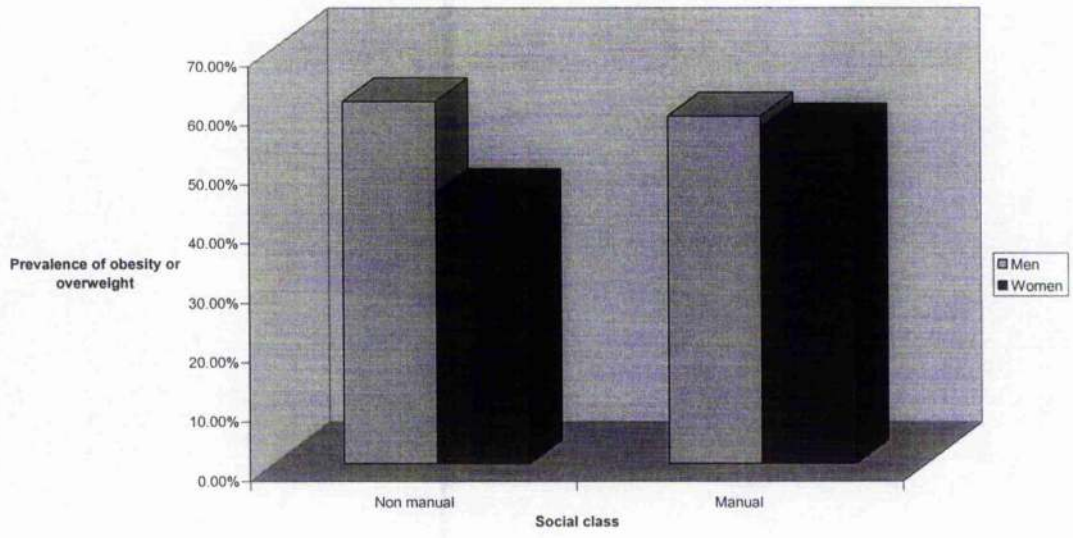


Table 4-9: Results of linear regression including BMI as dependent variable

	BMI	Coefficient	SE	t	P-value	95% CI	
Men							
	Age	-.0128	.0071	-1.79	0.074	-.027	.0012
Smoking status	Never						
	Former	-.0486	.121	-0.40	0.689	-.286	.1891
	Current <15	-1.603	.147	-10.89	0.000	-1.892	-1.314
	Current 15-24	-1.716	.118	-14.58	0.000	-1.947	-1.485
	Current >24	-1.017	.136	-7.46	0.000	-1.285	-.750
Social class	Non-manual						
	Manual	.1108	.086	1.28	0.199	-.058	.2799
	Model constant	27.236	.418	65.08	0.000	26.416	28.056
	Adjusted R^2=4.9%						
Women							
	Age	.0538	.0089	6.08	0.000	.0364	.0712
Smoking status	Never						
	Former	-.803	.1899	-4.23	0.000	-1.176	-.431
	Current <15	-1.87	.1326	-14.14	0.000	-2.135	-1.615
	Current 15-24	-2.105	.1230	-17.11	0.000	-2.346	-1.863
	Current >24	-1.545	.260	-5.93	0.000	-2.056	-1.035
Social class	Non-manual						
	Manual	1.151	.098	11.71	0.000	.958	1.3438
	Model constant	22.025	.501	43.91	0.000	21.043	23.009
	Adjusted R^2=6.9 %						

Table 4-10: Results of logistic regression including obesity as dependent binary variable

	Obesity	Odds Ratio	SE	z	P-value	95% CI	
Men							
	Age	.997	.0070	-0.29	0.775	.984	1.012
Smoking status	Never						
	Former	.906	.0955	-0.94	0.350	.737	1.114
	Current ≤14	.438	.0683	-5.29	0.000	.323	.595
	Current 15-24	.4247	.0498	-7.30	0.000	.337	.534
	Current >24	.688	.0864	-2.98	0.003	.538	.880
Social class	Non-manual						
	Manual	1.378	.121	3.64	0.000	1.159	1.637
Women							
	Age	1.031	.0060	5.14	0.000	1.019	1.042
Smoking status	Never						
	Former	.717	.089	-2.67	0.008	.562	.916
	Current ≤14	.472	.045	-7.86	0.000	.392	.570
	Current 15-24	.478	.042	-8.42	0.000	.403	.568
	Current >24	.9563	.1523	-0.28	0.779	.6998	1.307
Social class	Non-manual						
	Manual	1.744	.118	8.23	0.000	1.528	1.991

Figure 4-7: Fitted BMI distribution by age in men

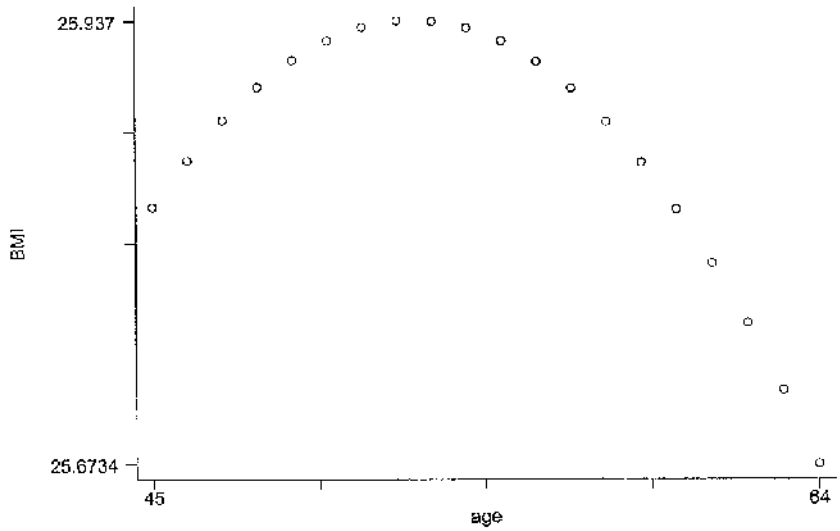
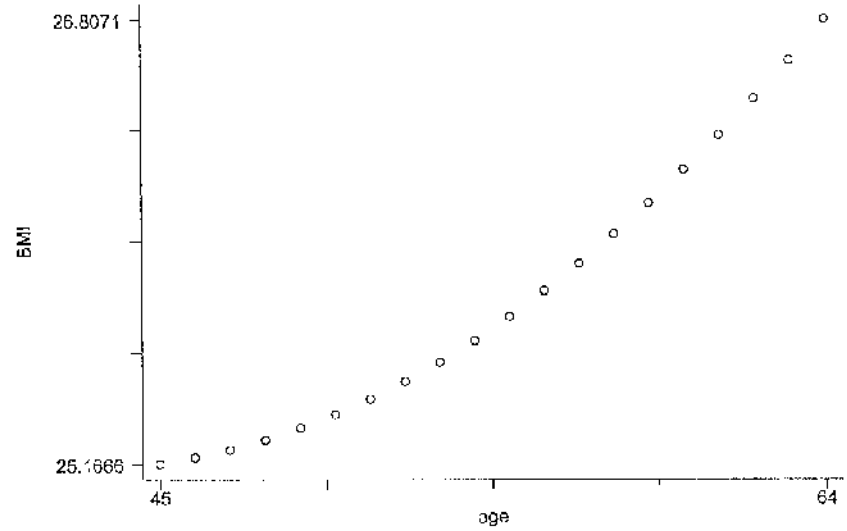


Figure 4-8: Fitted BMI distribution by age in women



CHAPTER 5

OBESITY AND HEALTH OUTCOMES

5.1 INTRODUCTION

Mortality attributable to obesity is a major public health problem. More than 80% of estimated obesity attributable deaths occur among individuals with BMI $\geq$30kg/m^2 (Allison et al. 1999). In Europe a minimum of 275000 deaths were attributable to excess weight, varying from 5.8% for France through to 8.7% for the UK (Banegas et al. 2003).

Obesity and mortality

Obesity and all cause mortality

The relationship between obesity, measured as body mass index (BMI), and mortality has been controversial. Some have proposed that there is no distinct relationship, while others have proposed that the relationship is J-shaped (Manson et al. 1995), U-shaped, directly linear or inversely linear. These patterns of association differ or sometimes disappear after adjustment for other risk factors (Folsom et al. 2000). For example, it was suggested that the apparent U-shaped association between BMI and total mortality might be a result of compound risk functions from body fat and fat-free mass (Allison et al. 1997;Heitmann et al. 2000).

Studies investigating the relationship between body fat and mortality have some methodological limitations. First, there is the failure to consider the effect of previous illness on weight. Some studies which reported a linear relationship between BMI and the risk of all cause mortality excluded the subjects who died during the first 4 years of follow up. Other studies still retained the U-shaped association even after controlling for previous illness and used more specific measurements (Allison et al 1997). Other studies found that this does not necessarily lead to a reduction in bias in the estimated effect of a risk factor on mortality when this relationship is confounded by the presence of hidden diseases (Allison et al. 1997). Moreover, it is possible for such exclusion to exacerbate the confounding due to pre-existing disease (Allison et al 1997). Some studies did not find any association between BMI and mortality among women in the first years of follow up (Manson et al 1995). Because the association between BMI and mortality might be confounded by

previous illness, Stevens et al compared weight loss prior to baseline among subjects who died during the early years of follow up with that among subjects who remained alive. His results showed that mean change in BMI prior to baseline was not different among ill participants compared with those who were healthy, but the odds of converting from obese to non-obese were higher in ill participants than in healthy ones (Stevens, Juhaeri, & Cai 2001).

Second, the relationship may differ according to smoking status. For women who never smoked, BMI was more directly related to all cause mortality, while for former and current smokers the relationship between body weight and mortality was U-shaped (Manson et al 1995). Among middle age men, a BMI of 25-30 was not associated with mortality, but a BMI of more than 30 was related to excess mortality among never and ex-smokers (Visscher et al. 2000). Furthermore, the relationship between BMI and death from all causes differed according to smoking status and the presence or absence of history of disease. Obesity was most strongly associated with an increased risk of death among those who had never smoked and who had no history of disease. In contrast, leanness was most strongly associated with an increased risk among current or former smokers with a history of disease (Calle et al. 1999).

The association between BMI and mortality is likely to be modified by age (Baik et al. 2000), partly because low body weight in the elderly may be due to depletion of lean body mass from pre-clinical or chronic illness and reduced physical activity at the same time as accumulation of fat mass intra-abdominally. In a national representative sample of US adults' aged 70 and over, the lowest all cause mortality was at a BMI in the low 30s for women and high 20s for men (Calle et al 1999). Selective survival and a higher mortality rate among older people may explain the lower risk ratios. In older populations, measures of body fat such as waist and hip circumferences (Folsom et al 2000) or waist to hip circumference ratio (WHR) may more specifically reflect body fatness and thus be better indicators than BMI for risk of overall and cardiovascular disease mortality (Baik et al 2000).

Among men younger than age 65 the lowest risk of overall mortality was seen for body mass indices below 23 (Baik et al 2000) while for women who had never smoked, lowest risk was seen at body mass indices below 22 (Manson et al 1995).

The use of more than one obesity measure is more informative. Results from the Iowa Women's Health Study showed that there was a positive age-adjusted association of mortality with WHR for each stratum of BMI, the highest mortality stratum was that with the lowest BMI and highest WHR (Folsom et al 2000).

Many studies have suggested that obesity is an independent risk factor for the ischemic heart disease mortality. Most studies agreed that the risk of cardiovascular mortality increases linearly with increasing BMI although not all the studies found a significant linear trend (Calle et al 1996). Further, waist circumference and waist-hip ratio were reported in some studies to be positively associated with cardiovascular mortality. The use of more than once measure is preferable in studying the risk of cardiovascular mortality in specific groups such as the elderly (Rimm et al. 1995).

Obesity and cancer mortality

The cause of death modified the relationship between BMI and the risk of death in both men and women. The risk of death from cancer was linearly related to BMI in a large cohort of the US population and a curvilinear relationship was found for the risks of death from cardiovascular disease and deaths from other causes (Calle et al 1999).

Obesity increases the risk of prostate cancer mortality. The results of two large American Cancer Society cohorts found that prostate cancer mortality rates were significantly higher among obese than non-obese men in both cohorts. Decreased survival among obese men was the likely explanation for this association (Rodriguez et al. 2001).

The risk of colon cancer mortality increased across the entire range of BMI. Results from prospective data from the American Cancer Society showed that the relationship between obesity and risk of colon cancer mortality is stronger and more linear in men than women (Murphy et al. 2000). A possible explanation for this weaker association in women may be the possible protective effects of oestrogen (Murphy et al 2000) where it is thought that

exogenous estrogens may decrease the concentration of secondary bile acids, thus potentially reducing the ability of these bile acids to promote tumours in the colon (Zhang et al. 2001). A low concentration of bile acids may reduce the ability of intestinal microflora to produce diacylglycerol, an activator for the key enzyme in growth stimulation and tumour production. Observational studies have reported an inverse association between oestrogen replacement therapy and colon polyps (Potter, Bostick, & Garndits 1996).

Obesity and cancer incidence

Each year about 34800 new cases of cancer in the European Union are related to obesity and a further 37000 cases to overweight (Bergström et al. 2001). A Swedish study indicated that cancer incidence among obese patients was 33% higher than in non-obese patients (Wolk et al. 2001).

Many studies have shown an association between different types of cancers and obesity. Obesity has a strong relationship with endometrium cancer (Austin et al. 1991;Goodman et al. 1997;LaVecchia et al. 1982), probable with breast (Cold et al. 1998) and kidney cancers (Chow et al. 2000), weaker association with gallbladder (women) and colon (less in women), insufficient with thyroid and probably none with pancreas (Silverman et al. 1998) and prostate cancers (Visscher & Seidell 2001).

It was suggested that the real explanation for the relationship between obesity and cancer is the large proportion of fat tissue. These tissues are metabolically active, producing hormones and growth factor proteins that cause cell division.

Once cancer has developed, several studies have shown that obese people have poorer outcomes than thinner people (Chlebowski, Aiello, & McTiernan 2002).

Here is a brief review of different types of cancer and obesity relationships:

Breast cancer: the first observation was the increased risk for breast cancer as body weight measured by BMI increased. This relationship was significant in postmenopausal women but not premenopausal women (van den Brandt et al. 2000). This observation was

explained by changes in sex hormones levels. Obese premenopausal women have irregular ovulatory cycles, and so oestrogen and progesterone surges will be less than that for thin women and their breast tissue will be exposed to less oestrogen. While in postmenopausal obese women oestrogen levels will increase because it will be produced mainly from fat tissue, not ovulation. At the same time, they will have less sex hormone binding globulin (SHBG) which blunt the effect of oestrogen (Magnusson et al. 1998). The association of obesity and increased risk of breast cancer does not emerge until at least 10 years after menopause (Magnusson et al 1998).

Other studies report that excess body weight might be protective among those who have lower body type of fat accumulation (low WHR), however, upper body fat accumulation (high WHR) was a predictor of breast cancer in premenopausal women, especially pronounced among subjects who were overweight (Sonnenschein et al. 1999; Kaaks et al. 1998). These results were supported by a study on Chinese women with a low risk of breast cancer and low prevalence of obesity. In this study, BMI was positively associated with postmenopausal women but was not associated with breast cancer risk in premenopausal women. However, WHR was associated with increased risk of breast cancer with premenopausal women after adjusting for BMI (Shu et al. 2001). A possible explanation might be due to insulin resistance associated with upper body fat. The resulted hyperinsulinemia is thought to enhance the availability of insulin-like growth factor 1 (ILGF-1), which is a potent mitogen in breast cancer cell cultures and is thought to increase ovarian androgen production (Magnusson et al 1998).

The risk of breast cancer associated with obesity is strongest when obesity is measured shortly before diagnosis, and excess risk declines significantly as duration of follow up increases to a maximum of 25 years (Kaaks et al 1998).

In most studies, height was an independent risk factor for breast cancer in post-menopausal women, but this relationship was less clear in pre-menopausal women(van den Brandt et al 2000; Alberg et al. 2000;Russo et al. 1998;Shu et al 2001). A possible explanation is the role of diet factors operating in early life (van den Brandt et al 2000).

Colon cancer:

The available studies show no consistent association between obesity and risk of colorectal cancer, although evidence now suggests an association between obesity and adenomas. The increased risk of colorectal cancer associated with energy intake does not seem to be the result of overeating; it may reflect differences in metabolic efficiency (Boyle & Langman 2000).

Physical activity, high level of energy intake and body mass index have been directly associated with colon cancer (Slattery et al. 1997b). A large population-based case-control study suggested that a high level of vigorous leisure time activity performed over the past 20 years was important in reducing colon cancer risk (Slattery et al. 1997a).

Results of a case-control study in Italy indicated that excessive weight at various ages predicted colorectal cancer risk in men while in women abdominal obesity represented a more reliable risk indicator (Russo et al 1998). If all men could reduce their BMI below 25 about 9% of male colorectal cancer might be avoided in Italy. A decrease of WHR below 0.82 might reduce colorectal cancer in women by 19%. Height appears unrelated to risk (Russo et al 1998).

Several mechanisms were proposed to explain the increasing risk of colon cancer through weight gain. First, obesity is strongly associated with insulin resistance. The high insulin level stimulates the growth of colonic epithelial cells (Giovannucci 2001;Murphy, Calle, Rodriguez, Kahn, & Thun 2000). Second, the high glucose and glycerides levels in obese subjects affect faecal bile acids, which were associated with the pathogenesis of colon cancer (Ford 1999).

Cancer of oesophagus

Excess weight was reported to be a strong risk factor for oesophageal adenocarcinoma, with risk rising consistently with increasing BMI (Chow et al. 1998). In this case control study, it was estimated that BMI accounted for 33% of oesophageal adenocarcinoma and 22% of gastric cardia adenocarcinoma cases over the period 1993-1995 in the United States (Chow et al 1998).

The mechanism by which overweight increases the risk of adenocarcinomas of the oesophagus is by promoting gastro-oesophageal reflux by increasing pressure. In turn, gastro-oesophageal reflux predisposes to Barrett's oesophagus, a metaplastic precursor state for adenocarcinomas of the oesophagus and gastric cardia (Chow et al. 1995;Chow et al 1998). In addition, some studies have shown that obesity interferes with how well the oesophagus moves food into the stomach. This impairment of oesophageal motility may contribute to cancer by prolonging irritating contact between food and the mucosal lining of the oesophagus.

Prostate cancer

In a population based case-control study, there was no association between adult height and BMI and prostate cancer.(Andersson et al. 1995). Similar results were reported by Hsing et al in a Chinese population, but suggest that upper body fat (measured by WHR) might be associated with increased risk of clinical prostate cancer (Hsing et al. 2000). On the contrary, in a Swedish prospective study all anthropometric measurements were positively associated with the risk of prostate cancer and were more strongly associated with mortality than incidence. Statistically significant linear dose-response relationships were also found with the incidence of prostate cancer, with the exception of BMI (Andersson et al. 1997). Similar results were found in an American cohort (Putnam et al. 2000). Obesity and risk of prostate cancer is expected because obesity is associated with several hormonal changes in men, including higher oestrogen and lower testosterone levels. In addition, obese men have a lower level of sex hormone binding globulin. Prostate cancer is thought to be associated with low physical activity and high-energy intake (Andersson et al 1995), and BMI might reflect this imbalance between energy intake and physical activity. Finally, it is suggested that there is positive association between obesity and sympathetic activity, where the balance between local sympathetic and parasympathetic activity influenced growth of prostate gland (Andersson et al 1997).

Pancreatic cancer: The effects of BMI on pancreatic cancer risk have been examined in at least 12 studies with inconsistent findings. BMI was associated with modest increased risks, with Odds ratios ranging from 1.2 to 1.7 in some studies form the United States

(Silverman et al 1998), China (Ji et al. 1996), Canada (Hanley et al. 2001) and in a cohort study of obese individuals in Denmark (Moller et al. 1994). In contrast, a multinational case-control study of pancreatic cancer (Bueno 1990, Ghadirian 1991, Howe 1992) and some case-control studies in the United States (Lyon 1993, Mack 1986, Olsen 1991) and Greece (Kalappthanki 1993) revealed no clear relationship to BMI.

Lung cancer: The risk of lung cancer was negatively associated with obesity, with lean individuals at greater risk of lung cancer compared to the overweight. Two case control (Kabat & Wynder 1992); Goodman 1993) and cohort (Chyou, Nomur, & Stemmermann 1994;Knekt et al. 1991) studies found this relationship, although it was considered by others to be a result of confounding. Weight loss due to sub-clinical illness and smoking were the main confounding factors masking the relationship between obesity and risk of lung cancer.

A recent study has examined the risk by histologic subtype of lung cancer (i.e. squamous cell carcinoma, adenocarcinoma and small cell carcinomas) with BMI and waist circumference (Olson et al. 2002). In this study, BMI was negatively associated with all lung cancer subtypes, especially squamous carcinoma. Conversely, waist circumference was positively associated with small cell and squamous cell lung cancer.

Obesity and health outcomes in the West of Scotland

Currently there are two cohorts from the West of Scotland, the Collaborative and the Renfrew/ Paisley (MIDSPAN) cohorts, both of which were initiated in the early 1970s.

Garn et al reported sixteen years mortality data for 2381 men aged 45 to 75 years. In this cohort all cause mortality rate was higher in lean rather than obese people (Garn et al. 1983). Nevertheless, obese people had higher cardiovascular mortality risk and lean ones had higher cancer related mortality. Initial results for the Renfrew and Paisley Family study showed that, over 10 to 14 years of follow-up, BMI was negatively associated with all cause mortality and stroke in women, but it was not associated with cardiovascular or ischemic heart disease deaths (Janghorbani et al. 1992). After 20 years of follow-up, BMI was not associated with the risk of stroke mortality although there was a U-shaped relationship in men and women (Hart et al. 2001).

The relationship between obesity and cancer incidence in these two cohorts has not been addressed. A detailed investigation of the type of association between obesity (as measured by BMI) and all cause and cause specific mortality and cancer incidence and possible confounding factors, in the Renfrew and Paisley Family study, are presented in this chapter.

5.2 METHOD

Study population

A detailed description of the study populations was given earlier in Chapter Two. In this section a brief description of the study populations, measurements used in the analysis and statistical methods used in this chapter are given.

Renfrew and Paisley survey

The population cohort from two towns, considered to be typical of the West of Scotland, was screened between 1972 and 1976 (Hawthorne et al 1995;Watt et al 1995). Men and women aged between 45 and 64 living in Renfrew and Paisley were identified and invited to take part in a cardiovascular screening. Participants completed a questionnaire, which was checked by trained nurses, when they attended the screening clinics. Physical measurements including height and weight, and blood samples were collected for each participant.

A second survey was conducted in the years 1977 and 1979. There were 3787 men and 4744 women who took part in the second screening.

Collaborative survey

This is a study of an occupational cohort recruited from 27 workplaces in Glasgow (in the West of Scotland) and screened between 1970 and 1973 (Davey Smith G et al. 1998). There were 6022 men and 1006 women, of which 5766 men were aged 35-64 at the time of screening. Participants completed an extensive questionnaire and had physical measurements at clinics at or near the workplace. The examinations used were similar to the Renfrew and Paisley survey.

Measurements

Follow-up data

Participants in the Renfrew and Paisley study were flagged at the NHS Central Register in Edinburgh, and notifications of deaths have been received for 25-year follow-up. Causes of death were coded to ICD-9 (International Classification of Diseases, ninth edition). IHD code was (410-414), stroke (430-438), all vascular diseases (390-459), all cancer (140-209), digestive (520-579), and respiratory (460-519).

Cancer incidence data was obtained from the Scottish Cancer Registry. Cancer specific site was coded according to the ICD-9 (International Classification of Diseases, 9th revision), breast cancer (174), lung cancer (162), prostate cancer (185), pancreatic (157), colon cancer (153), bladder and kidney (188-189), uterus and ovaries (182-183), oesophagus and larynx (150-161).

Statistical analysis

Social class was defined according to the Registrar General's classification based on occupation at the time of screening. Retired participants were classified according to their last full time occupation. Women were given their own occupation except housewives who were given their husband's or father's occupation. Social class was recoded into manual group (which included class III-M, IV and V) and non-manual (which included class I, II and III-NM)

Three categories of smoking habit were defined: never smoker, current smoker and former smoker. The number of smoked cigarettes was used as a continuous variable.

BMI (calculated by dividing weight by height squared) was divided into four groups according to the WHO criteria: under weight <18.5, normal weight 18.5-24.9, overweight 25-29.9, and obese $\geq$30.0 kg/m^2 to test the risk defined by the international studies using 18.5-24.9 as the reference group.

For mortality analysis, BMI was also divided into nine equal groups for the whole population and separately for men and women (<21.3, 21.3-22.8, 22.9-23.9, 24.0-24.9, 25.0-25.9, 26.0-27.0, 27.1-28.3, 28.4-30.4, >30.4 kg/m^2) to study the pattern of mortality risk with BMI distribution using the fifth group (25.0-25.9) as the reference group. To study the relative risk in the extreme lower and upper ends, cut-offs for eleven equal BMI groups were used. The cut-offs were <20.08, 20.09-21.3, 21.4-22.8, 22.9-23.9, 24.0-24.9, 25.0-25.9, 26.0-27.0, 27.1-28.3, 28.4-30.4, 30.5-32.2, >32.2 to define mortality basal risk level using the sixth group as the reference group.

Five equal groups <22.5, 22.5-24.5, 24.6-26.3, 26.4-28.7, >28.7 were used to study the risk of cardiovascular mortality over follow-up periods, the first group was the reference group. Five equal groups were used to get sufficient numbers and more reliable estimates of relative risk in each group.

For cancer analysis, BMI was divided into tertiles separately for men and women. BMI tertiles for men were <24.4, 24.4-27.1, and >27.1 kg/m2; for women BMI tertiles were: <23.6, 23.6-27, and >27 kg/m^2.

Cox's proportional hazards regression model was used to assess the association between body mass index (BMI) and death and cancer incidence with adjustment for known factors. These factors were age, sex, smoking status (never, former and current), number of smoked cigarettes, social class (manual and non-manual), blood pressure and cholesterol.

BMI groups were included as categorical variables to estimate the relative hazards ratios for each single group compared to the reference group. The reference groups were chosen either as the mid point between BMI groups in some analysis or as the first group of BMI groups. This depended on the purpose of analysis whether we were investigating the pattern of association between BMI and mortality and incidence or to estimate the risk in groups with higher BMI.

To test for linear trend, BMI was included in the model as a continuous variable and P-values indicating the significance of linear trend. Test for interaction between BMI and

different factors were also considered. When the interaction test was significant for a certain factor, Relative hazards ratio (RHR) of BMI was reported stratified by that factor.

5.3 RESULTS

Obesity and mortality

General characteristics of the Renfrew and Paisley cohort

About two thirds of the Renfrew and Paisley population are in the manual social class. 57% of men are smokers and 25% are ex-smokers, while almost half of the women are smokers, and 47% have never smoked (Table 5-1).

Out of 15406 subjects screened in the years 1972-76, 8182 (53%) had died by the year 1999: 61.9% (4366) were men and 45.7% (3816) were women. Mean age at the time of screening for men was 54.1 and 54.4 years for women.

Table 5-2 show mortality and cancer incidence by age at time of screening. The mortality rates are higher in the elderly group. The mortality rate for CVD for the oldest age group is more than double that of those younger than 50 years. Lung cancer mortality and cancer incidence rates were similar for those older than 50 years old.

Higher mortality was found among subjects with BMI <18.5 kg/m^2 or BMI $\geq$30 kg/m^2. CVD, IHD and stroke deaths were higher among those with BMI more than 30 kg/m^2, while a higher percentage of respiratory deaths occurred among those with a BMI <18.5 kg/m^2 (Table 5-3).

All cause mortality

The curve representing the relationship between all cause mortality and BMI was U-shaped with increased risk at both the lowest and highest BMIs. The Relative hazard ratio in the first group (BMI <21.3 kg/m^2) compared to the fifth group (BMI 25-25.9 kg/m^2) was 1.24 (95%CI: 1.14-1.36). At the higher end, the risk started to increase to 1.05 (95% CI: 0.96-1.15) in the 7^{th} group (BMI 27.1-28.3) and to a significant level in the 8^{th} (1.14) and 9^{th} (1.25) groups (Table 5-4). Test for linear trend was not significant for the total sample, or for men and women separately.

Relative hazard ratios were higher in men compared to women. The relationship between all cause mortality for women was similar to that for the total sample, while for men the RHR at the obese end was significant for the 9th group (Figure 5-1).

In order to study the two ends of BMI distribution further, BMI was divided into 11 equal groups (Table 5-5). The risk of all cause mortality started to increase at group 2 in the lower end and group 9 (28.4kg/m^2) in the upper end of BMI. Based on these results we can estimate the weight where mortality risk starts to increase, given the average height of Renfrew and Paisley population (163.12cm). Subjects with weight less than 56.7kg or with weight more than 75.6kg with average height have higher risk for all cause mortality.

All cancer mortality, lung cancer, colorectal cancer, breast, GI tract cancer and prostate cancer mortality

Cancer mortality accounted for about 28.6% (2345) of total mortality causes, with lung cancer (33%) as the major cause. The risk of all cancer, colorectal cancer, prostate cancer and gynecological cancer deaths were not associated with body weight measured by BMI (Table 5-4).

The risk of breast cancer death increases with increasing BMI, after adjusting for age, smoking status and social class (p for trend = 0.034).

High BMI shows a protective effect against the risk of lung cancer death. This protective effect was found after adjusting for age, smoking and social class. The same association was found even after restricting the analysis to heavy smokers defined as those who smoke more than 15 cigarettes a day (Table 5-4). Lung cancer mortality risk starts to increase in subjects, in average height, with weight less than 56.7kg (Table 5-5).

IHD

IHD accounted for 31% (2569) of all cause mortality in the study population. The relationship between death from IHD and BMI was J-shaped, with a high relative risk in the 1st and 2nd BMI groups (not significant). While a marginal increase started in the 6th to the 9th BMI group, significantly higher relative risks were apparent in the 8th and 9th groups.

The test for trend describing the relationship between IHD cause of mortality and BMI was highly significant (p for linear trend <0.0001).

Subjects with 80.9kg and average height are at higher risk of IHD mortality (Table 5-5).

As blood pressure and serum cholesterol are independent risk factors for IHD; we have adjusted for these factors by repeating the analysis including these factors in the hazard regression model. Test for trend in BMI groups was 0.009 controlling for systolic blood pressure, 0.042 controlling for diastolic blood pressure, and <0.0001 controlling for serum cholesterol. Test for trend was not significant (p=0.274) after controlling for systolic blood pressure, diastolic blood pressure and serum cholesterol in addition to age, sex, social class and smoking habits. However, the pattern of relationship between BMI groups and IHD was similar to that modelling including age, sex, social class and smoking habits. The risk starts in the 7th group (RHR: 1.08, 95% CI: 0.92-1.27) and the risk was significant in the 9th group (RHR: 1.22, 95% CI: 1.04-1.43)

Respiratory

The Relative hazard ratios of respiratory deaths decreased with increasing BMI. The highest risk of dying of respiratory disease was among people in the lowest BMI groups – bottom group (RHR 2.5, 95%CI: 1.9-2.8) and 2nd bottom (RHR 1.5, 95% CI: 1.1-2). A similar relationship was found when restricting the analysis for heavy smokers. A test for linear trend was highly significant (p<0.0001) (Table 5-6). Subjects with weight less than 64.7kg with average height are at higher risk of respiratory mortality (Table 5-5).

Stroke

The relationship between the risk of stroke mortality and BMI didn't show any clear pattern and test for trend was not significant (Table 5-4). On the other hand, the percentage of stroke deaths was higher in the obese group (8.4%) compared to the other groups (Table 5-3).

Including blood pressure in the model affected the relationship between BMI groups and risk of stroke mortality. A negative significant relationship with RHR of 0.966 (95% CI:

0.94-0.99, p=0.011) resulted from including systolic and diastolic blood pressure in the model. A significant interaction between BMI groups and blood pressure was found.

Digestive

The pattern of BMI and mortality from digestive diseases was J-shaped with increased risk in the upper end of the BMI distribution starting from the 7th group (Table 5-4). The test for trend was significant (p=0.001).

Other causes

Other causes of mortality showed a U-shaped pattern with BMI groups, but test for trend was not significant (Table 5-4).

Patterns of obesity associated mortality in different social classes

Obesity prevalence was higher in the manual men and women compared to those in non-manual class (Chapter Four). Analysis of the risk of all causes and cause specific mortality was run separately for manual and non-manual social class.

The relationship between BMI groups and relative hazard ratios of all cause and specific causes of death was not the same for the two social classes. Significant interaction tests were found for all cause mortality (p<0.001), all cancer (p=0.0008) and digestive causes of death (p=0.014).

Table 5-6 shows the relative hazard ratios for all cause and specific causes of death by equal BMI groups in manual and non-manual social classes. 68% (5393) of all deaths were in the manual group. All cause mortality risk was higher in the manual than non-manual social class in all BMI groups. Mortality risk increased significantly among subjects with BMI<21.3kg/m^2 (RHR 1.3, 95% CI: 1.2-1.5), and for subjects with BMI>28.4 kg/m^2 in the manual social class. A test for trend between BMI groups and relative hazard ratios was significant in non-manual social class (p=0.005) but not significant for manual social class.

Manual social class was representing those in social class III manual, IV and V. To investigate whether the risk of mortality was similar or different in the three groups, social

class was regrouped into three groups: group1- class I&II; group 2- class III non-manual & III manual; and group 3- class IV & V. Figure 5-2 shows the relationship between relative hazard ratios for all cause mortality and BMI groups by social classes groups. 15.7% of death were in group 1, 48.5% were in the second group and 35.8% were in the third group. Subjects with BMI >30 kg/m^2 had a higher mortality risk in the three social class groups, but subjects in the third social class (IV&V) had high mortality risk among subjects with BMI <21 kg/m^2 and BMI >27 kg/m^2 (Appendix A).

IHD deaths showed a J-shaped pattern with BMI groups in both manual and non-manual social classes (Table 5-6). Mortality risk increased significantly in subjects with BMI >28.4 kg/m^2 in manual social class and in subjects with BMI >30.4 kg/m^2 in the non-manual social class. The tests for trend are significant for both social class groups.

Respiratory, all cancer and lung cancer deaths show an inverse relationship with BMI, where the higher mortality risk was among subjects with lower BMI in both manual and non-manual social classes (Table 5-6). Subjects with BMI <22.8 kg/m^2 had a significant risk of any cancer mortality while subjects with BMI >30.4 kg/m^2 have a significantly lower risk from lung cancer mortality. The trends between BMI and risk of any cancer and lung cancer mortality were significant in manual social class but not in the non-manual social class, while the relationship for respiratory mortality risk trend was significant in both manual (p<0.0001) and non-manual (p=0.0003) social class groups.

Relative hazard ratio for deaths from digestive diseases increases significantly with increasing BMI in non-manual social class and no clear pattern was found for manual social class. The risk start to increase in subjects in the 7th group with BMI 27 kg/m^2 (RHR 1.6) and RHR reaches 2.2 in the 9th groups in subjects with BMI >30 kg/m^2.

The risk of other mortality causes and BMI didn't a have clear pattern in either manual or non-manual social classes.

Patterns of obesity associated mortality in different smoking groups

Obesity is negatively associated with smoking. Former and never smokers tend to be heavier than current smokers (Chapter Four) and thus, we investigated the risk of all cause and cause specific mortality and BMI for each smoking group.

The risks of all cause mortality and all cancer, colorectal cancer, IHD, stroke causes of death were different in smokers and non-smokers. 4598 (58%) of deaths occurred in the smoking group and 3341 (42%) were in the non-smoking group. Mortality risk from all cause, all cancers, IHD and respiratory causes showed an association with BMI which was significant in both smoker and non-smoker subjects (Table 5-7).

A U-shaped pattern of association between BMI groups and all cause mortality risk was found in both smokers and non-smokers. In smokers subjects with BMI <22.8 kg/m^2 or BMI >28.4 kg/m^2 had significantly increased mortality risk when compared to subjects with BMI 25-25.9 kg/m^2.

A J-shaped pattern was also found for the association between BMI groups and IHD cause of mortality (Table 5-7). Mortality risk was significantly higher in the 9th group for subjects with BMI >30 kg/m^2 among both smokers and non-smokers, but the risk differential was higher among non-smokers (RHR 1.6 for non-smokers and 1.3 for smokers).

Respiratory deaths were higher at the lower and upper ends of BMI groups for smokers, while it was higher at the lower end of BMI group and lowest at the upper end among non-smokers (Table 5-7). The risk of respiratory death was higher among smokers compared to non-smokers in all BMI groups. Higher mortality risk was found among subjects with BMI <21 kg/m^2 in non-smokers (RHR 2.4) and subjects with BMI <22.8 kg/m^2 in smokers group (RHR 1.6 for BMI 21.3-22.8 kg/m^2 and 2.9 for BMI <21.3 kg/m^2).

Colorectal cancer and digestive causes of mortality risk show positive association with BMI groups among non-smokers.

Lung cancer cause of mortality risk was higher among smokers compared to non-smokers in all BMI groups. Test for trend in the association between mortality risk and BMI was

significant among smokers, the risk of mortality being higher among subjects with BMI < 21.3 kg/m^2 (RHR 1.4).

Stroke and other causes of mortality risk didn't show any trend in the association with BMI groups.

Obesity associated mortality including and excluding the first 5 years of follow-up

This section tests whether the exclusion of the first five years of follow-up has an effect on the pattern of association between obesity and mortality. Similar patterns were found between causes of mortality and BMI groups for the total sample including and excluding the first five years of follow-up. All cause mortality shows a significant trend (p=0.047) after excluding the first five years of follow-up (Table 5-8).

Smokers and non-smokers had similar patterns for the association between BMI and risk of all cancers and respiratory mortality (Appendix A) before and after excluding the first five years of follow-up. The risk of all cause mortality was significant for both smokers and non-smokers before excluding the first five years and remained significant for non-smokers after excluding them.

There was no difference in the pattern of association between causes of mortality and BMI groups in the two social classes before and after excluding the first five years of follow-up (Appendix A). The risk of all cancer deaths was significant among manual social class before excluding the first five years of follow-up, but this association became insignificant after excluding these years; the association becomes significant in the non-manual group.

Mean BMI, for subjects dying from respiratory diseases, was lower than 25 kg/m^2 in all of the first 10 years of follow-up (Table 5-9) except in the 7th year where mean BMI was 26 kg/m^2. However, mean BMI for subjects dying from any cancer was low in the first three years. Mean BMI for all cause mortality was similar for all follow-up years (Figure 5-3).

Patterns of vascular and non-vascular causes of mortality associated with obesity in different follow-up periods

The risks of all vascular mortality were higher in the upper end of BMI distribution (Table 5-10). This was true for the three follow-up periods (first five years, 6-15 years and 16-25 years). Higher relative hazard ratios were found in the first five years of follow-up in all four BMI groups compared to the two follow-up periods. Mortality risk was significant in the fifth BMI group in the three follow-up periods but was highest in the first five years (1.69 in the first follow-up period, 1.2 and 1.19 in the second and third period).

Relative hazard ratios for non-vascular mortality were very close to one in all BMI groups in the three follow-up periods (Table 5-11). Test for trends in the relationship between mortality risk and BMI groups were insignificant in the three follow-up periods.

Subjects with BMI 22.5-24.5 had the lowest relative risk of mortality in all follow-up periods compared to the other BMI groups.

Relative hazard ratios for vascular mortality were higher than that for non-vascular mortality causes throughout all BMI groups in the three follow-up periods.

Patterns of all cause mortality with obesity by subject age at screening time

It was reported in the literature that the risk of mortality varies with subjects age. In this section we investigate the risk of mortality in two age groups as reported at the time of screening. The curve resulting from the relationship between relative hazard ratios from all mortality causes and BMI was U-shaped for all subjects included in the study. Similar curves were found for the subjects aged 45-54 years and 55-64 years at the time of screening (Figure 5-4). Although both age groups have similar curves, the younger group (45-54 years) shows a steeper relative risk of dying than the older age group across the BMI groups. At the same time, the base of the curve in older group (55-64 years) was slightly wider than that in the younger group. In the younger group (45-54 years) the risk of mortality was higher in those with high BMI than those with low BMI while in the older group the risk of mortality was higher in those with low BMI. The same observation was found for men and women (Appendix A).

Obesity and cancer

General characteristics of Renfrew and Paisley cohort

Table 5-9 shows the characteristics of Renfrew and Paisley cohort in BMI tertiles by sex. Men in the third tertile were less likely to be smokers, in the manual social class compared to men in the first tertile. Women in the third tertile were older, less likely to be smokers and in the manual social class.

Cancer incidence and BMI

This section describes the pattern of association between BMI and all cancer and site-specific cancer.

Over the 20 years of follow-up, 3057 (19.8%) cancer cases (first site cancer) were reported; 1588 were men and 1469 were women. There was no significant association between cancer incidences, any cancer, and BMI tertiles (p for trend =0.239).

Breast cancer

3.1% (260) of women had breast cancer over the 20 years of follow-up. The percentage of women with breast cancer increased from 2.5% in the first BMI tertile to 3.3% and 3.6% in the second and third tertile (Table 5-12). Relative hazard ratios of breast cancer incidence increased linearly with BMI tertiles (p=0.033), after controlling for age, smoking status and social class. Women in the third tertile had 1.4 (95% CI: 1.03-1.92) hazard ratio compared to women in the first tertile (Table 5-13).

Colon cancer

A total of 329 individuals had colorectal cancer over the follow-up period, 253 were colon cancer cases. The percentages of colon cancer were equal in the three BMI tertiles (Table 5-12). There was no significant relationship between colon cancer incidence and BMI (p=0.89). The same pattern was found for men (p=0.77) and women (p=0.98).

Prostate cancer

2.2% (149) of men had prostate cancer. Although a higher percentage of men with prostate cancer were in the third tertile compared to the percentage of prostate cancer in the first cancer, the percentage were 2.3% and 2.1% respectively (Table 5-12). There was no significant association between relative hazard ratio of prostate cancer and BMI tertiles (p=0.78).

Kidney and bladder cancers

The percentages of kidney and bladder cancers were 1.2%, 1.5% and 1.8% in the first, second and third tertiles (Table 5-12). Relative hazard ratio was 1.36 (95% CI: 0.98-1.92) for subjects in the third tertile compared to the first tertile, but test for trend was not statistically significant (Table 5-13).

Lung cancer

The percentages of subjects with lung cancer decreased from 6.6% in the first tertile to 3.6% in the third tertile (Table 5-12). Relative hazard ratios of lung cancer decreased significantly with increasing BMI (p=0.0001), with RHR of 0.69 (95% CI: 0.57-0.83) in the third tertile when compared to the first. Similar relationships were found in men (p=0.003) and women (p=0.0061) after controlling for age, smoking status and social class (Table 5-13). Detailed analyses of the relationship between the risk of lung cancer and BMI are described below.

Effect first year of follow-up on the risk of lung cancer

Relative hazard ratios for cancer incidence in different BMI tertiles did not change even after excluding the first three years of follow-up (Table 5-14). Relative hazard ratios were 0.76 (95% CI: 0.59-0.93) for men and 0.61 (95% CI: 0.42-0.88) for women, controlling for age, smoking status and social class.

Assuming that very thin people might have a disease or loss weight because of disease, we repeated the analysis excluding those with BMI < 18.5kg/m^2 and those with BMI <20kg/m^2. The test for trend was 0.001 and 0.004 respectively. Subjects in the third tertile of BMI had lower RHR compared to those in the first tertile, RHR were 0.69 (95% CI: 0.57-0.83) excluding those < 18.5kg/m^2 and 0.71 (95% CI: 0.59-0.87) excluding 20kg/m^2.

Lung cancer and BMI among smoking subjects

The majority of the study population were smokers. 83% (644) of cancer cases were smokers. Relative hazard ratios decrease from 0.85 (95% CI: 0.0.7-1.1) in the second BMI tertile to 0.65 (95% CI: 0.53-0.8) in the third tertile. There was no significant association between risk of lung cancer and BMI among never and former smokers, although the numbers were small, 47 cancer cases among never smokers and 73 cancer cases among former smokers (Table 5-15). The association between BMI and different smoking groups was not different, because test for interaction between smoking and BMI tertiles was not significant (P=0.683).

Figure 5-5 show that the risk of lung cancer was similar for the three BMI tertiles in the different smoking levels.

Effect of follow-up time on the risk of lung cancer

Table 5-14 shows the difference in BMI and lung cancer incidence relative hazard ratios, using the second tertile as the reference group, at different follow-up periods. The risk of lung cancer incidence in those in the first tertile of BMI was higher than that for those in the third tertile of BMI in all follow-up periods (Table 5-16). Higher risk estimates are found after 5 to 10 years of follow-up (Figure 5-6).

Characteristics of lung cancer cases and lung cancer free subjects

Table 5-18 shows the characteristics of lung cancer cases compared to controls free of cancer in the first and third BMI tertiles. Lung cancer cases and controls in the third tertile were fewer smokers, with high mean FEV1 and predicted FEV1 compared to the first tertile. Subjects in the third tertile with lung cancer were more smokers, with lower mean predicted FEV1 compared to those in the control group. Cholesterol level was similar in subjects in the first and third tertile in lung cancer cases and controls, but controls cholesterol level was higher than that for lung cancer cases in both tertiles.

Lung cancer and BMI in different social classes

72.4% (552) of lung cancer cases were in the manual social class and 27.6% (210) in the non-manual social class. The risk of lung cancer incidence was higher in the manual social class compared to non-manual social class in the four BMI groups (Figure 5-7). Relative hazard ratios of lung cancer were significantly associated with BMI groups in the manual group ($p<0.0001$), but not significant for non-manual group ($p=0.213$). The risks of lung cancer decreased as BMI increased in the manual group. Relative hazard ratios were 0.87, 0.77, 0.69 and 0. 49 in the second, third, fourth and fifth BMI quintiles compared to the first quintile (Table 5-16). Test for interaction between BMI and social class was not significant.

Lung cancer incidence over two periods of follow-up

This pattern of BMI groups and risk of lung cancer might be the result of sub-clinical disease, which cause weight loss. How long the effect of sub-clinical disease could operate is not clear; by looking at second screening we can study changes in weight between the two screenings and after the second screening.

There were 762 new lung cancer cases identified since the first screening in 1972-6 and only 301 lung cancer cases since the second screening in 1977-79. The negative association between BMI and risk of cancer incidence was found in the two follow-up periods (Table 5-19). Subjects in the second and third tertiles were significantly at lower risk of lung cancer compared to those in the first tertile in all subjects, especially in men. In women only those in the third tertile had significantly lower risk than those in the first tertile.

Cancer free subjects were slightly lighter in the second screening survey with a mean change in BMI of –0.197 (1.84). Lung cancer cases identified in the first two years of the second screening had higher BMI in the second screening (Table 5-20). However, lung cancer cases identified in after two years of the second screening had lower BMI values in the second screening compared to the BMI values in the first one. The mean BMI changes in lung cancer cases were not significantly different from cancer free subjects.

The risk of lung cancer mortality in different cohorts

To test the consistency of our findings in a different population, we used the collaborative occupational study, which was conducted in Great Glasgow area between 1970-73.

There were 4014 men aged 45-64 years in the collaborative study. Fifty percent of them have died over 20 years of follow-up. Lung cancer cause of mortality accounted for 11% (226) of total mortality (Table 5-21).

The risk of lung cancer mortality was negatively associated with BMI in the collaborative study (Table 5-22). Subjects in the fourth and fifth quintiles were at significantly lower risk than those in the first quintile. Similar associations were found in current smokers and heavy smokers but not to a significant level as in Renfrew/ Paisley study.

An unclear pattern of relationship between the risk of lung cancer mortality and BMI was found for non-smokers.

Using pooled data from both studies, the Collaborative and Renfrew/Paisley studies, suggested decreasing lung cancer mortality risk with increasing BMI in both smokers (RHR=0.89) and non-smoker (RHR=0.91). Relative hazard ratios were similar for current smokers in general and for heavy smokers who smoke more than 15 cigarettes per day.

5.4 DISCUSSION

Scotland has a high mortality rate compared to other European countries. More than half the population of Renfrew and Paisley towns has died over 25 years of follow-up and 50% of these deaths were CVD related deaths.

All cause mortality

In this cohort, the relationship of all cause mortality with body mass index was U-shaped with higher mortality risks at the lower and upper end of BMI distribution. Our results were consistent with the World Health Organisation cut-offs (World Health Organisation 1998) where higher risks were found for those with BMI less than 18.5 and BMI more than 30kg/m^2. However, in this cohort, Renfrew/Paisley, mortality risks start at BMI value of 28kg/m^2.

All cause mortality risks were higher for men compared to women. Both men and women have U-shaped relationship between all cause mortality and BMI and this relationship was retained after controlling for the possible confounding factors. Previous studies reported increased risk of all mortality at higher BMI values for men and women. However, some studies didn't find increased risk of all mortality at lower BMI for women (Manson et al 1995; Seidell et al. 1996).

The risks of all cause mortality were not the same for the two social classes. A positive interaction between social class and BMI groups was found. Higher mortality risks were found for subjects in the manual social class. In both manual and non-manual social class, the relationship between BMI and all causes mortality were U-shaped; a significant linear trend was found in the non-manual social class. Subjects in all social class have higher risks of all mortality at BMI greater than 30 kg/m^2; however, subjects in social class IV and V had higher mortality risk at BMI greater than 27 kg/m^2.

Fitzpatrick hypothesised that an individual social class is associated with higher mortality (Fitzpatrick 2001) and an increased mortality risk for those in lower social class has

previously been reported in this cohort (Davey Smith et al 1998). Our results confirm this hypothesis and show the added risks of excess weight.

Failure to adjust for smoking status was one of the explanations for the U-shaped relationship between obesity and mortality. Results form the Framingham study found a U-shaped relationship between obesity, measured by metropolitan relative weight (MRW), and death in smoking men but a direct relationship in non-smokers (Garrison et al. 1983). These results were based on visual inspection of the data. Re-examination of the relationship between obesity, measured by BMI and MRW, of the Framingham cohort using statistical methods found that there was no interaction between smoking and obesity measures. Furthermore, the estimated BMI at the minimum risk of death was similar for smokers and non-smokers in both men and women (Sempos et al. 1998).

In our study, there was a significant interaction between smoking and BMI groups suggesting different patterns for smokers and non-smokers. High risks of all cause mortality was found for both obese current smokers and non-smokers and in lean current smokers. This effect of high-risk mortality remains significant in current smokers after taking account of the number of cigarettes smoked.

Increased mortality associated with lower BMI has been reported previously. It has been hypothesised that higher mortality among those with a low BMI is the result of low lean body mass rather than low fat mass (Allison et al 1997). Thorogood et al has investigated the relationship between BMI and mortality in a slim vegetarian British cohort (Thorogood et al. 2003). They found that lean subjects with BMI less than 18 kg/m^2 had increased all cause mortality compared with those with a BMI between 20 and 22 kg/m^2 and this was consistent in different smoking groups, after excluding the first five years of follow-up cohort (Thorogood et al 2003). In this cohort we had a small number of subjects with BMI less than 18.5kg/m^2 so were unable to repeat this analysis.

Another explanation for the high risk of all causes mortality in lean subject (BMI <20kg/m^2) is weight loss due to pre clinical illness. Some studies confirm this hypothesis and others disagree with it. Our findings disagree with this explanation; the risk of all cause mortality was similar before and after excluding subjects who died in the first five years of

follow-up. The results were consistent in the different smoking and social class groups. Furthermore, mean BMI for all causes mortality were similar for all follow-up years. Stevens et al studied the mean changes in BMI among ill health participants and healthy ones. He found that the mean changes in BMI were similar in the two groups. However, the odds ratio for converting from obese to non-obese was higher in ill-health participants compared to the healthy ones (OR=1.29 (95% CI: 1.01-1.67) (Stevens, Juhaeri, & Cai 2001).

The risks of all cause mortality differ over the life span. It was reported that overweight or obesity was not associated with increased risk of all cause mortality in men and women over 70 years. The lower risks were explained by the selective survival or the higher mortality rate among older people. Our population was not very old. Nevertheless, those with higher BMI and aged 55 to 64 years have lower mortality risk compared to those with lower BMI. Consistent with previous studies, the younger groups (45-54 years) had a linear association between BMI and all cause mortality.

It should not be concluded from this results that overweight or obesity is protective for all causes mortality for elderly people. Loss of lean mass is common among the elderly because of inactivity and chronic diseases. In addition, fat mass tends to accumulate intra-abdominally with age, so a combination of waist circumference and waist-hip ratio in addition to BMI might be better measures in the elderly.

Cardiovascular mortality

Many studies have suggested that obesity is an independent risk factor for the ischemic heart disease mortality. Most studies agreed that the risk of cardiovascular mortality increases linearly with increasing BMI although not all of the studies found a significant linear trend. In our cohort the risk of IHD mortality formed a J-shape with BMI, where those with obesity have the highest mortality risk. Mortality risks for never smokers and those in the manual social class start at BMI less than 30kg/m^2 whereas mortality risk for smokers and those in the non-manual social class starts at BMI of 30kg/m^2 or more. Excluding individuals who died in the first five years of follow-up did not affect the relationship between BMI and risk of IHD mortality.

On the other hand, the risk of stroke mortality was not associated with BMI. A U-shaped relationship was found where higher mortality risks were found among lean and obese individuals. These results confirm previously reported results of 20 years follow-up for the same cohort (Hart, Hole, & Davey Smith 1999).

The length of follow-up period does not appear to affect the relationship between obesity and CVD related deaths, although long follow-up period might give lower mortality risk estimates. In the first five years of follow-up, CVD mortality risk was positively associated with BMI and the risks start at BMI of 26 kg/m^2 especially in men. In the second period of follow-up, 6-15 years, where the first five years were excluded, a positive association was still found, for all individuals and for men. Risk ratios were lower than that found in the first five years and the risks start at BMI greater than $28kg/m^2$. In the last ten years of follow-up, the same relationship was found as the other periods of follow-up but with lower risk ratios. Mortality risks started at BMI greater than 28 kg/m^2 as in the second period.

A follow-up period of 15 years provides good estimates for CVD mortality risks, including or excluding the first five years of follow-up. We expected to find high mortality risk among those with low BMI assuming that they have lost weight because of sub-clinical illness, but found the opposite. CVD mortality risk was higher in those with BMI greater than 26 kg/m^2 compared to those with BMI less than 23 kg/m^2 in the first 5 years of follow-up.

Furthermore, the lower risk ratios found in the last ten years of follow-up might be the result of age. The age of those surviving until the last ten years ranges between 60 to 80 years. Baik et al found that CVD mortality increases linearly with BMI in those aged less than 65 years old but this association was not found for those aged greater than 65 years old (Baik et al 2000). As previously discussed other measures should be used in addition to BMI for elderly people.

Given that half the deaths are CVD and the linear relationship between BMI and CVD mortality risk, we suggested that the U-shape of BMI and all causes mortality might be a result of a positive linear relationship with CVD mortality risk and a negative relationship with non-vascular mortality death. The results in the CVD mortality do support this

hypothesis but non-vascular diseases do not. The risks of non-vascular disease mortality were flat through out the BMI values. This suggests that the increased risk of all cause mortality in those with high BMI values is the result of increased risk in CVD mortality diluted by the lower risk from non-vascular diseases mortality. But this does not explain the high mortality risk in those with low BMI values.

Other mortality causes

The small number of site specific disease related mortality made it difficult to study the relationship with obesity. So a combination of all the diseases of the gastrointestinal tract were used. Nevertheless, a positive relationship between BMI and digestive causes of mortality was found. This linear relationship was specific to non-smoker and non-manual groups.

Respiratory related deaths were negatively related with BMI (Farrell et al. 2002). But respiratory diseases are related to smoking and smoking is associated with lower BMI. Smokers have relatively higher mortality risk than non-smokers through out the BMI groups. The risk of mortality was negatively associated with BMI in non-smokers but U-shaped in current smokers. These patterns were retained after excluding the first five years of follow-up to control for the sub-clinical illness.

Obesity and cancer

The risks of all cancer mortality and cancer incidence were not associated with BMI in men and women. Some studies reported a positive association between all cancer mortality and BMI; others reported this association to be true for men only or women only.

Studying all cancer mortality is difficult to interpret since it is a combination of different cancer sites, which might relate to obesity in different ways.

In this cohort only risk of lung cancer mortality and incidence and risk of breast cancer incidence were associated with BMI. Subjects with high BMI seem to have a higher incidence rate of ovary and uterus cancer, prostate cancer and kidney and bladder cancer. One possible bias might be the long period of follow-up, in which subjects BMI might have changes over the 20 years of follow-up.

Combinations of two or more cancer sites were done to increase the numbers but at the same time being aware of the fact that the cancers of these sites have similar relationships with BMI. These combinations might affect cancer incidence risk in these cancers.

The positive association between BMI and breast cancer reported in the literature was found in our study. The risk of breast cancer increases among overweight women. One explanation is that overweight and obese women were less likely to be screened for breast cancer with mammography, this remains even after adjustment for sociodemographic information, insurance and access to care, illness burden, and provider specialty (Wee et al. 2000), and leads to late diagnosis and increased risk of mortality.

The ages of women in our study ranged from 45 to 64 years, that is all were in the menopausal stage. In our cohort the women were not very old and BMI was a good measure of obesity and showed increased risk of breast cancer incidence and mortality. Recent prospective studies show that markers of increased breast cancer risk in older women included higher serum concentrations of free estradiol and free testosterone. These changes are often associated with abdominal fat accumulation and hyperinsulinemia (Stoll

2000) and so the use of waist circumference and WHR in addition to BMI would give better indicators of cancer risk.

It is worth mentioning that the risk of breast cancer in premenopausal women was reported to be less in women with BMI >30 kg/m^2 but higher among women with higher WHR.

Although the percentage of prostate cancer was higher in overweight men, the test for trend of increasing prostate cancer risk among obese men was not significant. The association between prostate cancer and obesity is still debatable. Some studies have reported an increased risk of prostate cancer with increasing body weight (Putnam et al 2000) while other have found no association (Andersson et al 1997). This variation of results also varied by the type of study, whether it was cross-sectional, case-control or cohort study. The weak association between BMI and the risk of prostate cancer could be explained by several mechanisms. First, obesity is associated with several hormonal abnormalities in men, including higher oestrogen and lower testosterone levels of sex hormone binding globulin, which should increase mainly the fraction of biologically available testosterone. Since sex hormones, especially androgens, have been implicated in the cause of prostate cancer, the endocrine aberration associated with obesity may play a role in the cause of this disease. Second, high BMI may reflect an imbalance between caloric intake and physical activity. High-energy intake and low physical activity are associated with risk of prostate cancer. Third, obesity may be involved in prostate carcinogesis through a relationship with sympathetic activity (Andersson et al 1997).

Although a compelling association between obesity and risk of colon cancer has been reported in prospective and retrospective studies, this association was not found in our study.

In a prospective study by Lee and Paffenbarger, men who were in the heaviest quintile of BMI during both college years and middle age had a RR of 2.4 (95% CI =1.4-4.1) compared to men consistently in the lowest quintile (Lee, Paffenbarger, & Hsieh 1991). In another prospective study, men in the top tertile of BMI had a RR of 2.4 (95% CI = 1.1 – 5.4) (Wu et al. 1987). In the same study, the RR for colon cancer in relationship to WHR was 3.41 (95% CI = 1.52-7.66) and for waist circumference it was 2.56 (95% CI = 1.33-

4.96). These were only modestly attenuated when controlled for BMI. In the Cardiovascular Health Study (Schoen et al. 1999), waist circumference (RR =2.2; 95% CI =1.2-4.1) between high and low quintiles) and WHR (RR= 2.6; 95% CI= 1.4-4.8) were risk factors, whereas BMI had a insignificant positive association (RR=1.4; 95% CI=0.8-2.5). Results from case-control studies were inconsistent for men.

Some prospective studies reported direct associations between BMI and colon cancer risk, but others have not supported this association including our study. In general, the association between BMI and colon cancer appears to be more consistently observed and stronger for men than for women. In the Nurses Health Study, women who had a BMI>29 had a RR of 1.45 (95% CI=1.02-2.07) in comparison with women whose BMI was <21. Data on body fat distribution and colon cancer risk are very limited. Two studies in women reported suggestive but not significant positive associations between WHR and risk of colon cancer.

In women, the association between BMI and colon cancer appears to exist at younger ages but is less evident at older ages (Chute et al. 1991;Slattery et al 1997a;Wu et al 1987) suggesting that the effect of obesity may differ by menopausal status. Thus, the apparently more complex relationship between BMI and colon cancer in women may stem from potentially complex interactions among insulin, insulin-like growth hormone (IGF-1) and oestrogen (Calle et al. 1995;Grodstein et al. 1998).

Previous studies found an increased risk of kidney cancer and bladder cancer among obese people. Such relationships were not found in our study. This may be because of the small number of kidney and bladder cases, or because we looked at the relationship of both cancers sites together. However, the percentages of cancer cases were higher in the overweight group people compared to the normal weight ones.

Lung cancer

An inverse association was found between obesity and the risk of lung cancer where lean or normal weight individuals were at higher risk of lung cancer than obese ones. These results have been reported by some studies. A significant inverse gradient between body mass index and the incidence of lung cancer was found in a prospective study of men aged 20-75 years in Finland (Knekt et al 1991). Similar observations were found in case-control studies in the USA: the American Health Foundation (AHF) hospital-based study of tobacco-related cancers (Kabat & Wynder 1992) and in the Missouri Women's Health Study, where the strongest association of leanness was observed in women who never smoked (Swanson et al. 1997). In the Iowa prospective cohort study, the results of multivariate analysis suggested that the inverse association of body mass index with lung cancer could be explained by smoking status (Drinkard et al. 1995).

Another possible explanation is that low body mass index is more likely to be the result, rather than the cause, of early stage lung cancer (Kubik et al. 2001). This explanation was not supported by our findings where same pattern was found; higher risk among normal weight individuals and lower risk among overweight ones even after excluding those identified in the early years of follow up.

The risk of lung cancer and obesity among smokers was similar to that found for all lung cancer cases regardless of smoking status. A lower risk of lung cancer was found among the smoking obese. Testing the relationship between the risk of lung cancer and obesity in the different smoking groups was difficult because of the small number of never and former smokers. However, there was no interaction between body size and smoking status in the increasing risk for lung cancer, indicating that the relationship between obesity and the risk of lung cancer incidence was the same among smokers, former smokers and current smokers.

Rauscher and his colleagues reported interesting results when they restricted their sample to subjects both never smokers and former smokers in a population-based case-control study. A positive association was found between body mass index and lung cancer incidence for

both never smokers and former smokers. The BMI-lung cancer odds ratio was slightly greater for women versus men (OR =1.35 vs. OR =1.22 respectively), and was greater for younger subjects (aged less than 70 years) compared to older subjects (OR=1.42 vs. OR=1.13, respectively) (Rauscher, Mayne, & Janerich 2000).

Another way of looking at the different relationships between the risk of lung cancer incidence and obesity was comparing cancer cases with cancer free individuals in the normal weight group and overweight group. We were able to calculate the rate of lung cancer incidence by dividing the number of lung cancer cases to lung cancer free individuals in both normal weight and overweight groups. Higher lung cancer rates were found in lean individuals regardless of their smoking status. Out of one thousand smokers, 104 normal weight individual will develop lung cancer, compared to 70 overweight individuals. Opposite findings were found in former smokers; the rate of developing lung cancer was higher in overweight individuals (37 per 1000) compared normal weights ones (28 per 1000). It is difficult to interpret the results of former smokers, since we don't know their weight when they stopped smoking.

To exclude the confounding effect of smoking we looked at the pattern between the risk of smoking related cancers and BMI. There was no clear pattern between obesity and smoking related cancers emphasizing that the negative relationship between leanness and risk of lung cancer is purely due to the leanness itself.

About two thirds of lung cancer cases were in the manual social class. Higher body mass index was found to be associated with lower risk of lung cancer incidence in the manual social class and was insignificant in the non-manual social class. A higher proportion of the manual social class individuals were smokers which is thought to confound the observed association, but tests for interaction between body mass index and smoking groups and body mass and social class were insignificant. That is the pattern of association between the risk of lung cancer incidence and body mass index was the same in manual and non-manual social class.

Almost half the Renfrew/Paisley cohort participated in a second screening 2 to 4 years after the first screening. This allowed us to study the relationship of BMI and lung cancer

assuming that after these 2-4 years we reduced the bias of weight loss due to sub-clinical illness, and furthermore, allowing for weight change over time. In the second screening, subjects in the second and third tertiles were at significantly lower risk of lung cancer compared to those in the first tertile. The relationship between BMI and risk of lung cancer was the same using the baseline and the second screening data.

Unexpectedly, BMI of lung cancer cases identified after two years from the second screening has increased in the second screening compared to the baseline BMI, but it was lower for cases identified after two years of the second screening.

Since, BMI is highly correlated with serum cholesterol, we investigated the association between serum cholesterol and the risk of lung cancer. Serum cholesterol was negatively associated with the risk of lung cancer. Individuals with higher serum cholesterol had significantly lower risk of lung cancer. This negative relationship was first reported by the International Collaborative Group (1982). There results were based on a pooled data from 11 population studies in eight countries (International Collaborative Group 1982). Isles and his colleagues reported a similar association using the data from the Renfrew/ Paisley cohort over 12 years of follow-up. The negative association persisted after excluding cases in the first five years of follow-up (Isles et al. 1989).

Finally, we were able to compare results of men aged 45-64 years from the two cohorts in the west of Scotland. Similar patterns were found in the two cohorts between lung cancer mortality and BMI. Stronger risks and narrower confidence intervals were found in Renfrew/ Paisley cohorts possibly because of the larger number of cases.

Strengths and limitations

The Renfrew/Paisley cohort is a representative cohort of people living in the west of Scotland. This population comes from a highly deprived area with high incidence and mortality of chronic diseases, mainly coronary heart diseases, and cancer. High mortality rate and cancer incidence over a long follow-up provided good estimates of risks.

On the other hand, this cohort has some limitation in its data. First, BMI is the only measure of obesity in this cohort. Unfortunately, we don't have addition information about body fat, neither anthropometrics such as waist circumference nor biologic such as serum leptin or other biological marker. Such measures would help in explaining the type of association of obesity and mortality when BMI is not a good measure.

Second, we were unable to control for the confounding effects of physical activity and nutrient intake. Low level of physical activity is associated with obesity, and was also reported to be associated with obesity related cancers (Rissanen & Fogelholm 1999) and chronic diseases including CVD (Seidell et al 2001). High energy, high fat intake were reported to be associated with chronic diseases incidence and mortality. Contrary, high fruits, high vegetable intake and specific anti-oxidants were found to be associated with lower mortality and incidence risk of many diseases.

5.5 SUMMARY

Renfrew and Paisley population is characterised with high deprivation has high mortality rate. Consistent with the literature, the risk of all causes mortality was high in the two ends of BMI distribution.

It is important to report associations between BMI and cause specific mortality separately. Cardiovascular mortality was positively associated with BMI while respiratory mortality was negatively associated.

The risks of all cause mortality differ over the life span. Lower mortality was found in older groups with high BMI compared to those with lower BMI. A linear association between BMI and all cause mortality was found in the younger group.

Mortality data might be confounded by other underlying factors, because mortality represents the accumulation of many different factors. However, results from site-specific cancer provide strong evidence of the association between BMI and the risk of cancer.

Breast cancer in women and lung cancer in men and women were strongly associated with BMI. The risk of breast cancer was higher in those with high BMI while the risk of lung cancer was higher in those with lower BMI. Colon, prostate and pancreas cancers were not associated with BMI in this cohort.

The association between obesity and the risk of lung cancer was not confounded by sub-clinical illness or smoking. Further, this association was confirmed in other cohort screened at the same time as Renfrew and Paisley cohort.

Table 5-1: Characteristics of Renfrew/Paisley population 1972-6 by gender.

		Men	Women
		n=7052	n=8354
Smoking %	Never	18.8	45.9
	Former	24.6	7.5
	Current	56.6	46.7
Social class %	Manual	69.0	57.1
	Non-manual	31.0	42.9
Age (mean)		54.1±5.58	54.4+5.58
Mortality rates	All deaths	61.9	45.8
	CVD deaths	31.9	23.0
	All cancer deaths	18.5	13.4
	Lung cancer deaths	7.5	3.1
Incidence rates	All cancer	22.5	17.6
	Colon cancer	1.6	1.7
	Lung cancer	7.8	2.8

Table 5-2: Characteristics of Renfrew/Paisley population 1972-6 by age groups

		Age groups			
		45-49	**50-54**	**55-59**	**60-64**
		n=3852	n=4282	n=3723	n=3549
Sex	Male	47.2	46.2	46.2	44.4
	Female	52.8	53.8	54.8	55.6
Mortality	All causes	32.8	45.7	59.9	77.2
	CVD	15.5	21.6	31.3	41.6
	All cancers	11.7	16.0	16.7	18.7
	Lung cancer	3.6	5.2	5.8	5.9
Cancer incidence	All cancers	15.6	19.2	21.8	23.2
	Colon cancer	1.0	1.7	2.0	2.0
	Lung cancer	3.7	5.1	5.7	6.1

Table 5-3: Percentage of cause specific mortality in different BMI categories

	BMI categories				
Mortality cause	**<18.5**	**18.5-24.9**	**25-29.9**	**≥30**	**Total**
All causes	65.0% (158)	51.6% (2425)	52.7% (3422)	58.5% (1177)	53.1%(8182)
Men	77.4% (41)	63.5% (1787)	59.9% (2054)	64.3% (484)	53.4%(4366)
Women	61.6 (117)	42.8% (1368)	44.6% (1368)	55.1% (693)	46.6%(3546)
All cancer	16.9% (41)	16.2% (1077)	15.8% (1023)	13.9% (279)	15.7%(2420)
CVD	23.7% (57)	24.3% (16.14)	27.6% (1795)	34.6% (696)	27%(4162)
IHD	14.0% (34)	15.0% (995)	18.2% (1183)	21.5% (432)	17.2%(2644)
Stroke	6.2% (15)	6.3% (420)	6.2% (405)	8.4% (432)	8.3%(1272)
Respiratory	15.2% (37)	5.7% (376)	3.9% (251)	3.7% (74)	4.8%(738)
Digestive	2.5% (6)	1.3% (86)	1.6% (103)	1.9% (74)	1.7%(269)

Table 5-4: Relative hazard ratios (95% confidence interval) for mortality for all cause and specific cause of death by equal groups of BMI

		BMI equal groups									
Cause of death	**No**	**Group1**	**Group2**	**Group3**	**Group4**	**Group5**	**Group6**	**Group7**	**Group8**	**Group9**	**P-value**
All causes	7939	1.24 (1.14-1.36)***	1.07 (0.98-1.17)	0.97 (0.91-1.16)	0.92 (0.82-1.01)	1	0.96 (0.91-1.06)	1.05 (0.96-1.16)	1.14 (1.02-1.24)*	1.25 (1.15-1.42)**	0.12
All cancer	2345	1.16 (0.99-1.38)	1.06 (0.90-1.26)	1.01 (0.85-1.19)	0.95 (0.79-1.12)	1	0.98 (0.82-1.16)	1.07 (0.91-1.27)	0.96 (0.71-1.14)	1.02 (0.85-1.21)	0.14
Lung cancer	769	1.33 (1.0-1.7)*	1.27 (0.96-1.7)	1.04 0.77-1.4)	1.04 0.77-1.4)	1	0.90 (0.66-1.2)	1.14 (0.85-1.6)	0.76 (0.54-1.1)	0.62 (0.42-0.89)**	<0.001
Lung cancer for heavy smokers	531	1.49 (1.07-2.09)	1.44 (1.02-2.02)	1.11 (0.77-1.61)	1.27 (0.88-1.84)	1	1.11 (0.75-1.6)	1 (0.68-1.51)	0.78 (0.51-1.2)	0.75 (0.48-1.18)	<0.001
Colorectal cancer	255	0.89 (0.5-1.5)	0.89 (0.5-1.5)	0.79 (0.5-1.3)	0.83 (0.5-1.4)	1	0.58 (0.3-1.02)	0.99 (0.6-1.6)	0.88 (0.5-1.4)	1.01 (0.6-1.6)	0.68
IHD	2569	1.13 (0.92-1.2)	1.09 (0.91-1.21)	0.87 (0.73-1.03)	0.88 (0.74-1.1)	1	1.03 (0.87-1.19)	1.12 (0.95-1.32)	1.15 (1.02-1.4)*	1.5 (1.28-1.71)***	<0.001
Stroke	976	1.29 (0.87-1.5)	1.03 (0.78-1.4)	1.17 (0.86-1.5)	0.89 (0.67-1.2)	1	0.93 (0.7-1.2)	0.95 (0.72-1.2)	1.17 (0.94-1.6)	1.28 (0.99-1.7)	0.3
Respiratory	723	2.59 (1.9-3.4)***	1.49 (1.1-1.99)**	1.20 (0.9-1.67)	1.14 (0.82-1.6)	1	0.70 (0.5-1.02)	1.04 (0.7-1.5)	1.15 (0.83-1.6)	1.03 (0.7-1.5)	<0.001
Respiratory mortality for heavy smokers	338	2.45 (1.59-2.75)***	1.4 (0.87-2.27)	1.39 (0.86-2.26)	1.19 (0.72-1.98)	1	0.596 (0.31-1.14)	1.15 (0.67-1.95)	1.68 (1.02-2.75)*	1.08 (0.62-1.88)	0.001
Digestive	227	1.03 (0.58-1.8)	0.64 (0.3-1.2)	0.99 (0.56-1.8)	0.88 (0.5-1.6)	1	0.89 (0.5-1.6)	1.41 (0.83-2.4)	1.55 (0.9-2.6)	1.60 (0.9-2.7)	0.001
Other causes	1088	1.3 (1.05-1.7)	1.1 (0.8-1.4)	0.86 (0.7-1.1)	0.85 (0.7-1.1)	1	0.9 (0.72-1.2)	0.89 (0.7-1.2)	1.1 (0.8-1.4)	1.3 (1.02-1.7)*	0.83
Breast cancer	169	0.52 (0.27-1.02)	0.4 (0.2-0.81)*	0.65 (0.36-1.17)	0.48 (0.25-0.92)*	1	0.72 (0.4-1.28)	0.81 (0.46-1.42)	0.77 (0.43-1.37)	0.87 (0.64-1.19)	0.036
Gynaecological cancer	121	0.797 (0.38-1.66)	0.72 (0.34-1.52)	0.42 (0.18-0.99)	0.63 (0.31-1.4)	1	0.66 (0.31-1.41)	0.67 (0.31-1.42)	0.83 (0.4-1.7)	0.895 (0.49-1.83)	0.97
Prostate cancer	104	0.86 (0.33-2.22)	1.41 (0.63-3.16)	0.97 (0.41-2.29)	0.64 (0.25-1.65)	1	1.19 (0.54-2.62)	1.57 (0.73-3.35)	1.1 (0.48-2.49)	1.3 0.58-2.9)	0.31

BMI groups: Group1<21.3, Group2: 21.3-22.8, Group3: 22.9-23.9, Group4: 24-24.9, Group5: 25-25.9, Group6: 26-27, Group7: 27.1-28.3, Group8: 28.4-30.4, Group 9: >30.4
Adjusted for age, sex, smoking status and social class
*P<0.05, **P<0.01, ***P<0.001
Follow up form time of screening 1972-6 till December 1999

Figure 5-1: Relative hazard ratios for all cause mortality by equal groups of BMI for men and women

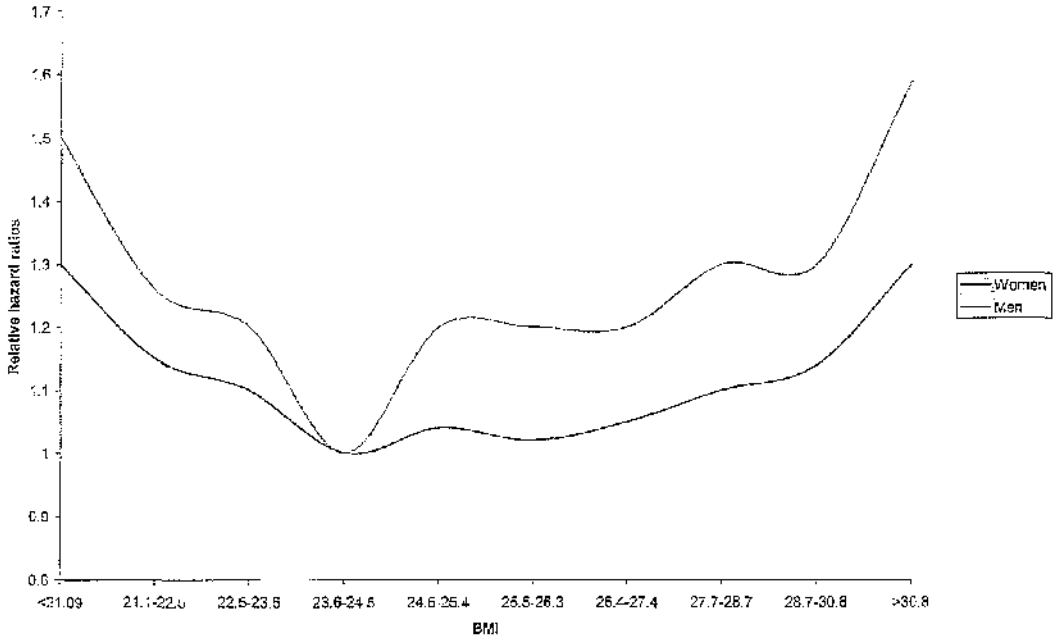


Table 5-5: Relative hazard ratios (95% confidence interval) for mortality for all cause and specific cause of death at the extreme upper and lower BMI values

Cause of death	Group1	Group2	Group3	Group4	Group5	Group6	Group7	Group8	Group9	Group10	Group11	P-value
All causes	1.4	1.12	1.11	0.92	1	1	1	1.1	1.17	1.24	1.22	**0.002**
	(1.26-1.58)***	(1.01-1.25)*	(1.01-1.23)*	(0.83-1.02)	(0.9-1.12)		(0.94-1.12)	(0.98-1.19)	(1.1-1.29)**	(1.1-1.39)***	(1.26-1.7)***	
Respiratory	4.98	2.32	1.94	1.74	1.28	1	1.42	1.38	1.63	1.34	1.49	**<0.001**
	(3.43-7.22)***	(1.59-3.38)***	(1.34-2.79)***	(1.19-2.54)**	(0.86-1.9)		(0.96-2.13)	(0.92-2.05)	(1.12-2.39)*	(0.838-2.25)	(0.94-2.38)	
Lung cancer	1.87	1.32	1.38	1.18	1.29	1	1.15	1.3	0.82	0.78	0.62	**<0.001**
	(1.32-2.67)***	(0.9-1.8)	(1.01-1.88)*	(0.85-1.6)	(0.93-1.78)		(0.82-1.6)	(0.93-1.8)	(0.57-1.18)	(0.47-1.29)	(0.355-1.07)	
IHD	0.94	0.91	0.86	0.79	0.84	1	0.86	0.99	1.1	1.29	1.45	**<0.0001**
	(0.75-1.17)	(0.75-1.09)	(0.72-1.02)	(0.67-0.95)*	(0.71-1)		(0.72-1.02)	(0.83-1.17)	(0.92-1.3)	(1.1-1.57)**	(1.19-1.75)***	

BMI groups: Group1: <20.08, Group2: 20.09-21.3, Group3: 21.4-22.8, Group4: 22.9-23.9, Group5:24.0-24.9, Group6: 25.0-25.9, Group7: 26.0-27.0, Group8: 27.1-28.3, Group9:28.4-30.4, Group10: 30.5-32.2, Group11: >32.2

Table 5-6: Relative hazard ratios (95% confidence interval) for mortality for all causes and specific of death by equal groups of BMI, by social class

			BMI equal groups									
	Cause of death	No	Group1	Group2	Group3	Group4	Group5	Group6	Group7	Group8	Group9	P-value
All causes	Non-manual	2546	1.1 (0.9-1.3)	1.02 (0.9-1.2)	0.9 (0.77-1.1)	0.82 (0.7-0.96)*	1	0.97 (0.8-1.14)	1.1 (0.9-1.2)	1.1 (0.9-1.3)	1.3	**0.005**
	Manual	5393	1.3 (1.2-1.5)***	1.1 (0.97-1.2)	1 (0.89-1.14)	0.98 (0.87-1.1)	1	1.96 (0.85-1.1)	1.1 (0.9-1.2)	1.1 (1.01-1.3)*	1.2 (1.1-1.4)***	0.99
All cancer	Non-manual	787	0.9 (0.68-1.2)	0.8 (0.6-1.1)	0.89 (0.7-1.2)	0.8 (0.6-1.10	1	89 (0.67-1.2)	0.87 (0.99-1.5)	0.95 (0.7-1.3)	1.2 (0.86-1.60	0.09
	Manual	1558	1.33 (1.01-1.6)*	1.25 (1.01-1.5)*	1.1 (0.87-1.3)	1.03 (0.8-1.3)	1	1.05 (0.8-1.3)	1.22 (0.99-1.5)	0.99 (0.8-1.2)	0.9 (0.79-1.2)	**0.006**
Lung cancer	Non-manual	205	1.5 (0.9-2.6)	1.02 (0.6-1.8)	0.98 (0.55-1.7)	1.04 (0.6-1.8)	1	1.2 (0.7-2.2)	1.2 (0.7-2.2)	0.83 (0.4-1.6)	0.94 (0.5-1.90	0.25
	Manual	564	1.3 (0.9-1.7)	1.4 (0.97-1.9)	1.1 (0.7-1.5)	1.02 (0.7-1.5)	1	0.8 (0.5-1.5)	1.1 (0.8-1.6)	0.7 (0.5-1.1)	0.54 (0.3-0.84)***	**<0.0001**
Colorectal cancer	Non-manual	83	0.4 (0.2-1.02)	0.4 (0.2-0.99)*	0.6 (0.3-1.3)	0.6 (0.3-1.2)	1	0.2 (0.1-0.7)**	0.6 (0.3-1.3)	0.5 (0.2-1.2)	0.8 (0.3-1.7)	0.46
	Manual	172	1.5 (0.8-2.9)	1.5 (0.77-2.9)	1.03 (0.5-2.1)	1.2 (0.58-2.3)	1	0.99 (0.5-2)	1.5 (0.76-2.8)	1.3 (0.68-2.5)	1.3 (0.7-2.7)	0.92
IHD	Non-manual	815	0.91 (0.67-1.2)	1.1 (0.83-1.51)	0.85 (0.63-1.5)	0.9 (0.63-1.4)	1	1.01 (0.76-1.3)	1.2 (0.9-1.6)	1.2 (0.86-1.5)	1.4 (0.13-1.8)*	**0.027**
	Manual	1754	1.1 (0.87-1.3)	0.99 (0.81-1.2)	0.87 (0.71-1.1)	0.87 (0.7-1.1)	1	1.04 (0.8-1.3)	1.1 (0.88-1.3)	1.22 (1.01-1.5)*	1.49 (1.24-1.8)***	**<0.0001**
Stroke	Non-manual	312	1.2 (0.8-1.9)	1.1 (0.7-1.8)	1.03 (0.66-1.6)	0.6 (0.38-1.05)	1	1.2 (0.75-1.8)	1.1 (0.7-1.8)	1.1 (0.7-1.8)	1.3 (0.8-2.1)	0.52
	Manual	664	1.14 (0.8-1.6)	0.99 (0.7-1.4)	1.2 (0.8-1.6)	1.1 (0.8-1.5)	1	0.82 (0.6-1.2)	0.9 (0.62-1.2)	1.3 (0.9-1.7)	1.3 (0.9-1.8)	0.44
Respiratory	Non-manual	195	3.1 (1.8-5.6)***	1.9 (1.02-3.5)*	1.2 (0.6-2.3)	1.4 (0.8-2.7)	1	0.9 (0.4-1.8)	1.3 (0.7-2.6)	0.9 (0.4-1.9)	1.7 0.9-3.40	**0.0003**
	Manual	528	2.4 (1.7-3.3)***	1.3 (0.9-1.9)	1.2 (0.8-1.8)	1.03 (0.7-1.5)	1	0.7 (0.42-1.01)	0.9 (0.6-1.40	1.2 (0.8-1.7)	0.9 (0.6-1.3)	**<0.0001**
Digestive	Non-manual	83	0.6 (0.2-1.8)	0.6 (0.2-1.6)	0.8 (0.3-1.95)	0.5 (0.2-1.3)	1	0.9 (0.3-2.2)	1.6 (0.7-3.6)	1.6 (0.7-3.6)	2.2 (0.98-5)	**0.0001**
	Manual	144	1.3 (0.6-2.6)	0.7 (0.3-1.6)	1.2 (0.7-2.4)	1.2 (0.6-2.6)	1	0.9 (0.4-2)	1.3 (0.7-2.7)	1.6 (0.8-3.2)	1.4 (0.7-2.8)	0.18
Other causes	Non-manual	347	1.3 (0.85-1.99)	1.14 (0.7-1.7)	0.83 (0.53-1.3)	0.66 90.4-1.1)	1	0.97 (0.6-1.5)	0.9 (0.6-1.4)	1.4 (0.9-2.1)	1.2 (0.8-1.9)	0.57
	Manual	741	1.4 (1.01-1.8)*	1.01 (0.7-1.4)	0.87 (0.6-1.2)	0.96 (0.7-1.3)	1	0.92 (0.67-1.3)	0.88 (0.6-1.2)	0.96 (0.7-1.3)	1.3 (0.9-1.8)	0.85

BMI groups: Group1<21.3, Group2: 21.3-22.8, Group3: 22.9-23.9, Group4: 24-24.9, Group5: 25-25.9, Group6: 26-27, Group7: 27.1-28.3, Group8: 28.4-30.4, Group 9: >30.4; Adjusted for age, sex, smoking status and social class

*p<0.05, **P<0.01, ***P<0.001; Follow up form time of screening 1972-6 till December 1999

Figure 5-2: Relative hazard ratios for all cause mortality at different BMI values by social class.

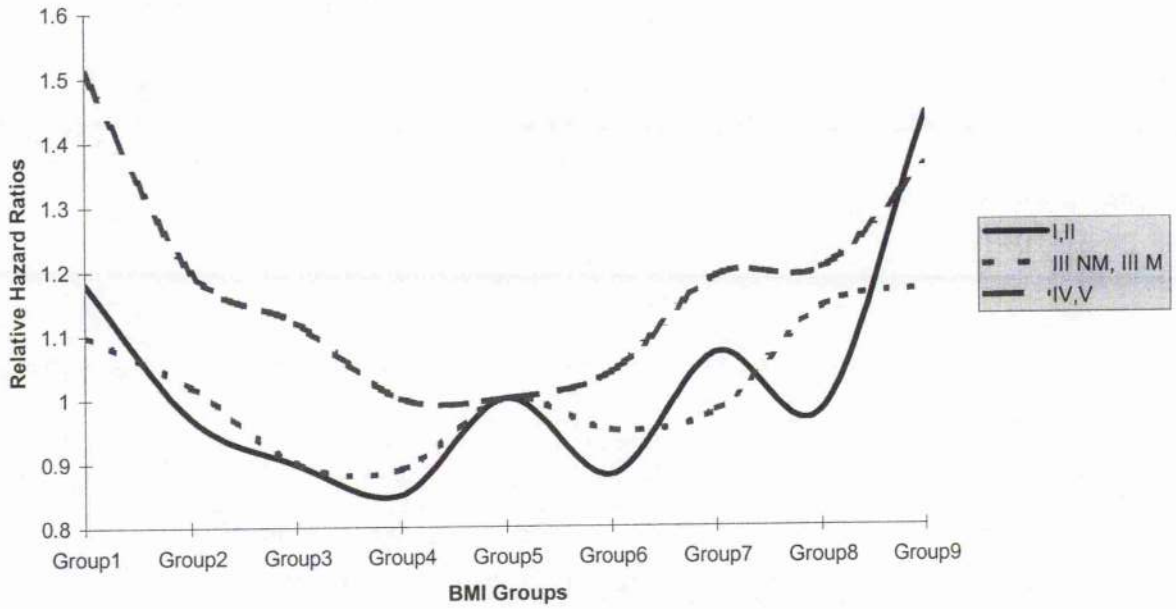


Table 5-7: Relative hazard ratios (95% confidence interval) for mortality for all cause and specific cause of death by equal groups of BMI, by smoking status

			BMI equal groups									
	Cause of death	No	Group1	Group2	Group3	Group4	Group5	Group6	Group7	Group8	Group9	p-value
All causes	Non-smoker	3341	1.2 (0.97-1.4)	0.84 (0.7-0.99)*	0.86 (0.7-1.01)	0.84 (0.7-0.97)	1	0.93 (0.8-1.1)	1.02 (0.89-1.2)	1.02 (0.89-1.2)	1.3 (1.13-1.5)**	<0.0001
	Smoker	4598	1.3 (1.2-1.5)***	1.2 (1.1-1.4)**	1.1 (0.9-1.2)	0.99 (0.87-1.1)	1	0.99 (0.86-1.1)	1.1 (0.95-1.2)	1.2 (1.1-1.4)**	1.2 (1.01-1.3)*	0.026
All cancer	Non-smoker	894	0.82 ((0.82-1.2)	0.62 (0.45-0.85)	0.8 (0.6-1.1)	0.74 (0.56-0.98)*	1	0.9 (0.7-1.2)	1.01 (0.8-1.3)	0.85 (0.7-1.1)	0.98 (0.77-1.3)	0.0062
	Smoker	1451	1.4 (1.1-1.7)**	1.3 (1.1-1.7)**	1.2 (0.9-1.5)	1.1 (0.89-1.4)	1	1.03 (0.8-1.3)	1.1 (0.88-1.4)	1.1 (0.8-1.4)	1 (0.77-1.3)	0.0002
Lung cancer	Non-smoker	116	0.99 (0.4-2.4)	0.8 (0.4-1.9)	0.6 (0.3-1.4)	1 (0.5-1.9)	1	0.6 (0.3-1.3)	1.3 (0.7-2.4)	0.8 (0.4-1.6)	0.3 (0.1-0.7)***	0.23
	Smoker	653	1.4 (1.03-1.9)*	1.4 (0.99-1.8)	1.1 (0.8-1.6)	1.1 (0.8-1.5)	1	0.9 (0.7-1.4)	1.1 (0.77-1.5)	0.7 (0.5-1.1)	0.7 (0.5-1.1)	<0.0001
Colorectal cancer	Non-smoker	130	0.4 (0.15-1.3)	0.3 (0.1-0.8)**	0.58 (0.3-1.23)	0.74 (0.4-1.4)	1	0.4 (0.2-0.87)	0.88 (0.5-1.6)	0.8 (0.4-1.5)	1 (0.6-1.8)	0.01
	Smoker	125	1.3 (0.7-2.7)	1.6 (0.8-3.2)	1.1 (0.5-2.4)	1.01 (0.5-2.2)	1	0.9 (0.4-2.1)	1.1 (0.5-2.5)	0.94 (0.4-2.2)	0.79 (0.3-2)	0.59
IHD	Non-smoker	1124	1.07 (0.78-1.5)	0.92 (0.69-1.2)	0.8 (0.6-1.1)	0.84 (0.6-1.1)	1	1.02 (0.8-1.3)	1.2 (0.91.5)	1.2 (0.9-1.5)	1.6 (1.3-1.97)***	<0.001
	Smoker	1445	1 (0.81-1.2)	1.1 (0.86-1.3)	0.9 (0.7-1.1)	0.9 (0.7-1.1)	1	1.03 (0.8-1.3)	1.05 (0.8-1.3)	1.2 (0.9-1.5)	1.3 (1.1-1.7)*	0.0036
Stroke	Non-smoker	466	1.4 (0.89-2.2)	0.79 (0.5-1.2)	0.95 (0.6-1.4)	0.96 (0.7-1.4)	1	0.9 (0.6-1.3)	0.86 (0.59-1.3)	0.9 (0.6-1.3)	1.4 (0.99-1.9)	0.26
	Smoker	510	1.2 (0.8-1.7)	1.2 (0.9-1.8)	1.3 (0.9-1.9)	0.85 (0.6-1.3)	1	0.99 (0.6-1.3)	1.1 (0.72-1.6)	1.7 (1.7-2.5)**	1.03 (0.7-1.6)	0.82
Respiratory	Non-smoker	257	2.4 (1.5-4)***	1.4 (0.8-2.3)	0.99 (0.58-1.7)	0.99 (0.59-1.6)	1	0.69 (0.4-1.2)	0.85 (0.5-1.4)	0.77 (0.5-1.3)	0.87 (0.5-1.5)	0.0001
	Smoker	466	2.9 (1.9-4.2)***	1.6 (1.04-2.4)*	1.4 (0.9-2.12)	1.3 (0.8-2)	1	0.7 (0.4-1.2)	1.2 (0.8-1.9)	1.6 (1.04-2.5)*	1.2 (0.7-1.9)	<0.0001
Digestive	Non-smoker	91	0.88 (0.3-2.8)	0.4 (0.1-1.5)	0.6 (0.2-1.8)	0.7 (0.3-1.9)	1	1.01 (0.4-2.4)	1.3 (0.6-0.9)	1.6 (0.7-3.5)	1.7 (0.8-3.6)	0.0011
	Smoker	136	1.1 (0.5-2.1)	0.7 (0.3-1.6)	1.2 (0.6-2.4)	0.98 (0.3-1.8)	1	0.79 (0.3-1.8)	1.5 (0.7-3)	1.5 (0.7-3)	1.4 (0.7-2.9)	0.11
Other causes	Non-smoker	501	1.4 (0.87-2.1)	1.03 (0.7-1.6)	1.05 (0.7-1.6)	0.86 (0.6-1.3)	1	0.9 (0.7-1.4)	0.9 (0.6-1.3)	1.2 (0.8-1.7)	1.4 (1-1.9)*	0.18
	Smoker	587	1.3 (0.9-1.8)	1.1 (0.8-1.5)	0.7 (0.5-1.5)	0.85 (0.6-1.2)	1	0.9 (0.7-*1.3)	0.9 (0.6-1.3)	0.85 (0.7-1.4)	1.2 (0.8-1.7)	0.34

BMI groups: Group1<21.3, Group2: 21.3-22.8, Group3: 22.9-23.9, Group4: 24-24.9, Group5: 25-25.9, Group6: 26-27, Group7: 27.1-28.3, Group8: 28.4-30.4, Group 9: >30.4
; Adjusted for age, sex and social class. *P<0.05, **P<0.01, ***P<0.001; Follow up form time of screening 1972-6 till December 1999

Table 5-8: Relative hazard ratios (95% confidence interval) for mortality for all cause and specific cause of death by equal groups of BMI (excluding the first five years of follow-up)

Cause of death	No	Group1	Group2	Group3	Group4	Group5	Group6	Group7	Group8	Group9	P-value
All causes	7020	1.22 (1.11-1.4)***	1.09 (0.99-1.2)	0.98 (0.89-1.08)	0.93 (0.84-1.04)	1	0.997 (0.9-1.1)	1.09 (0.98-1.2)	1.11 (1.01-1.23)*	1.29 (1.2-1.4)***	0.047
All cancer	2070	0.98 (0.83-1.20)	0.91 (0.76-1.1)	0.86 (0.72-1.03)	0.92 (0.77-1.1)	1	0.91 (0.77-1.1)	1.01 (0.84-1.2)	0.83 (0.69-1.01)	0.93 (0.77-1.12)	0.34
Lung cancer	674	1.34 (1.002-1.8)*	1.4 (1.04-1.9)*	1.1 (0.8-1.5)	1.02 (0.7-1.4)	1	0.96 (0.7-1.4)	1.3 (0.9-1.7)	0.8 (0.55-1.1.2)	0.6 (0.4-0.9)**	<0.0001
Lung cancer for heavy smokers	472	1.63 (1.13-2.35)**	1.66 (1.15-2.4)**	1.2 (0.81-1.8)	1.32 (0.89-1.97)	1	1.22 (0.798-1.85)	1.18 (0.77-1.8)	0.9 (0.57-1.44)	0.71 (0.43-1.18)	<0.0001
Colorectal cancer	218	0.55 (0.29-1.04)	0.89 (0.52-1.5)	0.75 (0.4-1.3)	0.82 (0.48-1.4)	1	0.61 (0.3-1.08)	0.93 (0.55-1.5)	0.83 (0.49-1.4)	1.04 (0.6-1.7)	0.18
IHD	2229	1.06 (0.87-1.3)	1.07 (0.89-1.3)	0.89 (0.74-1.07)	0.93 (0.78-1.12)	1	1.07 (0.89-1.3)	1.13 (0.95-1.4)	1.19 (0.99-1.4)	1.5 1.3-1.8)***	<0.0001
Stroke	907	1.23 (0.92-1.6)	1.13 (0.85-1.5)	1.23 (0.9-1.6)	0.95 (0.7-1.3)	1	1.01 (0.76-1.4)	1.04 (0.78-1.4)	1.28 (0.97-1.7)	1.4 1.04-1.8)*	0.42
Respiratory	654	2.4 (1.8-3.3)***	1.5 (1.04-2.04)**	1.17 (0.82-1.66)	1.12 (0.79-1.6)	1	0.74 (0.5-1.08)	1.14 (0.8-1.6)	1.15 (0.8-1.6)	1.13 (0.79-1.6)	<0.0001
Respiratory for heavy smokers	300	2.6 (1.62-4.2)***	1.59 (0.94-2.67)	1.47 (0.87-2.5)	1.29 (0.74-2.5)	1	0.68 (0.34-1.350	1.42 (0.81-2.5)	1.87 (1.1-3.2)*	1.34 (0.75-2.4)	0.0024
Digestive	200	0.89 (0.47-1.67)	0.62 (0.31-1.2)	0.97 (0.53-1.8)	0.83 (0.44-1.55)	1	0.93 (0.5-1.7)	1.4 (0.77-2.4)	1.6 (0.95-2.8)	1.5 (0.84-2.2.6)	0.0005
Other causes	950	1.3 (0.99-1.7)	1.02 (0.78-1.4)	0.85 (0.64-1.13)	0.85 (0.64-1.13)	1	0.95 (0.72-1.25)	0.92 (0.7-1.2)	1.12 (0.86-1.46)	1.3 (1.04-1.7)*	0.286
Breast cancer	142	0.37 (0.17-0.83)*	0.33 (0.15-0.74)**	0.57 (0.29-1.1)	0.54 (0.28-1.04)	1	0.75 (0.41-1.4)	0.76 (0.42-1.4)	0.78 (0.43-1.43)	0.695 (0.37-1.31)	0.015
Gynaecological cancer	100	0.78 (0.35-1.7)	0.76 (0.34-1.67)	0.48 (0.196-1.5)	0.74 (0.33-1.61)	1	0.58 (0.26-1.4)	0.59 (0.26-1.37)	0.54 (0.23-1.3)	0.87 (0.398-1.89)	0.45
Prostate cancer	103	0.74 (0.27-2.01)	1.4 (0.63-3.2)	0.97 (0.41-2.3)	0.64 (0.25-1.65)	1	1.19 (0.54-2.62)	1.57 (0.73-3.3)	1.1 (0.48-2.49)	1.3 (0.58-2.91)	0.244

BMI groups: Group1<21.3, Group2: 21.3-22.8, Group3: 22.9-23.9, Group4: 24-24.9, Group5: 25-25.9, Group6: 26-27, Group7: 27.1-28.3, Group8: 28.4-30.4, Group 9: >30.4

; Adjusted for age, sex, smoking status and social class

*P<0.05, **P<0.01, ***P<0.001; Follow up form time of screening 1972-6 till December 1999 excluding the first five years of follow up.

Table 5-9: Mean BMI for subjects dying from all cause, cancer and respiratory diseases in the first 10 ycars of follow up

	Years of follow-up									
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year5**	**Year 6**	**Year 7**	**Year 8**	**Year 9**	**Year 10**
Cancer										
No of death	27	52	67	76	67	87	79	100	89	102
Mean BMI	25.2	24.2	25.2	26.2	25.4	25.7	25.9	25.4	24.8	26.0
All causes										
No of death	117	176	183	235	240	246	234	301	273	294
Mean BMI	25.7	25.8	25.7	25.3	25.4	25.7	25.8	25.9	25.3	25.7
Respiratory										
No of death	5	14	13	21	16	13	7	23	29	17
Mean BMI	24.2	22.9	23.8	22.8	21.6	22.1	26.0	23.7	23.1	23.9

Figure 5-3: Mean BMI for subjects dying from all cause, cancer and respiratory diseases in the first 10 years of follow-up

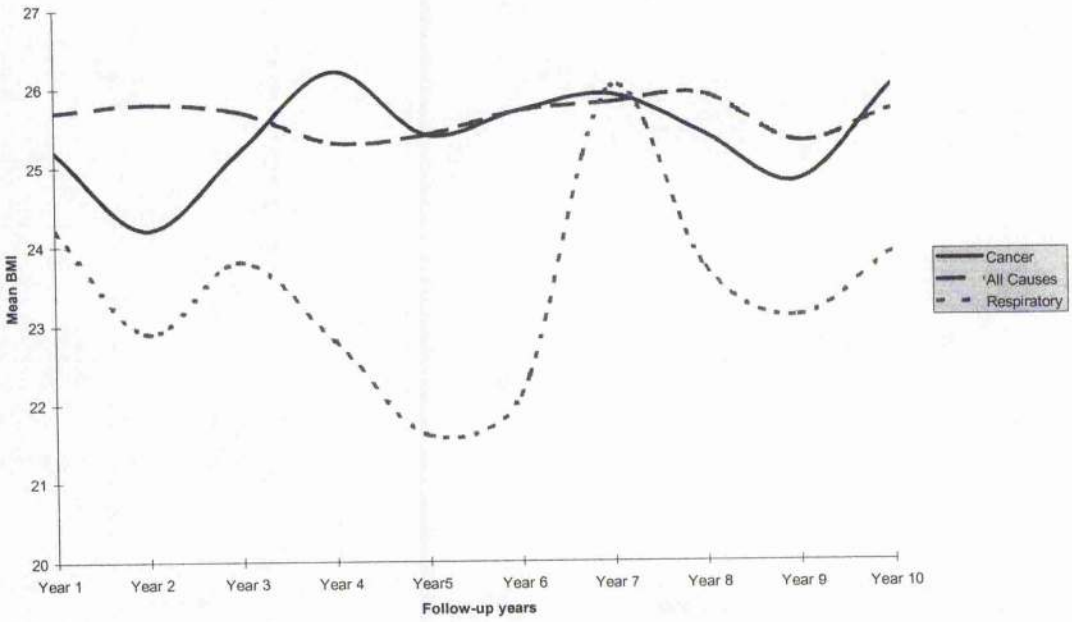


Table 5-10: Relative hazards ratio for all vascular cause mortality for three follow-up periods

First 5 years of follow-up

	no of death	1	2	3	4	5	P-value
		<22.5	22.5-24.6	24.7-26.4	26.5-28.7	>28.7	
Total	464	1	0.99 (0.71-1.36)	1.25 (0.93-1.68)	1.85 (1.39-2.47)***	1.69 (1.27-2.24)***	<0.0001
Men	317	1	1.23 (0.83-1.8)	1.32 (0.91-1.91)	2.14 (1.47-3.11)***	1.74 (1.2-2.5)**	0.0001
Women	147	1	0.59 (0.31-1.1)	1.31 (0.78-2.2)	1.39 (0.85-2.3)	1.62 (0.99-2.6)	0.009

6-15 years of follow-up

	no of death	1	2	3	4	5	P-value
		<22.5	22.5-24.6	24.7-26.4	26.5-28.7	>28.7	
Total	1599	1	0.99 (0.85-1.17)	1.05 (0.89-1.23)	1.12 (0.96-1.31)	1.2 (1.04-1.4)*	0.004
Men	943	1	0.99 (0.79-1.22)	0.99 (0.8-1.24)	1.1 (0.89-1.36)	1.26 (1.02-1.5)*	0.022
Women	656	1	0.98 (0.77-1.26)	1.1 (0.85-1.4)	1.13 (0.88-1.45)	1.13 (0.91-1.42)	0.16

16-25 years of follow-up

	no of death	1	2	3	4	5	P-value
		<22.5	22.5-24.6	24.7-26.4	26.5-28.7	>28.7	
Total	1992	1	0.97 (0.83-1.2)	1.07 (0.92-1.24)	1.07 (0.92-1.24)	1.19 (1.03-1.4)*	0.005
Men	973	1	1.01 (0.8-1.27)	1.24 (0.999-1.53)	1.19 (0.96-1.48)	1.26 (1.01-1.57)*	0.015
Women	1019	1	0.96 (0.79-1.17)	0.92 (0.75-1.13)	0.97 (0.79-1.18)	1.13 (1.04-1.5)*	0.17

BMI groups: Group1: <22.5, group2: 22.5-24.5, Group3: 24.6-26.3, Group4: 26.4-28.7, Group5: >28.7; Adjusted for age, sex and smoking status

*P<0.05, **P<0.01, ***P<0.001; Follow up form time of screening 1972-6 till December 1999 excluding the first five years of follow up

Table 5-11: Relative hazards ratio for all non-vascular cause mortality for three follow-up periods

first 5 years of follow-up							
	no of death	**1**	**2**	**3**	**4**	**5**	**P-value**
		<22.5	**22.5-24.6**	**24.7-26.4**	**26.5-28.7**	**>28.7**	
Total	919	1	0.85 (0.69-1.05)	0.98 (0.8-1.2)	1.11 (0.91-1.4)	1.08 (0.89-1.3)	0.1
Men	577	1	0.92 (0.7-1.2)	1 (0.78-1.3)	1.3 (1.02-1.7)	0.98 (0.75-1.3)	0.36
Women	342	1	0.73 (0.5-1.05)	0.99 (0.7-1.4)	0.79 (0.56-1.15)	1.23 (0.91-1.7)	0.34
6-15 years of follow-up							
	no of death	**1**	**2**	**3**	**4**	**5**	**P-value**
		<22.5	**22.5-24.6**	**24.7-26.4**	**26.5-28.7**	**>28.7**	
Total	3929	1	0.89 (0.81-0.99)	0.97 (0.88-1.1)	0.93 (0.85-1.03)	0.88 (0.83-0.94)	0.49
Men	2301	1	0.89 (0.78-1.01)	0.95 (0.83-1.1)	0.92 (0.81-1.05)	0.94 (0.83-1.1)	0.61
Women	1628	1	0.9 (0.77-1.05)	0.99 (0.84-1.19)	1.02 (0.87-1.19)	0.92 (0.8-1.1)	0.61
16-25 years of follow-up							
	no of death	**1**	**2**	**3**	**4**	**5**	**P-value**
		<22.5	**22.5-24.6**	**24.7-26.4**	**26.5-28.7**	**>28.7**	
Total	4010	1	0.98 (0.89-1.1)	1 (0.9-1.1)	1.03 (0.92-1.14)	1.04 (0.94-1.15)	0.25
Men	2017	1	0.97 (0.84-1.12)	1.02 (0.88-1.18)	1.1 (0.94-1.25)	1.1 (0.94-1.27)	0.07
Women	1993	1	1 (0.88-1.16)	1 (0.88-1.17)	0.98 (0.85-1.13)	1.01 (0.88-1.16)	0.97

BMI groups: Group1: <22.5, Group2: 22.5-24.5, Group3: 24.6-26.3, Group4: 26.4-28.7, Group5: >28.7; Adjusted for age, sex and smoking status

*P<0.05, **P<0.01, ***P<0.001; Follow up form time of screening 1972-6 till December 1999 excluding the first five years of follow up

Figure 5-4: Relative hazard ratios for all cause mortality by subjects at the time of screening

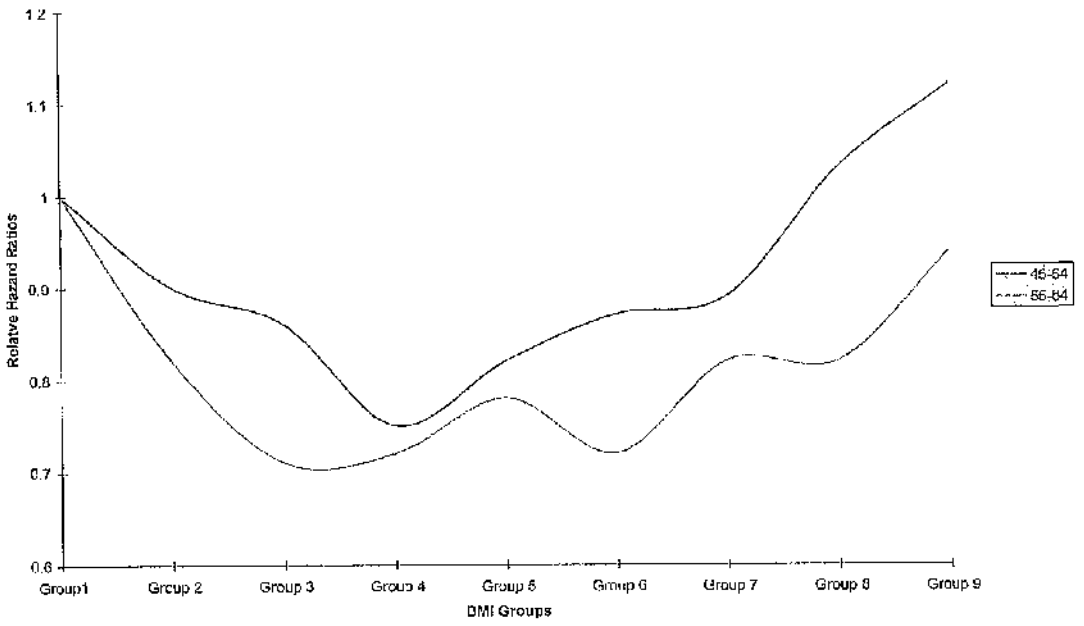


Table 5-12: Characteristics of study population by BMI tertiles.

	BMI tertiles		
	1	2	3
men			
Mean age	54.1	54.2	54.2
% (n) never smokers (n=1324)	18.1% (239)	35.5% (527)	42.1% (558)
% (n) current smokers (n=3991)	36.9% (1472)	35.5% (1415)	27.7% (1104)
% (n) manual social class (n=4813)	29.8% (1434)	36.3% (1747)	33.9% (1632)
Mean height	1.69	1.7	1.69
Mean BMI	22	25.5	29.5
Women			
Mean age	53.8	54.2	55.2
% (n) never smokers (n=1324)	27.6% (1057)	31.9% (1221)	40.5% (1548)
% (n) current smokers (n=3991)	47.2% (1837)	27.6% (1075)	25.2% (981)
% (n) manual social class (n=4813)	33.8% (1540)	28.8% (1316)	37.4% (1706)
Mean height	1.58	1.58	1.57
Mean BMI	21.7	25.4	30.8

Table 5-13: Percentage of cancer cases over 25 years of follow up, by BMI tertiles

Cancer type	BMI tertiles			Total %
	1	2	3	
Any cancer	20.7%	19.5%	19.4%	19.8 %(3057)
Lung cancer	6.6%	5.1%	3.6%	5.1% (787)
Breast cancer	2.5%	3.3%	3.60%	3.1% of females (260)
Pancreas cancer	0.8%	0.7%	0.6%	0.7% (109)
Prostate cancer	2.1%	1.9%	2.3%	2.2% of males (149)
Colon cancer	1.6%	1.7%	1.6%	1.6% (253)
Ovary and uterus cancer	1.5%	1.5%	2.0%	1.7% of females (138)
Kidney and bladder cancer	1.2%	1.5%	1.8%	1.5% (232)
Oesophagus and larynx cancer	0.9%	0.7%	0.7%	0.8% (119)

Table 5-14: Relative hazard ratio for cancer incidence by BMI tertiles

Cancer	No of subject	1	2	95% CI	3	95% CI	trend test
All cancer							
Total	2956	1	0.93	(0.85-1.02)	0.95	(0.87-1.04)	0.239
Men	1567	1	0.86	(0.76-0.97)*	0.89	(0.79-1.01)	0.08
Women	1389	1	1.04	(0.91-1.18)	1.01	(0.89-1.16)	0.819
Breast cancer	251	1	1.3	(0.95-1.8)	1.4	(1.03-1.92)	**0.033**
Lung cancer							
Total	762	1	0.85	(0.72-1)	0.69	(0.57-0.83)	**0.0001**
Men	546	1	0.83	(0.69-1.02)	0.73	(0.58-0.90)	**0.0031**
Women	216	1	0.91	(0.67-1.2)	0.59	(0.42-0.85)	**0.0061**
Pancreas cancer	104	1	1.1	(0.69-1.7)	0.90	(0.55-1.5)	0.69
Prostate cancer	147	1	0.88	(0.58-1.33)	1.04	(0.69-1.58)	0.78
Colorectal cancer	328	1	1.01	(0.77-1.33)	1.03	(0.79-1.4)	0.81
Colon cancer	234	1	1.05	(0.77-1.44)	0.98	(0.71-1.35)	0.886
Men	106	1	1.13	(0.71-1.82)	0.94	(0.56-1.56)	0.771
Women	128	1	0.97	(0.63-1.50	0.01	(0.66-1.54)	0.981
Ovary and uterus cancer	133	1	0.88	(0.57-1.4)	1.1	(0.71-1.9)	0.74
Kidney and bladder cancer	221	1	1.18	(0.84-1.66)	1.36	(0.98-1.92)	0.082
Oesophagus and larynx cancer	111	1	0.69	(0.44-1.09)	0.76	(0.48-1.2)	0.26

RHR adjusted for age, sex, smoking status and social class

Table 5-15: Relative hazards ratios for lung cancer by equal groups of BMI excluding the first 3 years of follow-up.

	No. Subjects	BMI groups				Test for trend
		1	2		3	
Total	703	1	0.82	(0.69-0.98)*	0.71 (0.58-0.85)***	0.0003
Men	497	1	0.79	(0.64-0.97)*	0.75 (0.59-0.93)*	0.008
Women	206	1	0.94	(0.69-1.29)	0.61 (0.42-0.88)**	0.012

RHR adjusted for age, smoking status and social class

Table 5-16: Relative hazard ratios for lung cancer by smoking groups

		BMI tertiles			
	No. of death	**1**	**2**	**3**	**P trend**
Never smoker	47	1	1.12	0.81	0.872
			(0.5-2.4)	(0.4-1.7)	
Former smoker	73	1	0.85	1.1	0.719
			(0.44-1.7)	(0.57-2)	
Current smoker	643	1	0.85	0.65	**0.0001**
			(0.7-1.1)	(0.53-0.80)**	

Figure 5-5: Relative hazard ratios for lung cancer incidence in different smoking levels

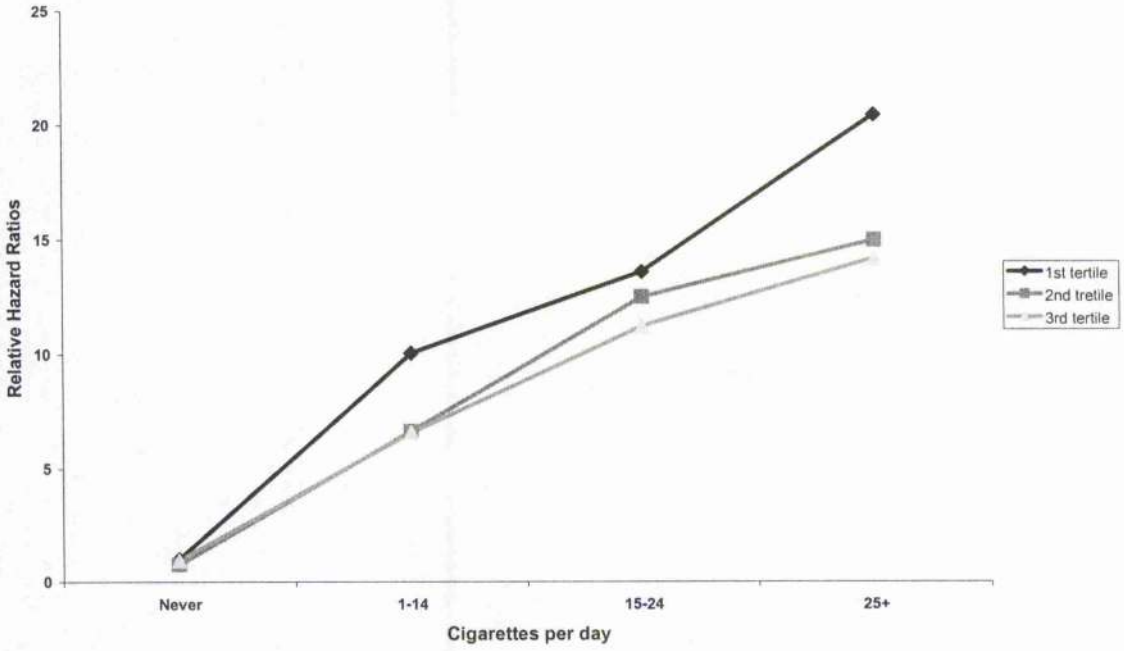


Table 5-17: Relative hazard ratio for lung cancer over follow-up time for subjects in BMI first and third tertiles

	No. of cases	1st tertile	3rd tertile
0-5 years	122	0.91	0.75
		(0.59-1.39)	(0.46-1.24)
6-10 years	174	1.33	1.03
		(0.95-1.9)	(0.69-1.3)
11-15 years	196	1.23	0.85
		(0.93-1.8)	(0.59-1.25)
16-20 years	205	1.14	0.75
		(0.83-1.56)	(0.52-1.09)
21-25 years	65	1.38	0.88
		(0.78-2.44)	(0.45-1.72)

RHR adjusted for age, sex, social class and smoking status, using the second tertile as reference group.
BMI cut -off points: <23.9, 24-27, >27 kg/m^2

Table 5-18: Characteristics of subjects in the first and third tertiles among lung cancer cases and controls

	BMI 1st tertile			BMI 3rd tertile		
	Lung cancer case	Lung cancer free		Lung cancer case	Lung cancer free	
	n=338	n=4786	Rate per 1000	n=187	n=4938	Rate per 1000
Smoking habit % (n)						
Never	3.60%	26.80%		9.1%	42.30%	
	(12)	(1284)	9.3	(17)	(2089)	8.1
Former	4.10%	10.60%		17.6%	18.30%	
	(14)	(506)	27.7	(33)	(903)	36.5
Current	92.30%	62.60%		73.3%	39.40%	
	(312)	(2996)	104.1	(137)	(1946)	70.4
Cholesterol (mean SD)	5.8 (1.02)	6.08 (1.1)		5.9 (0.95)	6.3 (1.1)	
FEV1	1.99 (0.66)	2.02 (0.7)		2.15 (0.752)	2.12 (0.7)	
Predicted FEV1	80.5 (21)	89.2 (24)		82.8 (21.5)	91.9 (22)	

Table 5-19: Relative hazard ratios for lung cancer by social class groups

		BMI tertiles					
	No. of cases	**1**	**2**	**3**	**4**	**5**	**P-value**
Manual	552	1	0.87	0.77	0.69	0.49	<0.0001
			(0.68-1.1)	(0.60-0.98)*	(0.53-0.89)**	(0.37-0.66)***	
Non-manual	210	1	0.92	1.1	0.99	0.67	0.213
			(0.61-1.36)	(0.71-1.6)	(0.65-1.5)	(0.41-1.12)	

BMI cut-off points: <22.5, 22.5-24.5, 24.6-26.4, 26.5-28.7, >28.7 kg/m2
RIIR for cancer incidence controlling for age, sex and smoking status.

Figure 5-6: Relative hazard ratios for lung cancer incidence over follow-up time for subjects in BMI first and third tertiles compared to the second tertile.

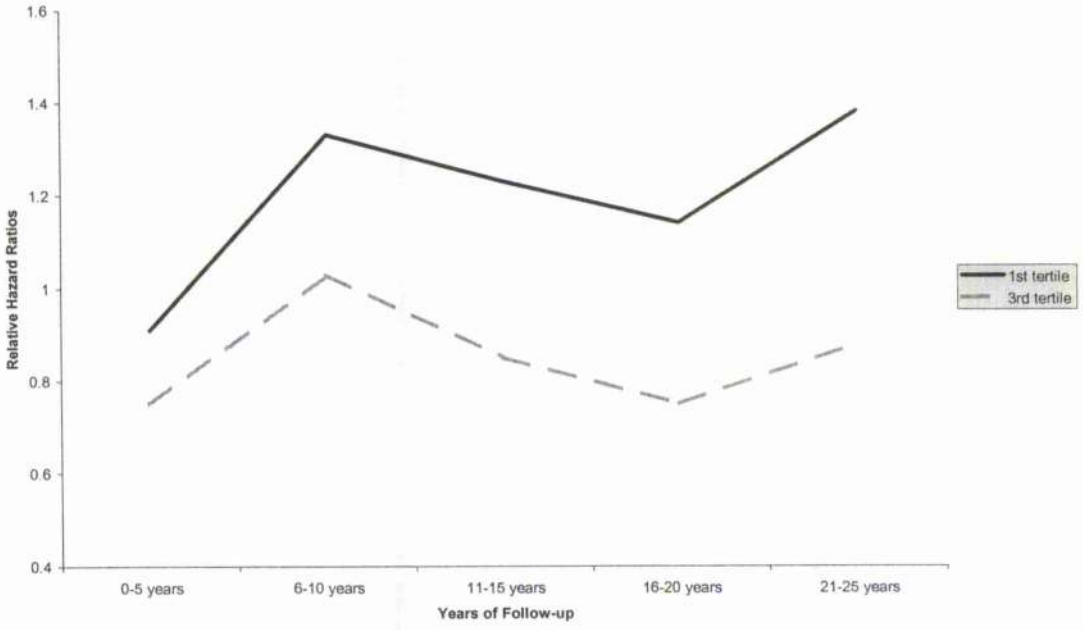


Figure 5-7: Relative hazard ratios for lung cancer by social class groups

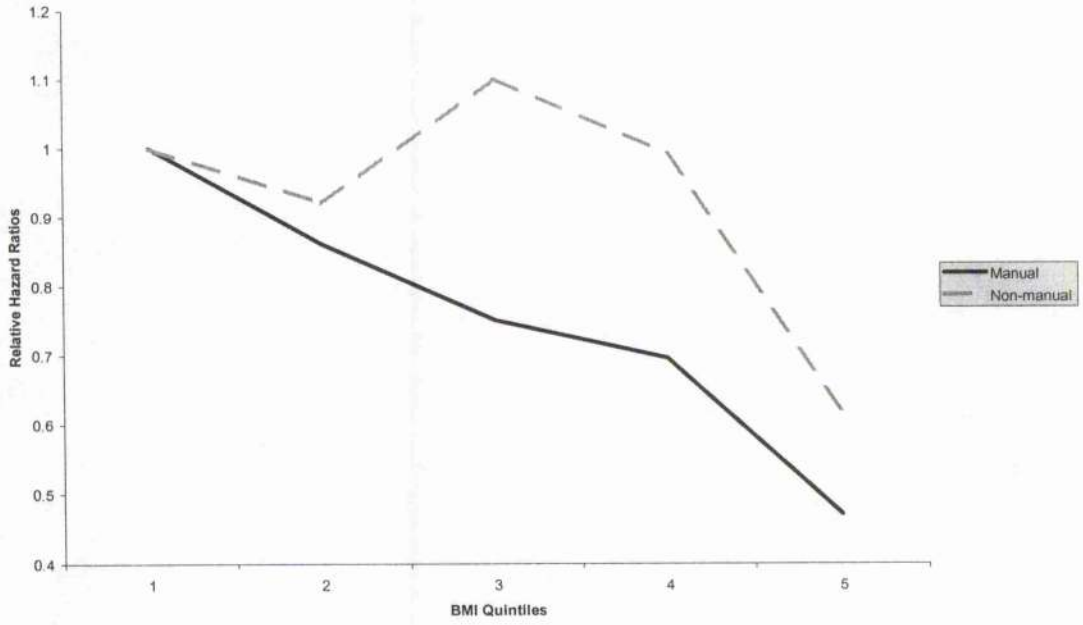


Table 5-20: Relative hazard ratio for lung cancer

First screening

		BMI tertiles			
	No	**1**	**2**	**3**	**Test for trend**
Total	762	1	0.85 (0.72-1.0)	0.69 (0.57-0.83)**	<0.001
Men	546	1	0.83 (0.89-1.02)	0.73 (0.58-0.90)*	0.0031
Women	216	1	0.91 (0.67-1.2)	0.59 (0.42-0.85)**	0.0061
Second screening					
Total	301/7951	1	0.68 (0.52-0.89)**	0.67 (0.51-0.89)**	0.0031
Men	199	1	0.70 (0.51-0.98)*	0.69 (0.49-0.98)*	0.029
Women	102	1	0.64 (0.39-1.04)	0.61 (0.38-0.99)*	0.032
Smoking related cancers					
Total	174	1	0.85 (0.58-1.25)	0.91 (0.63-1.33)	0.686
Serum cholesterol					
Total	764	1	0.81 (0.69-0.96)**	0.81 (0.67-0.97)*	0.0145

Table 5-21: Mean BMI changes in lung cancer cases over different follow-up periods from the second screening

	No	BMI		P-value*
		Mean	SD	
After 2 years	40	0.543	2.4	0.059
2-5 years	50	-0.459	2.1	0.317
5-10 years	114	-0.389	1.3	0.269
>10 years	163	-0.286	1.8	0.542
Cancer free subjects	8137	-0.1971	1.84	

* *P*-value of t-test comparing mean BMI changes for cancer free and cancer cases in each period.

Table 5-22: Cause specific mortality for men in the Collaborative study.

	45-64 years
Total	4014
Alive	50.0%
	(2008)
CHD	38.2%
	(767)
Stroke	8.9%
	(179)
Other CVD	5.2%
	(105)
Lung cancer	11.3%
	(226)
Other smoke related cancer	4.8%
	(97)
Other cancer	14.0%
	(281)
Respiratory	8.2%
	(164)
Other	9.3%
	(187)

Table 5-23: RHR[1] for lung cancer mortality for men aged 45-64 years in the Collaborative study and Renfrew/ Paisley study

	No	BMI groups					β	Linear trend test
		1	2	3	4	5	Overall risk	
Collaborative study[3]								
Total	226	1	0.81 (0.56-1.18)	0.69 (0.46-1.01)	0.47 (0.30-0.73)***	0.65 (0.44-0.96)*	0.87 (0.79-0.96)	**0.003**
Non-smoker	26	1	0.23 (0.05-1.12)	0.39 (0.11-1.38)	0.44 (0.13-1.43)	0.76 (0.27-2.16)	1.14 (0.82-1.59)	0.864
Current smoker	200	1	1.03 (0.70-1.52)	0.94 (0.63-1.42)	0.64 (0.40-1.03)	0.89 (0.58-1.38)	0.94 (0.85-1.04)	0.185
Heavy smokers[2]	181	1	0.93 (0.60-1.42)	0.80 (0.51-1.25)	0.68 (0.43-1.07)	0.75 (0.48-1.17)	0.96 (0.87-1.07)	0.084
Renfrew/ Paisley study[4]								
Total	529	1	0.82 (0.64-1.05)	0.76 (0.59-0.98)*	0.84 (0.65-1.08)	0.51 (0.37-0.69)***	0.89 (0.83-0.95)	**0.0005**
Non-smoker	79	1	0.75 (0.31-1.82)	0.87 (0.39-1.88)	0.99 (0.47-2.11)	0.39 (0.15-0.94)*	0.87 (0.73-1.04)	0.121
Current smoker	450	1	0.82 (0.63-1.06)	0.74 (0.56-0.97)*	0.81 (0.61-1.07)	0.55 (0.39-0.78)***	0.89 (0.83-0.96)	**0.002**
Heavy smokers[3]	380	1	0.80 (0.60-1.07)	0.79 (0.59-1.06)	0.78 (0.57-1.05)	0.59 (0.41-0.84)**	0.90 (0.84-0.97)	**0.007**
Pooled data of the two studies								
Total	795	1	0.76 (0.62-0.92)*	0.62 (0.50-0.77)**	0.65 (0.53-0.80)***	0.49 (0.39-0.61)***	0.85 (0.81-0.89)	**<0.001**
Non-smoker	84	1	0.70 (0.31-1.59)	0.64 (0.30-1.35)	0.97 (0.49-1.91)	0.51 (0.25-1.08)	0.91 (0.78-1.07)	0.265
Current smoker	711	1	0.82 (0.67-1.01)	0.75 (0.59-0.93)**	0.73 (0.58-0.92)**	0.63 (0.49-0.81)***	0.898 (0.85-0.95)	**0.0001**
Heavy smokers[2]	598	1	0.84 (0.67-1.05)	0.77 (0.60-0.97)**	0.79 (0.62-1.01)	0.68 (0.53-0.89)***	0.92 (0.86-0.97)	**0.0030**

[1]RHR adjusted for age, smoking and social class; [2] Heavy smoker who smoke ≥15 cigarettes per day
[3]BMI groups: <22.5, 22.6-24.4, 24.5-25.7, 25.8-27.6, >27.6 kg/m^2; [4]BMI groups: <22.5, 22.5-24.5, 24.6-26.3, 26.4-28.7, >28.7 kg/m^2.

CHAPTER 6

INTERGENERATIONAL TRENDS IN THE PREVALENCE OF OBESITY

6.1 INTRODUCTION

As mentioned in chapter one, the prevalence of obesity has reached epidemic proportions in the developed and developing countries. These trends are based on comparison between two or more cross-sectional surveys. Generally, subjects in these surveys are randomly selected from different populations. Changes in environmental and behavioural factors have been the main explanation for the rising trends in obesity whereas genetic factors were considered to have a minor role.

There are sufficient numbers of studies investigating the importance of genetics in obesity development. Many family studies, such as Framingham Heart Study, Quebec Family Study, and Victorian Family Heart Study, have focused on estimating familial correlations and heritability of obesity and BMI.

Generally data collected in families studies are collected at one survey, which usually results in young offspring. The offspring in most of the family studies, have been less than 18 years old. Only in Framingham Heart Study, were offspring aged 20-49. The parent generation, aged 30-62 were screened in 1948-55 and offspring generation were screened in 1971-75. Comparison between parents and offspring was restricted to the overlapping age groups 30-49. Age was grouped into four 5 years age band. The sons and daughters were taller than fathers and mothers for every age group. Body weight was compared using the Quetelet's index (w/h^2). The sons were heavier than fathers, the average difference being 6 kg, but daughters appear to weigh less per unit of height (squared) than mothers at the same age, especially in older age group (Feinleib et al. 1979).

The aim of this chapter is to describe intergenerational trends in obesity and BMI using the MIDSPAN Family data. The data allow investigation of obesity trends in subjects sharing similar genetic and environmental background. Later chapters will investigate environmental and genetic determinants of obesity and the interaction between them.

6.2 METHODS

Study populations

The parent generation age ranged between 45-64 years where the offspring generation age ranged between 30-59 years. The main analyses, in this chapter, were restricted to the overlapping age group between the two generations, ages 45-59. Thus, 340 males and 179 females were excluded from the parent generation because they were older than 59 years and 486 males and 580 females were excluded from the offspring generation because they were younger than 45 years. The sample studied consists, therefore, of 1137 males and 1298 females from the parent population and 554 males and 718 female from offspring population (Table 6-1).

Further trend analyses included parent-offspring pairs. These pairs might include more than one son for the same father and the same for mothers and daughters.

Table 6-1: Number of subjects in different sampling frames

	Total	**45-59 years**	**45-59 years (within families[2])**
Men			
1972-6	7052	4340	
1972-6 (parents[1])	1477	1137	326
1996	1040	558	554
Women			
1972-6	8354	5799	
1972-6 (parents[1])	1477	1298	509
1996	1298	718	718

[1]Parents of eligible offspring

[2] parent-offspring pair

Statistical analyses

Statistical procedures were performed using STATA (StataCorp 1999). Summary statistics were age standardised to the Scottish age distribution for the year 1995 using direct standardisation. Age was divided into three groups of five year bands: 45.0-49.9, 50.0-54.9, and 55.0-59.0. Logistic regression was used to estimate the differences between overweight and obesity prevalences in parents and offspring; linear regression was used to estimate differences in mean BMI.

We calculated age-adjusted BMI percentiles (5^{th}, 10^{th}, 15^{th}, up to the 95^{th}) for the two generations. For each percentile level, we calculated the mean value of BMI and the difference between BMI values of the corresponding percentiles of the two distributions. The difference was calculated as the offspring percentiles minus the parental percentile. Tukey mean-difference plots (Cleveland 1993) (m-d plots) were used to describe the change in BMI distribution between the parent and offspring generations. The m-d plot was obtained by graphing the differences between the corresponding percentiles of BMI on the y-axis, against the means of the same percentiles on the x-axis. The points on the line represent the differences between two distributions at a given percentile level plotted against the means of the same percentile level for the two distributions.

All regressions were adjusted for age (years), smoking status, social class (manual or non-manual) and familial clustering using the method of generalised estimated equations.

6.3 RESULTS

Age selection

A complex association was found between BMI and age in men and women in the two generations. In the parent generation, aged 45 to 64 years, BMI decreases with age in men and increases with age in women ($p<0.001$). On the other hand, in offspring generation, aged 30 to 59 years, BMI increases with age in men ($p=0.01$) and decreases with age in women ($p=0.154$).

Restricting the analysis to the overlapping age group 45 to 59 years the association between BMI and age becomes similar between generations but different between sexes. BMI decreases with age in father and son generations and increases with age in women generations. BMI was significant with age only in women in the parent generation ($p<0.001$). Figure 6-1 shows BMI–age associations in the two generations in men and women.

Table 6-2 shows mean BMI and obesity prevalence in those excluded from the analysis and how they differ from those included in the analysis. In the parent generation, mean BMI and obesity prevalences were similar for those included in the analysis (<60years) and those excluded (≥60years) in both men and women. In offspring generation, younger (<45 years) men and women have lower mean BMI than those included in the analysis (≥45years). Obesity prevalence was higher older men ($p=0.04$) but not women.

Migrants and non-participating offspring

The characteristics of migrants and non-participating offspring were discussed in chapter three in detail. This section will focus on those aged 45 to 59 years.

As mentioned earlier, the only information available for offspring aged 45-59 who did not participate in the study in 1996 comprises their personal age, sex and parental BMI and social class. 27% of sons and 24% of daughters no longer lived locally (Table 6-3). 29% of sons and 23% of daughters lived locally but did not participate. Participants in the study comprised 44% of all sons and 53% of all daughters aged

45-59. There were no significant differences between participating and non-participating offspring with respect to personal age, parental social class, mid-parental BMI or mid-parental prevalence of obesity (Table 6-3). Offspring response rates were not significantly different in families with mid-parental BMI in the ranges <25, 25-29.9 and ≥30 kg/m^2 respectively.

Comparing non-participating offspring (i.e. living locally and non-participant or living away and not invited) there were no differences in male/female ratio or mid-parental BMI (Table 6-3). Offspring who no longer lived locally had slightly higher prevalences of obese mothers (18.4 v 13.3%, p=0.003) and fathers in manual social classes (71.9 v 64.5%, p=0.005).

Parent characteristics

There were no significant differences in never and former smokers, mean BMI and obesity prevalence between parents included in the analyses and the general population of adults participants aged 45-59 years in the original Paisley and Renfrew Study in 1972-76 (Table and Table 6-5). Fathers in this analysis included fewer current smokers (55 v 59%, p<0.05) than other men in the parent generation who took part in the original study. There were few current smoker (47% v 51%, p=0.019) and more manual (67 v 61, p<0.001) mothers compared to women in the original study.

Trends in obesity in parent and offspring generations

On average, men in offspring generation were 0.7kg/m^2 heavier (p<0.001) than men in parent generation (Table 6-4). On average, women were 0.4kg/m^2 heavier (Table 6-5). Further, median BMI was higher in men in offspring generation (26.5 kg/m^2) compared to men in parent generation (26.1 kg/m^2), while similar median was found for women in both generations (25.4 kg/m^2).

The prevalence of overweight and obesity (BMI≥25kg/m^2) was similar for both generations in both men and women. Almost two thirds of men in both generations are either overweight or obese. However, only half the women in both generations are either overweight or obese.

The prevalence of obesity (BMI $\geq$30kg/m^2) increased in men from 9.1% to 18.4% (odds ratio 2.1, 95% CI: 1.6-2.8, p<0.001) and in women from 15.4% to 17.4% (odds ratio 1.2, 95% CI: 0.94-1.5).

Restricting the analyses to parent-offspring pairs reveals similar results (Table 6-6). Slight increase in mean BMI was reflected by higher increase in obesity prevalence. The differences in mean BMI and obesity prevalence, between father-son, were significant.

In both generations, the distributions of BMI were skewed towards higher values, particularly in men (Figure 6-2). BMI values within successive 5% intervals of the distributions were similar for men in both generations until the 40th percentile, above which the values for men in offspring generation were higher (Figure 6-3). A similar pattern was observed in women for BMI values above the 70th percentile.

The Tukey m-d plot (Figure 6-4) shows these observations more clearly. Within equivalent percentile ranges, the differences in mean BMI at the lower end of the distribution were close to zero for men and lower than zero for women. Above 26% kg/m^2 in men and 28 kg/m^2 in women, mean BMI values in corresponding percentiles were progressively higher in the offspring generation.

Factor associated with raised BMI within generations

In parents and offspring aged 45 to 59 years, BMI was positively associated with age in women and negatively associated with age in men. Multiple regression analyses showed statistically significant relationships between BMI and manual occupation, current smoking, blood pressure and plasma cholesterol in parents and between BMI and age, manual occupation, current and former smoking, systolic BP, serum cholesterol and mid-parental BMI in offspring (Table 6-7).

Factors available for both generations (age, gender, social class, smoking status, blood pressure and cholesterol) explained 17.2% of the variation in BMI in parents and 13.5% of the variation in offspring. Adding mid-parental BMI to the offspring model explained 24.1% of the variation in BMI.

Obesity trends by smoking status

The prevalence of current smokers in the offspring generation (29% in men and 24% in women) was about half that observed in the parent generation (55% in men and 47% in women). The prevalence of former smokers increased between the two generations, particularly in women (Table 6-5). The prevalence of never smokers increased in men in offspring generation compared to men in parent generation (Table 6-4), while the prevalence of never smokers was similar in women in the two generations (Table 6-5).

In the parent generation, never and former smokers were heavier than current smokers in both men and women. Moreover, the prevalence of obesity was higher in former smokers than in never smokers and current smokers had the lowest obesity prevalence. Offspring generation showed a similar pattern as parent generation, with former and never smokers being heavier than current smokers in men and women. However, the distribution of obesity prevalence was different for men and women. In men, the highest prevalence of obesity was found in former smokers and the lowest in never smokers. Whereas, in women, the highest obesity prevalence was in never smokers and the lowest obesity prevalence was in current smokers.

In men, on average, offspring who were former smokers were 0.8kg/m^2 heavier than parents who were former smokers (p=0.003). Mean BMI in current and never smokers were similar in both generations (Table 6-8). However, there were no differences in mean BMI between women in the two generations in never, former or current smoking groups.

The prevalence of obesity increased in offspring who were never, former and current smokers in offspring men. Obesity prevalence almost doubled in current (7.5% v 15.1%, p=0.008) and former (11.7% v 24.8%, p=0.005) offspring smokers compared to the parent generation (Table 6-8). In women, the prevalence of obesity increased slightly in never and current smokers but decreased in former smokers compared to women in the parent generation.

Figure 6-5 shows the difference in BMI values, within equivalent percentile ranges, in never smokers between the two generations. In men, the lower part of offspring BMI distribution was almost zero in men and less than zero in women. In the top part

of distribution, above the value 27kg/m^2 the difference between the two generations starts to increase progressively. Whereas, in women the difference in BMI values, for corresponding percentiles, started to increase after BMI value of 30kg/m^2.

Figure 6-6 shows the m-d plot for current smokers. The difference in BMI values for equivalent percentiles for parent and offspring generations starts to increase above BMI values of 25kg^2 in men and 29kg/m^2 in women.

Obesity trends by social class

Two thirds of parent (67.2% in men and 66.8% in women) generation were in the manual social class compared to 47% of men and 26.1% of women in offspring generation.

In the parent generation, however, there was no difference in mean BMI between manual and non-manual men while the manual women were 1.0kg/m^2 heavier than non-manual women. In the offspring generation, however, manual men were 0.4 kg/m^2 heavier than non-manual men and manual women were 0.5 kg/m^2 heavier than non-manual women.

On average, manual men in the offspring generation were 0.9kg/m^2 heavier than manual men in parent generation (p=0.028). Further, non-manual were 0.6kg/m^2 than non-manual men in parent generation (p=0.003) (Table 6-8). The difference in mean BMI between the two generations in non-manual group was insignificant after controlling for smoking status (p=0.285).

Manual and non-manual women in the offspring generation were heavier than women in the parent generation but the difference in mean BMI was insignificant in both manual and non-manual groups after controlling for smoking.

The prevalence of obesity has increased considerably in manual and non-manual offspring men compared to the prevalence in the parent generation screened 20 years ago. The increases in manual group from 9.4% to 22.0% and in non-manual group from 8.5% to 15.4% were significant after controlling for smoking groups. In women, the change in obesity prevalence, between offspring and parent generations, in the non-manual group from 11.0% to 16.0% was significant taking account of age

and familial clustering, but becomes insignificant after controlling for smoking status.

Figure 6-7 shows the difference in BMI distribution between manual parent and offspring generations. The difference in BMI values, for equivalent percentiles, in the lower part of the distribution was lower than zero for men and women, but above BMI value of 24kg/m^2 offspring generation have progressively higher BMI values than the parent generation. In the non-manual group, however, the difference in BMI distribution between the two generations was above zero across all BMI percentiles indicating a positive shift in offspring BMI distribution (Figure 6-8). Further, with this major observation, the difference in BMI distribution between the two generations is minor in the lower part of the distribution but starts to widen above BMI value of 25kg/m^2.

6.4 DISCUSSION

Several studies in the UK have reported an increase in obesity prevalence in children (Bundred, Kitchiner, & Buchan 2001;Chinn & Rona 2001), and adults (Prentice & Jebb 1995), usually by comparing cross-sectional surveys carried out at different points in time. In our study, obesity trends were studied in parents and adult offspring over a 20 year period.

An advantage of this study design is that offspring are more likely to have passed critical periods in development and to display the results of interaction between environmental and susceptibility factors. Similar survey and measurement methods were used.

Given the complex associations observed between BMI and age in men and women in the two generations, we confined analysis to parents and offspring in the 45-59 year age group. The offspring included in the analysis are a subset of all offspring born to these parents, and aged 30-59 years when studied in 1996. Non-participating offspring, aged 45-59 years, include 640 offspring living locally, who declined to take part, and 628 living further afield, who were not approached. Although migrant offspring had heavier mothers than other offspring, there were no other significant detectable differences between offspring participating and non-participating in the 1996 survey.

The parents in our study were similar to the larger population of adults studied in Paisley and Renfrew in 1972-76, which comprised a 78% sample of the general populations of these two towns. The parent generation may be considered reasonably representative, therefore, of families living in an area characterised by high rates of socio-economic deprivation and all cause mortality (Davey Smith et al. 1997). Such factors may explain the higher mean values of BMI compared with other British studies carried out at that time (Shaper et al. 1981;West, Ford, Hunt, MacIntyre, & Ecob 1994).

Mean BMI and the prevalence of obesity in offspring were slightly lower than the figures observed in men and women of comparable age, who took part in the Scottish Health Survey in 1995 (The Scottish Office: Scotland's Health 1995). A possible

explanation of this difference is that the higher proportion of offspring in non-manual occupations (58 v 45% in men; 77 v 63% in women) had a larger effect in reducing mean population BMI than the higher prevalence of former smokers (30 v 21% in men; 25 v 18% in women) had in raising it.

BMI and obesity prevalence behave differently in this study. The slight differences in mean BMI demonstrated between the two generations included a doubling in the prevalence of obesity (BMI $\geq$30 kg/m^2) in men but not in the prevalence of overweight or obese individuals (BMI $\geq$ 25 kg/m^2).

Although the prevalence of obesity was similar in both men and women, the increase in the prevalence of obesity between the two generations was less in women than in men. This is probably because women in the parent generation had higher obesity prevalence than men at that time, or because women in the offspring generation are influenced by the increase in health or fashion-related weight awareness.

Flegal has suggested alternative explanations for the increase in the population prevalence of obesity (Flegal & Troiano 2000). Either all subgroups in the offspring generation might be heavier than the comparable subgroups in the parent generation, or one subgroup might be heavier than the comparable subgroup with little or no change in other subgroups of the offspring generation. Our results are consistent with the latter hypothesis (Figure 6-2) suggesting "anchoring" and "skewing" effects at the lower and upper ends of the distribution of BMI, respectively (Figure 6-3).

The findings of this study support the gene-environment effect, where the factors associated with increased obesity appear to have a stronger effect on the subgroup in the upper part of BMI distribution suggesting that this subgroup of the population is more susceptible to these effects. Further, this does not support Rose's suggestion that changes in the upper portion of the distribution reflect changes occurring in the whole distribution (Rose & Day 1990).

The "anchoring" and "skewing" effect was found, but to a different extent, across smoking and social class groups suggesting the influence of different environmental factors in addition to the individual susceptibility.

Our study shows the usual, expected relationships between BMI, age, social class and smoking behaviour. These were the only environmental and behavioural variables measured in both generations. Although the prevalence of non-manual occupations and of never smokers was higher in the offspring generation, these differences, and their associations with BMI, were insufficient to explain the observed increase in the prevalence of obesity.

In the offspring generation, however, mid-parental BMI increases the proportion of "explained" variation in BMI from 13.5 to 24.1%. These observations are consistent with mid-parental BMI being a significant determinant of raised BMI levels in a substantial minority of offspring, via either the sharing of adverse behaviours within families, or increased susceptibility to adverse behaviours, or a combination of these explanations.

6.5 SUMMARY

In this study population, increases in BMI in the offspring generation compared to the parent generation, particularly in sons, are concentrated in the top half of the population distribution of BMI, resulting in a doubling of the prevalence of obesity. Possible explanations include increases in the prevalence of adverse behaviours and/or increased susceptibility to such factors in association with raised levels of mid-parental BMI

Potential explanatory variables measured only in offspring will be investigated in detail in the coming chapters. First, environmental factors including physical activity, food frequencies converted to estimates of nutritional intake, smoking and social class (Chapter Seven). Second, genetic factors including estimating familial correlates and the heritability of BMI (Chapter Eight). Finally, gene-environment interactions including the association of environmental factors within offspring with different familial susceptibility (Chapter Nine).

Table 6-2: Characteristics of parents and offspring in different age groups

	Parents			Offspring		
	<60	≥60	*P*-value	<45	≥45	*P*-value
Men	*1137*	*340*		*486*	*558*	
BMI (mean, SD)	26.0 (3.2)	25.8 (3.4)	0.059	26.2 (3.9)	26.8 (4.1)	0.01
Obesity % (BMI≥30kg/m^2)	10.6%	10.7%	0.464	15.5%	19.9%	0.04
Women	*1298*	*179*		*580*	*718*	
BMI (mean)	25.8 (4.3)	25.8 (4.5)	0.93	25.6 (4.9)	26.1 (4.9)	0.07
Obesity (BMI≥30kg/m^2)	14.9%	15.1%	0.42	19.1%	17.3%	0.22

Table 6-3: Characteristics of offspring aged 45-59 years identified for couples living in Renfrew and Paisley towns

		Participants	Non-participants	
			Locals	Migrants
N		1207	640	628
Sex	**M**	44.0	53.8%	52.4
		(531)	(344)	(329)
	F	56.0	46.3%	47.6
		(676)	(296)	(299)
Age	**M**	49.3±3.5	49.6±3.6	49.4±3.4
	F	49.4±3.5	49.9±4.0	49.6±3.7
Father BMI categories	**<25**	36.6	41.3	37.2
		(441)	(264)	(233)
	25-29.9	51.8	48.9	49.8
		(624)	(313)	(312)
	≥30	11.6	9.8	13.1
		(140)	(63)	(82)
Mother BMI categories	**<25**	41.5	48.2	39.7
		(500)	(308)	(248)
	25-29.9	42.4	38.5	41.9
		(511)	(246)	(262)
	≥30	16.1	13.3	18.4
		(193)	(85)	(115)
Mid-parental BMI	**Mean**	26.2±3.0	25.8±2.8	26.3±3.1
Mid-parental BMI categories				
	<25	36.2	41.0	35.5
		(435)	(262)	(222)
	25-29.9	54.4	51.3	54.6
		(658)	(328)	(341)
	≥30	9.1	7.7	9.9
		(110)	(49)	(62)
Fathers social class	**NM**	33.3	35.5	28.1
		(369)	(225)	(174)
	M	66.7	64.5	71.9
		(826)	(408)	(446)

Table 6-4: Comparison of age, BMI, smoking and social class in MIDSPAN population (except Family Study parents), Family Study parents and Family Study offspring, restricted to age 45-59 years men

		Male				
		MIDSPAN	**Parents**	**p (MID=Par)**	**Offspring**	**p (Off=Par)**
N		4341	1137		558	
Age (years)	N_{TOTAL} Mean (SD)	4341 51.7 (4.3)	1137 52.9 (3.6)	<0.0001	558 49.6 (3.5)	<0.0001
Never Smoker	N_{TOTAL} %	4341 18.4%	1137 20.4%	0.12	558 34.5%	<0.0001
Former Smoker	N_{TOTAL} %	4341 22.8%	1137 25.0%	0.061	558 36.8%	<0.0001
Current Smoker	N_{TOTAL} %	4341 58.8%	1137 54.6%	0.0042	558 28.6%	<0.0001
Manual Social Class	N_{TOTAL} %	4317 69.2%	1137 67.2%	0.076	558 47.0%	<0.0001
BMI (kg/m^2)	N_{TOTAL} Mean (SD)	4340 25.9 (3.4)	1136 26.0 (3.1)	0.092	558 26.7 (4.0)	0.0002
Overweight or Obese (BMI ≥25 kg/m^2)	N_{TOTAL} %	4340 58.5%	1136 62.3%	0.0044	558 61.6%	0.86
Obese (BMI ≥30 kg/m^2)	N_{TOTAL} %	4340 10.7%	1136 9.1%	0.82	558 18.4%	<0.0001

NB: all summary statistics (except for age) directly standardized to 1995 Scottish population age distribution in 5-year bands, i.e. 45-49, 50-54, 55-59 year age groups;
all p-values (except for age) test age-adjusted differences between groups from linear (age and BMI) or logistic (smoking, social class, obesity) regression models (age included as a linear term).

Table 6-5: Comparison of age, BMI, smoking and social class in MIDSPAN population (except Family Study parents), Family Study parents and Family Study offspring, restricted to age 45-59 years women

		Female				
		MIDSPAN	**Parents**	***p*** **(MID=Par)**	**Offspring**	***p*** **(Off=Par)**
N		5081	1298		719	
Age (years)	N_{TOTAL} Mean (SD)	5081 52.2 (4.2)	1298 51.6 (3.9)	<0.0001	719 49.7 (3.6)	<0.0001
Never Smoker	N_{TOTAL} %	5081 41.6%	1298 44.4%	0.14	719 45.0%	0.10
Former Smoker	N_{TOTAL} %	5081 7.0%	1298 8.3%	0.088	719 30.9%	<0.0001
Current Smoker	N_{TOTAL} %	5081 51.4%	1298 47.3%	0.019	719 24.1%	<0.0001
Manual Social Class	N_{TOTAL} %	4936 60.6%	1298 66.8%	0.0001	719 26.1%	<0.0001
BMI (kg/m^2)	N_{TOTAL} Mean (SD)	5074 25.4 (4.3)	1298 25.8 (4.3)	0.0079	718 26.2 (5.0)	0.019
Overweight or Obese (BMI ≥25 kg/m^2)	N_{TOTAL} %	5074 47.8%	1298 53.3%	0.0008	718 53.6%	0.64
Obese (BMI ≥30 kg/m^2)	N_{TOTAL} %	5074 13.2%	1298 15.4%	0.097	718 17.4%	0.077

NB: all summary statistics (except for age) directly standardized to 1995 Scottish population age distribution in 5-year bands, i.e. 45-49, 50-54, 55-59 year age groups;
all p-values (except for age) test age-adjusted differences between groups from linear (age and BMI) or logistic (smoking, social class, obesity) regression models (age included as a linear term).

Table 6-6: Comparison of BMI and obesity prevalence in parents and their adult offspring populations[1] in 45 to 59 age groups

	Parents (1972-6)	Offspring (1996)	*p*-value
Men	**326**	**554**	
BMI (mean)	26.2 (3.3)	26.7 (4.1)	0.012
Obesity (BMI >30 kg/m^2)	11.7%	18.4%	0.001
Women	**509**	**718**	
BMI (mean)	26.0 (4.4)	26.2 (5.0)	0.524
Obesity (BMI >30 kg/m^2)	15.7%	17.4%	0.258

[1]Parent-offspring pairs: father and his sons, mother and her daughters. A father or a mother might have more than a son or a daughter

Table 6-7: Results of regression analysis in parent and offspring generations aged 45-59

BMI	β	SE	P value	95% Confidence Interval	
Parent generation					
Age	.033	.019	0.093	-.005	.071
Sex	-.159	.158	0.310	-.469	.149
Manual	.571	.147	>0.001	.283	.859
Former smoker	.064	.223	0.773	-.372	.501
Current smoker	-1.196	.165	>0.001	-1.519	-.871
Systolic blood pressure	.010	.004	0.012	.002	.019
Diastolic blood pressure	.086	.007	>0.001	.071	.100
Cholesterol	.146	.068	0.032	.012	.280
Constant	14.389	1.209	>0.001	12.018	16.762
R^2=17.2%					
Offspring generation					
Model I					
Age	-.105	.036	0.003	-.174	-.036
Sex	-.063	.278	0.820	-.609	.482
Manual	.908	.267	0.001	.384	1.431
Former smoker	.634	.286	0.027	.073	1.195
Current smoker	-1.403	.311	>0.001	-2.014	-.792
Systolic blood pressure	.079	.011	>0.001	.058	.101
Diastolic blood pressure	-.011	.017	0.513	-.045	.022
Cholesterol	.623	.129	>0.001	.369	.877
Constant	17.768	2.087	>0.001	13.674	21.862
R^2=13.5%					
Model II					
Age	-.129	.034	>0.001	-.196	-.064
Sex	.126	.264	0.634	-.393	.645
Manual	.679	.255	0.008	.179	1.178
Former smoker	.383	.273	0.161	-.153	.919
Current smoker	-1.519	.296	>0.001	-2.099	-.939
Systolic blood pressure	.082	.010	>0.001	.061	.102
Diastolic blood pressure	-.019	.016	0.232	-.051	.012
Cholesterol	.621	.123	>0.001	.379	.862
Mid-parental BMI	.506	.038	>0.001	.431	.581
Constant	17.997	1.853	>0.001	14.362	21.632
R^2=24.1%					

Table 6-8: Changes in BMI[1] between parents in 1972-76 and offspring in 1996 aged 45-59 years, by social class and smoking status

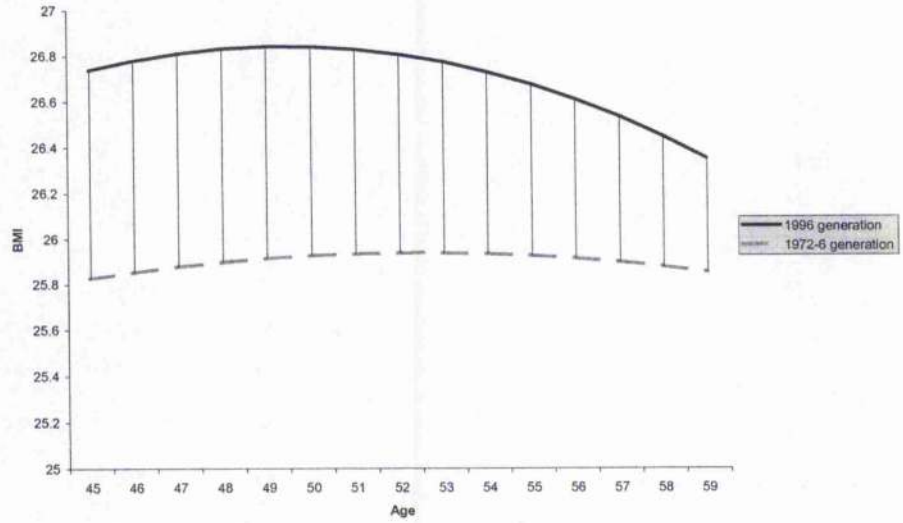
				Parents	Offspring	P[1]	P[2]
Male	BMI	N_{TOTAL} Mean (SD)	Manual	757 26.0 (3.1)	254 26.9 (4.4)	0.028	0.043
			Non-manual	379 25.9 (3.1)	304 26.5 (3.5)	0.003	0.285
	Obesity	N_{TOTAL} %	Manual	757 9.4%	254 22.0%	0.0001	<0.0001
			Non-manual	379 8.5%	304 15.4%	0.014	0.041
	BMI	N_{TOTAL} Mean (SD)	Never Smoker	233 26.6 (3.0)	214 26.4 (3.3)	0.175	0.437
			Former Smoker	297 26.6 (2.9)	193 27.8 (3.9)	0.004	0.003
			Current Smoker	606 25.5 (3.1)	151 25.5 (4.4)	0.179	0.166
	Obesity	N_{TOTAL} %	Never Smoker	233 10.3%	214 14.0%	0.43	0.178
			Former Smoker	297 11.7%	193 24.8%	0.007	0.008
			Current Smoker	606 7.5%	151 15.1%	0.002	0.005
Female	BMI	N_{TOTAL} Mean (SD)	Manual	864 26.2 (4.3)	178 26.6 (5.7)	0.065	0.39
			Non-manual	434 25.2 (4.0)	540 26.1 (4.7)	0.004	0.144
	Obesity	N_{TOTAL} %	Manual	864 17.6%	178 22.2%	0.23	0.168
			Non-manual	434 11.0%	540 16.0%	0.042	0.114
	BMI	N_{TOTAL} Mean (SD)	Never Smoker	567 26.7 (4.4)	332 26.6 (5.2)	0.369	0.326
			Former Smoker	109 26.8 (3.6)	216 26.9 (4.7)	0.872	0.398
			Current Smoker	622 24.8 (4.0)	170 24.6 (4.3)	0.794	0.379
	Obesity	N_{TOTAL} %	Never Smoker	567 18.5%	332 20.3%	0.526	0.063
			Former Smoker	109 22.7%	216 17.8%	0.389	0.86
			Current Smoker	622 10.7%	170 12.0%	0.355	0.089

Regression model controlling for age and familial clustering

[2] Regression model included age, smoking (for social class strata), social class (for smoking strata), generation and controlling for familial clustering.

Figure 6-1: a-BMI-age relationship in son and father generations, b-BMI-age relation in mother and daughter generations

a.



b.

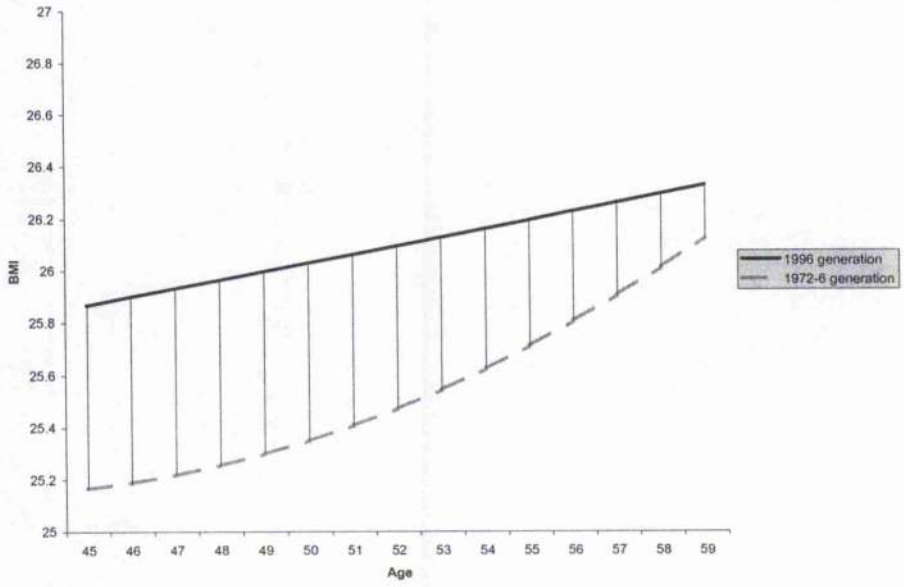


Figure 6-2: BMI distribution curves for parents and their offspring by sex.

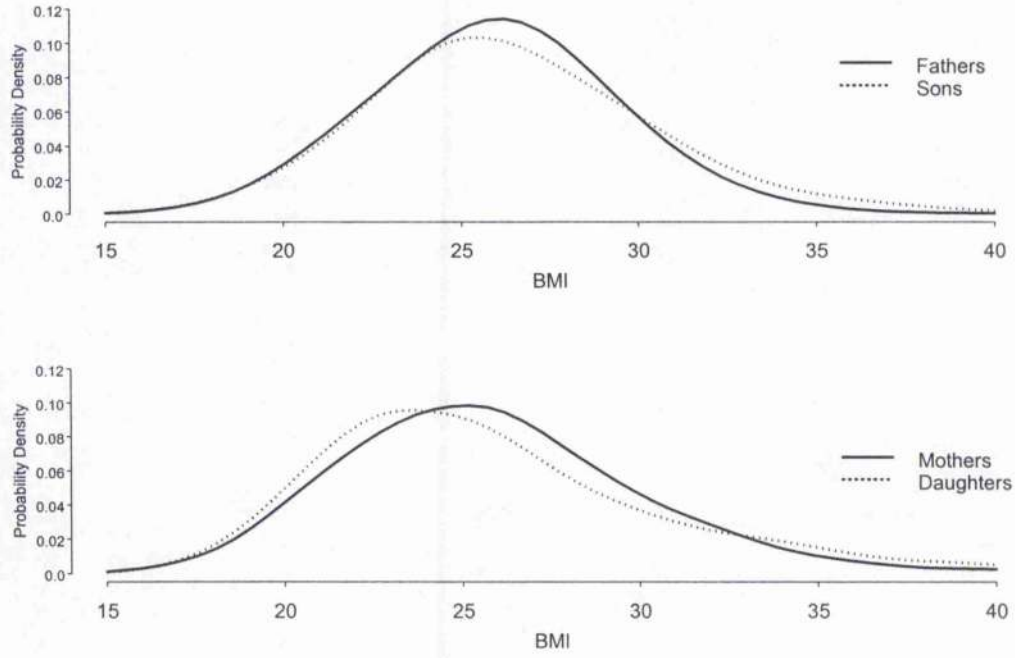
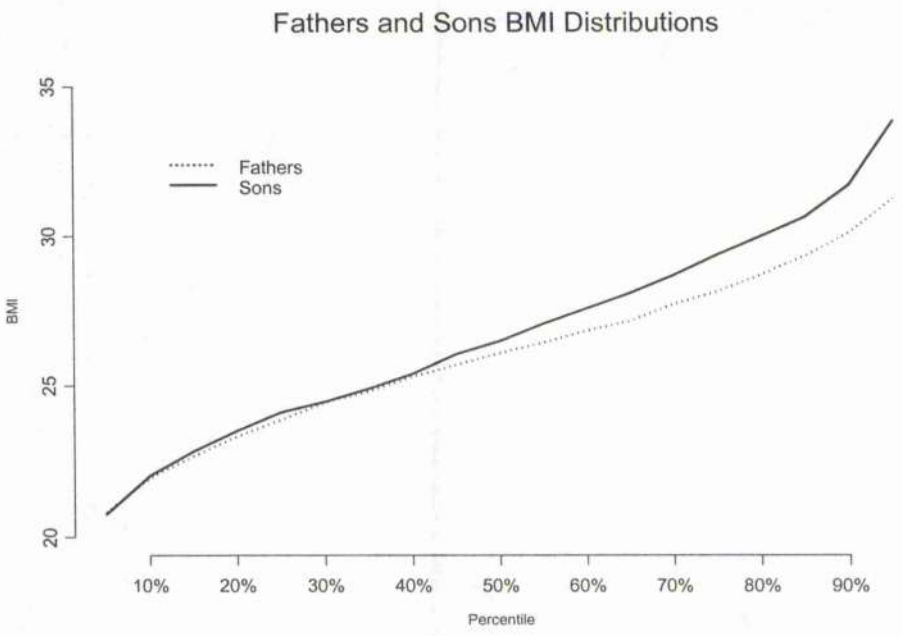


Figure 6-3: The 5% centiles and the corresponding BMI values for parents compared to their offspring.



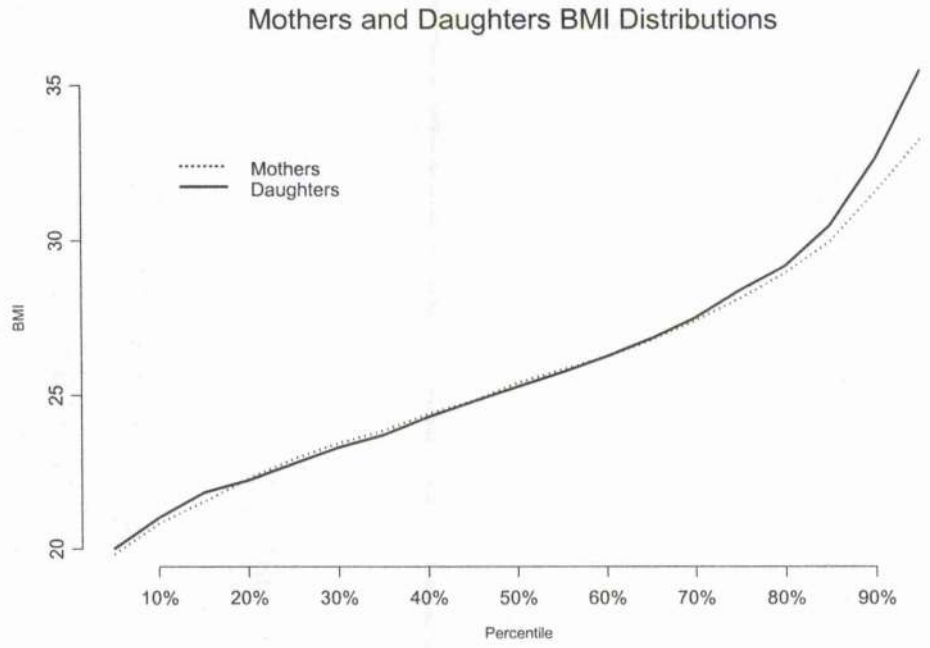


Figure 6-4: Intergenerational comparison of BMI distribution for parents and their offspring using m-d plot.

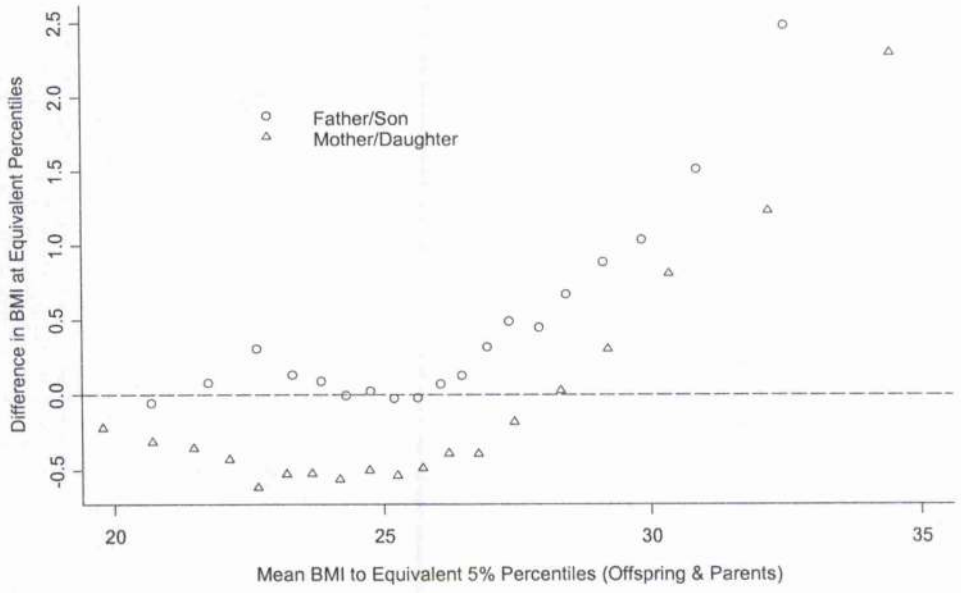


Figure 6-5: Intergenerational comparison of BMI distribution for never smoker parents and their offspring using m-d plot

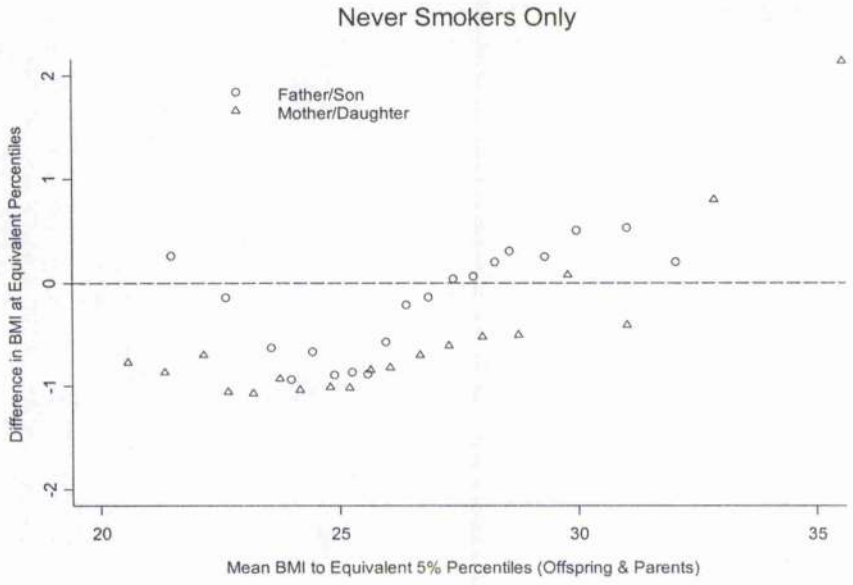


Figure 6-6: Intergenerational comparison of BMI distribution for current smoker parents and their offspring using m-d plot

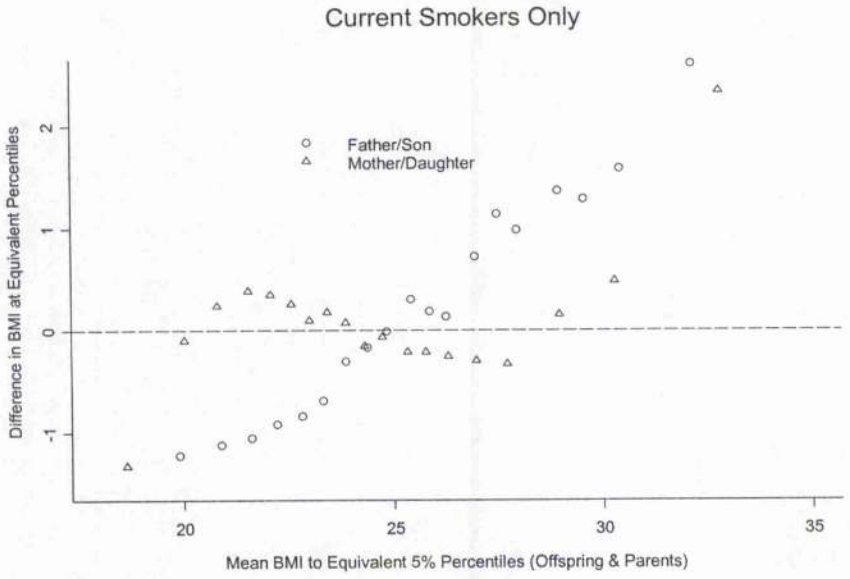


Figure 6-7: Intergenerational comparison of BMI distribution for manual parents and their offspring using m-d plot

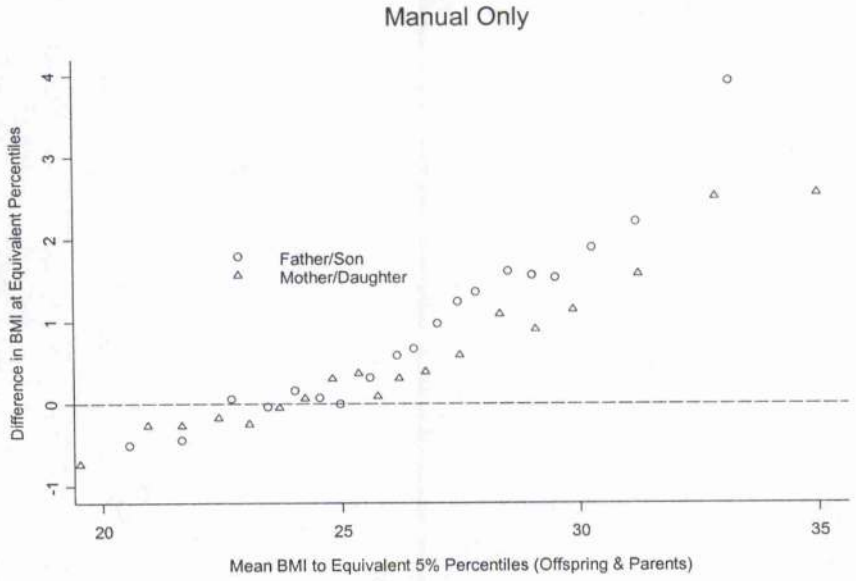
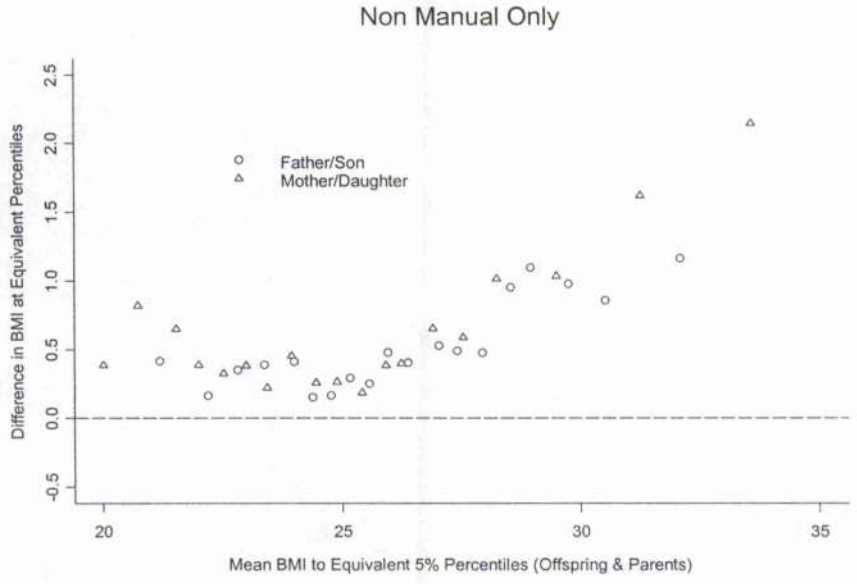


Figure 6-8: Intergenerational comparison of BMI distribution for non-manual parents and their offspring using m-d plot



CHAPTER 7

ENVIRONMENTAL AND BEHAVIOURAL DETERMINANTS OF OBESITY IN OFFSPRING

7.1 INTRODUCTION

As our genes have not changed substantially during the last two decades, it is clear that environmental and behavioural factors are the most likely causes of the increased prevalence of obesity in recent decades (Hill & Peters 1998).

Obesity results when energy intake exceeds energy expenditure. The current environment is characterised by the unlimited supply of highly palatable, energy-dense and relatively inexpensive foods (Piper 1996), and at the same time, less need for physical activity (Sørensen 2000).

In the literature, dietary intake appears to have received more attention than physical activity in relation to body weight. A brief review of the literature investigating dietary intake and physical activity and their associations with obesity is described below.

Dietary intake

The percentage of energy intake from dietary fat is considered an important determinant of body fat. Several mechanisms have been proposed to explain this relationship. First, dietary fat is the most energy-dense macronutrient, providing ≈38kJ/g as opposed to 17kJ/g for carbohydrate or protein. Second, fat gives food greater flavour and palatability, which leads to over consumption of food. Third, dietary fat is utilised more efficiently and accumulates as body fat more than carbohydrate, which produces a greater thermogenic effect than fat. Finally, fat intake is not regulated in the same way as carbohydrate intake and thus, individuals eating a high-fat diet are more likely to consume more total energy to obtain the same amount of carbohydrate intake as someone eating a low-fat diet (Sclafani 1996).

Lissner and Heitmann have reviewed the various epidemiological methods that have been used to investigate the relationships between obesity and high-fat diet (Lissner & Heitmann 1995). The most basic epidemiological studies are ecological studies, which describe dietary intake and obesity at the population level and provide mixed messages. Comparison of diet and obesity between affluent and poor populations provides a positive association. However, comparison of populations within regions with similar economic development, such as the European countries, showed no association between diet and obesity in men and negative association in women. Ecological studies are also confounded by differences in physical activity, smoking, cultural attitudes toward body fat and food availability (Lissner & Heitmann 1995;Willett 1998a).

Cross-sectional studies are considered to be unhelpful in determining the causality of the relationship between fat consumption and body fat. That is because of the serious potential for confounding, including health consciousness, in cross-sectional studies (Lissner & Heitmann 1995;Willett 1998a). Although prospective studies are generally considered a stronger epidemiologic design than cross-sectional studies, they are susceptible to confounding when individuals are aware of the dependent variable (obesity or body weight) and also have control over the determinants (physical activity, total fat and total energy intake) (Willett 1998b).

Clinical trials are considered the strongest method to evaluate the causal nature of observed associations between fat intake and body fat. Short-term clinical trials provide consistent evidence of weight loss on low-fat diets (fat consumption within the range of 18-40% of energy). However, long term trials, lasting more than a year, show little if any effect of low-fat diets on body weight (Lissner & Heitmann 1995;Willett 1998a). A major limitation of long-term trials is that the control groups tend not to receive as much dietary instruction and motivation as the intervention groups which may result in greater attention to intake of total energy rather than just attention to fat in the intervention groups. Such studies also lack a well-documented measure of compliance (Willett 1998b).

Moreover, it has been reported in the United States that substantial reductions in fat and caloric intake have been associated with a puzzling increase in the prevalence of obesity in the last two decades. These trends suggest a dramatic reduction in total physical activity related to energy expenditure (Heini & Weinsier 1997).

The "fat-sugar theory" suggests that high carbohydrate foods may influence energy balance by reducing food intake through a greater satiety effect, reducing the energy density and displacing fat from the diet (Stubbs, Mazlan, & Whybrow 2001). In a review of carbohydrate, appetite and feeding behaviour in humans, it was concluded that replacing fat with carbohydrate in the diet may not be as protective against over-consumption as the energy density or fat-sugar arguments suggest. It was observed that an increase in carbohydrate intake has accompanied the reduction of fat intake in the US. But the carbohydrate that replaced fat in low fat diets was high in glycemic index (which characterises the rate of carbohydrate absorption after a meal). The hormonal response to high glycemic index seems to lower circulating levels of metabolic fuels, stimulate hunger, favour storage of fat, and therefore, stimulate weight gain (Ludwig 2000).

Dietary sugar like dietary fat has been the subject of extensive research with regard to its effects on obesity. Despite the idea that sugar causes excessive energy intake and obesity because of its strong, pleasant sweet taste, there is not strong evidence supporting this theory (Anderson 1995;Hill & Prentice 1995). Further, there was no difference between the effect of simple sugar and complex sugar in this regard (Hill & Prentice 1995). It was found that sugar intake was negatively associated with fat intake, and that sugar and carbohydrate intakes are associated with leanness not obesity (Anderson 1995;Hill & Prentice 1995).

A recent study, however, provided evidence about the relation between sugar intake and the development of adiposity in children (Bellisle & Rolland-Cachera 2001). This study showed that the consumption of sugar-sweetened beverages is an independent risk factor for obesity in children aged 11-12 years. Even so, these results are not widely accepted

and have some limitations (Fishbein 2001;Henry & Warren 2001;Ludwig, Peterson, & Gortmaker 2001).

There are not many data investigating the relationship between protein intake and body weight. A positive relationship has been reported (Metges & Barth 2000). In a comparison between normal weight, overweight and severely obese subjects, there was a strong association between BMI and fat intake as well as protein intake (Alfieri, Pomerteau, & Grace 1997). However, the association might be a result of under-reporting of non-protein energy intake(Voss et al. 1998).

Moderate alcohol consumers usually add alcohol to their daily energy intake rather than substituting it for food, thus increasing positive energy balance (Suter, Hasler, & Vetter 1997). It would seem surprising if their consumption of alcohol did not contribute directly to body weight. However, the relationship between alcohol consumption and body weight remains inconsistent (Jequier 1999). Epidemiological studies reported absence or weak positive relationships in men and strong inverse associations in women (Colditz et al. 1991;Suter, Hasler, & Vetter 1997;Westerterp-Plantenga & Verwegen 1999). A recent study of middle-aged British men found that heavy alcohol intake (>30g/d) is directly related to weight gain and obesity irrespective of the type of alcohol consumed (Wannamethee & Shaper 2003).

Under-reporting

Under-reporting of dietary intake in overweight and obese people is one of the problems in interpreting data from self-administered food frequency questionnaires. The relative validity of a food frequency questionnaire is usually assessed by comparing it with those of a reference method, such as weighed food records. Biomarkers, such as urinary nitrogen excretion that helps in the determination of protein intake, may also be used in nutrient intake validation (Kroke et al. 1999). The doubly labeled water is the only method that provides valid estimates of energy expenditure in free-living subjects (Hise et al. 2002;Kroke et al 1999). The doubly labeled water method is based on the

differential disappearance rates of the stable isotopes ^{2}H and ^{18}O. Urine samples are collected from participants before they drink the isotope mixture (≈0.10g $^{2}H_2O$/kg body weight and 0.15g $H_2{}^{18}O$/kg body weight and a rinsing solution of 100mL tap water) and another sample collected after participants were free to engage in their usual daily activities (Hise et al 2002;Kroke et al 1999).

Although studies using the doubly labeled water methods have shown the existence of under-reporting in many groups within the population, its use in large population studies is not practical because of the cost (Macdiarmid & Blundell 1998).

Black et al have introduced a measure of energy expenditure, depending on the fact that energy intake must equal energy expenditure, which was compared to the doubly labelled water method and has the ability to detect under-reporting in many subgroups of the population (Goldberg et al. 1991). In a review of 37 dietary studies providing 68 subgroups classified according to sex and dietary method (Black et al. 1991), under-reporting was determined based on the ratio of mean energy intake (EI): basal metabolic rate (BMR) below a cut-off which defined the minimum energy requirement compatible with survival. BMR can be calculated from standard equations (Department of Health 1991). 68% of these studies had a ratio of EI: BMR below the cut-offs. In these studies, under-reporting was found in both genders and across a wide range of ages and countries (Black et al 1991;Macdiarmid & Blundell 1998)

Under-reporting of dietary intake appears to be selective to certain foods. Obese people seem to under-report fatty foods and foods rich in carbohydrates rather than their total dietary intake (Heitmann & Lissner 1995;Lissner, Heitmann, & Bengtsson 2000).

However, a study of healthy middle-aged British women showed that although under-reporting is more common in people with higher BMI, it is not necessarily that these people are fat (using direct measure of body fat) (Samaras, Kelly, & Campbell 1999).

Physical activity

Increasingly, people tend to adopt sedentary life styles with low physical activity. Urbanisation is associated with motorised transport and mechanised equipment such as televisions, computers and video games, and all these factors have a negative effect on individual levels of physical activity (Prentice & Jebb 1995). Even in the workplace, computerisation and mechanisation have negatively influenced physical activity. For example it is estimated that one hour of average office work uses only 10 to 15 calories (Kirschmann & Kirschmann 1996). Only a small proportion of manual work now involves relatively high activity (World Health Organisation 1998).

Studies investigating the effect of television viewing estimated that men who watch television for more than 3 hours a day and women who watch television between 3 to 4 hours a day are twice as likely to be obese than those who view television less than one hour a day (Tucker LA & Bagwell M. 1991;Tucker LA & Friedman GM 1989). Buchowski and colleagues explain this by changes in energy balance. They observed that obese individuals choose to watch television as a form of leisure activity more often than non-obese individuals. As a result they reduce other forms of physical activity (Buchowski & Sun 1996;Fitzgerald et al. 1997;From The Centers For Disease Control And Prevention 1996).

Exercise is negatively associated with obesity and is considered one of the treatment options for obesity (Pescatello & VanHeest 2000;Weinstoch, Dai, & Wadden 1998) and weight control. Ross and Jansson presented the available evidence for physical activity as a means of weight reduction in two categories based on the study duration. Short term studies (<16wk) with exercise programs that increased energy expenditure by 2200 $kcal \cdot wk^{-1}$ and long term studies with energy expenditure of 1100 $kcal \cdot wk^{-1}$. In short-term trials, increases in physical activity were related to reductions in total adiposity in a dose-response manner, but there was insufficient evidence to determine a dose-response relationship in long term trials (Ross & Janssen 2001).

Although the negative association between physical activity level and body weight has been found in many cross-sectional studies, there are some methodological issues that hinder the ability to determine this association accurately (DiPietro 1995;Jebb & Moore 1999). These include the diverse definitions of physical activity and exercise and the absence of valid assessment instruments that can be used across studies (Wareham & Rennie 1998).

7.2 METHODS

Study populations

Details of the study populations have been described in chapter two. Contrary to chapter six, all offspring participating in 1996 (i.e. aged 30 to 59) were included in the analyses of this chapter.

Statistical analyses

Dietary intake was assessed using a modified version of the food frequency questionnaire developed by Yarnell et al (Yarnell et al 1983). The food frequency questionnaire included 50 questions on the weekly frequency of consumption of all the major food types, average daily milk intake, and family weekly consumption of cheese, cooking oil, butter and margarine. Alcohol intake was assessed by 7-day recall question and standard drinks were adjusted to the Scottish measures (Bolton-Smith et al 1991). Nutrient intakes were calculated using a computer program by multiplying food frequency by average portion size and nutrient values from the UK food composition tables (Paul & Southgate 1978). Nutrient intake calculation was done at Dundee University.

Foods were grouped into major food groups in order to study the patterns of daily intake of these food groups by study population as a whole and by population sub-groups. Foods included in each food groups are shown in **Appendix B**.

Under-reporting was estimated using the energy intake (EI): basal metabolic rate ratio (BMR). BMR was calculated from standard equation based on body weight and age.

The equations were (Department of Health 1991), page 202):

BMR (kcal/d), weight (kg)

BMR=11.4W+873 for men

BMR=8.3W+846 for women.

Two cut-off's were used 1.1, recommended by Doldberg et al 1991 (Goldberg et al 1991) and 1.28, recommended by the WHO (WHO 1985).

Reported physical activity was based in two questions about the usual daily activities and the frequency of non-working time physical activity.

The distribution of offspring BMI was divided into tertiles to compare the behavioural, environmental and parental characteristics of offspring with lower, medium and higher BMI. Testing for differences between BMI tertiles was assessed using ordinal logistic regression in a separate model for men and women. This analysis included all 2338 offspring aged 30 to 59 years. A similar analysis was repeated stratifying by social class separately for men and women. Statistical procedures were performed using STATA (StataCorp 1999).

Multiple linear regressions were run separately for men and women to investigate the different factors associated with BMI as continuous variable. These analyses provide a general idea about the type of association between BMI and the different variables.

Patterns of food consumptions in subgroups were studied by comparing means of estimated daily intake using the ANOVA test. Means (SD) and p-values were reported for each food group.

7.3 RESULTS

Characteristics of participants of Family Study

A total of 2338 participants took part in the Family Study in 1996, including 1040 (44.5%) men and 1298 (55.5%) women. Participants were aged between 30-59 years, with a mean (SD) age of 44.9(6.3) in men and 45.2(6.1) women.

Smoking status did not differ in men and women. 47% of women and 44% of men were never smokers and one quarter of men and women were current smokers (Table 7-1). Within the smoking group, 11% of women and 7% of men were light smokers (<14 cigarettes per day) while 3% of women and 7% of men were heavy smokers (>24 cigarettes per day). There was a lower prevalence of former smoking and a higher prevalence of current smoking men in these data, all offspring aged 30-59, compared to the finding reported in chapter six, population subgroup aged 45-59. Similar prevalences of smoking groups were found in women in the two data subsets. These differences are a result of age adjustment. Prevalences in this chapter where adjusted using the offspring population as a reference while the data in chapter six were adjusted using the Scottish Health Survey population as a reference population.

Over all, 69% of offspring were in the non-manual social class, 59% of men and 77% of women (Table 7-1).

Epidemiology of obesity in the offspring generation

This section describes the prevalence of obesity in offspring in different age, smoking and social class groups.

Prevalence of obesity and overweight

The prevalence of obesity (BMI≥30kg/m^2) was 18% in both men and women. The prevalence of obesity and/or overweight combined (BMI≥25kg/m^2) was 62% in men and 50% in women (Table 7-2). The prevalence of morbid obesity (BMI≥40kg/m^2) was about 1% in both men and women (Table 7-3). On the other hand, the prevalence of underweight (BMI<18.5kg/m^2) was almost 2% in women and less than 1% in men (Table 7-2).

Prevalence of Obesity with age

There was no clear pattern of obesity prevalence across age groups in men or women (Figure 7-1). The highest prevalences of obesity were 22% in men aged 45-49 and 21% in women aged 30-34 years. The lowest prevalence of obesity was 11% in men aged (35-39years) and 16% in women aged 50-54 years (Table 7-4).

Prevalence of obesity and smoking habit

The highest obesity prevalence was found in former smokers and the lowest prevalence in current smokers, in both men and women (Figure 7-2). Never smoking women had a relatively higher obesity prevalence compared to never smoking men. However, former and current smoking men had higher obesity prevalence compared to former and current smoking women (Table 7-5).

Prevalence of obesity and social class

The prevalence of obesity was higher in manual groups (20% in men and 23% in women) compared to non-manual groups in both men and women (16% in men and 17% in women, (Table 7-6).

Dietary intake patterns

Each participant provided a food intake record based on a 7-day food frequency questionnaire, allowing comparison of dietary patterns between sexes, smoking groups and social classes.

Dietary patterns in men and women

The patterns of estimated daily intake of food groups were different in men and women (Table 7-7). Total consumption of reported food groups was higher in men compared to women (2260 v 1649, p<0.001). Men reported higher consumption of bread (156 v 125g/d, p<0.001), red meat (59 v 51, p<0.001), potatoes (188 v 86g/d, p<0.001), sugar (21 v 8g/d, p<0.001), eggs (26 v 20g/d, p<0.001) and alcohol (560 v 70g/d, p<0.001), than women. Men also reported less consumption of breakfast cereals (21 v 24g/d, p=0.002), rice/pasta (79 v 86g/d, p=0.004), poultry (40 v 42g/d, p=0.008), fish (34 v 36g/d, p=0.005), green vegetables (80 v 96g/d, p>0.001), root vegetables (54 v 46g/d, p<0.001), fruits (102 v 119g/d, p<0.001), cheese (21 v 19g/d, p=0.002) and oil (7.3 v 5.4g/d, p<0.001) than women. There were no differences in reported levels of puddings, milk, butter, margarine and soft drinks between men and women.

Dietary patterns by smoking status

The total consumption of reported food groups was not different between smoking groups in men (p=0.138) and women (p=0.330). Men never smokers reported a high consumption of breakfast cereals, rice/pasta, poultry, puddings, milk, fruit and soft drinks compared to former and current smokers (Table 7-8). Men former smokers reported higher consumption of green vegetables, milk and cheese compared to other smoking groups. Men smokers reported higher consumption of red meat, offal, potatoes, sugar, eggs, cheese, butter, margarine, oil and alcohol.

Current and never smoking women had similar dietary intake to current and never smoking men. Never smoker women reported higher consumptions of breakfast cereals, poultry, pudding and fruit than former and current smoker women. Current smoking women reported high consumption of red meat, offal, potatoes, sugar, eggs, butter, margarine, oil and alcohol compared to other smoking groups. Former smoking women had higher intake of breakfast cereals, poultry and fish compared to current smoking women (Table 7-7).

The reported daily consumption of bread, root vegetables and fish was similar between the smoking groups in men, while, daily consumption of bread, rice/pasta, green and root vegetables, milk, cheese and soft drinks were similar between smoking groups in women (Table 7-8).

Dietary patterns by social class

Men and women had similar dietary pattern across the social class groups. Men and women in the two social groups reported similar level of reported consumption of breakfast cereals, fish, root vegetables, puddings and cheese. Further, women reported similar consumption patterns in milk, soft drinks and alcohol in the two social groups (Table 7-9). However, total consumption of reported food groups were higher in manual men compared to non-manual men (2348 v 2200g/d, p=0.004) but similar in women in manual and non-manual groups (1625 v 1655g/d, p=0.345)

Both men and women in the manual social class had reported a higher consumption of red meat (64 v 56g/d in men and 58 v 48g/d in women), offal (3.1 v 1.8g/d in men and 2.2 v 1.6g/d in women), potatoes (199 v 180g/d in men and 95 v 83g/d in women), sugar 28 v 17g/d in men and 12 v 7g/d in women), eggs (31 v 23g/d in men and 23 v 19g/d in women), butter (14 v 10g/d in men and 13 v 11g/d in women), margarine (17 v 12g/d in men and 17 v 12g/d in women) and oil (6.3 v 4.7g/d in men and 8.3 v 7.0g/d in women) than non-manual men and women. On the other hand, manual men and women had reported a lower consumption of rice/pasta (74 v 83g/d in men and 80 v 87g/d in

women), poultry (38 v 41g/d in men and 39 v 43g/d in women) and green vegetables (74 v 83g/d in men and 87 v 98g/d in women) than non-manual men and women.

In addition to the previous differences, manual men had reported higher consumption of bread (175 v 142g/d) and alcohol (661 v 488g/d) and lower consumption of soft drinks (157 v 183g/d) and milk (511 v 595g/d) than non-manual men.

Under-reporting

The prevalence of under-reporters, measured by the proportion of those having EI:BMR <1.1, was 22% in men and 13% in women (Table 7-24). A higher proportion of estimated under-reporters was found in the obese (BMI≥30kg/m^2) group compared to non-obese group (31 v 20% in men and 25 v 11% in women).

The prevalences of estimated under-reporting, using the WHO cut-off (1.28), were higher in men and women, 46% and 36% respectively. Obese group had higher prevalence of under-reporting compared to non-obese group in both men and women.

The prevalence of estimated under-reporting, using the 1.28 cut-off, was higher in non-manual men compared to manual men (56 v 33%, p<0.001), while there was no difference in the prevalence of under-reporting between manual and non-manual women (Table 7-24).

Environmental and behavioural factors associated with high BMI

This section describes the environmental and familial factors associated with high BMI. Environmental factors include social class, smoking, physical activity, nutrient intake and eating habits. Familial factors include parental obesity.

Men in the top tertile of BMI were 1.6 years older ($p<0.001$) than men in the lowest tertile (Table 7-10). There were no significant differences between tertiles in height or social class, but 34% of men in the top tertile were former smokers compared with 20% in the lowest tertile ($p<0.0001$). Individual and fathers social class did not differ between BMI tertiles. Men in the top tertile had a lower prevalence of physical activity (47 v 60% "very" or "fairly" active, $p<0.001$) and were more likely to own one or more car. Further they had higher serum cholesterol levels (5.6 v 5.1 mmol/l, $p<0.001$), higher systolic blood pressure (131 v 119mmHg, $p>0.001$), higher diastolic blood pressure (74 v 68mmHg, $p<0.001$) and lower HDL-cholesterol level (1.37 v 1.60mmol/l, $p<0.001$), and lower levels of carbohydrate intake (303 v 320 g/day, $p<0.01$)) compared with men in the lowest tertile (Table 7-10). 75% of those in the top tertile were on special diet to lose weight compared to only 22% of men in the lower tertile ($p<0.001$). 48% of men in the top tertile of BMI had parents in the top tertile of mid-parental BMI compared with 16% of men in the lowest tertile ($p<0.001$).

Looking at the mean sources of the macronutrients including protein, carbohydrate and fat using food groups, men in the top tertiles had higher daily consumption of poultry (42 v 37 g/d), green vegetables (83 v 76g/d), fruit (107 v 93g/d), milk (624 v 452g/d), cheese (21 v 18g/d) and soft drinks (188 v 148g/d) and a lower sugar intake (33 v 16g/d) than men in the lower tertile (Table 7-12). These results may appear counter-intuitive. However, those in the top tertile reported a higher level of food intake of all food items compared to those in the lower tertile (2346 v 2100g/d, $p<0.001$). The role of under-reporting as a likely explanation in this situation is discussed later.

Regression results show that BMI in men was positively associated with former smoking, manual social class, systolic blood pressure, serum cholesterol, lower level of physical activity and higher level of reported protein intake and negatively associated with current smoking, HDL-cholesterol and reported carbohydrate intake (Table 7-15).

All these factors explain 25.6% of BMI variation in men. In a simple linear regressions, smoking and physical activity were the important environmental factors associated with BMI variation, as well as blood pressure and cholesterol. Mid-parental BMI was positively associated with BMI in men and explained a further 12.7% of BMI variation. The model including both environmental and parental BMI explained 32.4% of BMI variation in men (Table 7-15).

Women in the top tertile of BMI were 1.0 year older ($p<0.05$) and 2.0 cm shorter ($p<0.001$) than women in the lowest tertile and a higher proportion (29 v 20%, $p<0.001$)) were in manual occupational groups and a higher percentage of them had a father with manual occupation (76 v 66%, $p=0.001$) (Table 7-13). 29% of women in the top tertile were former smokers compared with 20% in the lowest tertile ($p<0.001$). Women in the top tertile also reported less physical activity (49 v 64% "very" or "fairly" active, $p<0.001$), had lower serum cholesterol levels (4.5 v 4.9 mmol/l, $p<0.001$), lower HDL-cholesterol level (1.19 v 1.41mmol/l, $p<0.001$) but had higher systolic blood pressure (137 v 136mmHg, $p<0.001$) and diastolic blood pressure (76 v 83mmHg, $p<0.001$). There were no significant differences between women's tertiles in reported total intakes of energy, fat, carbohydrate or alcohol, but women in the top tertile had higher levels of protein intake (86 v 82 g/day, $p<0.05$). 91% of women in the top tertile were on a special diet to lose weight compared to 29% of those in the lower tertile (Table 7-14). Women in the top tertile appear to be on special diet for personal rather than medical reasons. 46% of women in the top tertile of BMI had parents in the top tertile of mid-parental BMI compared with 23% of women in the lowest tertile ($p<0.0001$).

Although fat, carbohydrate and alcohol intake were not associated with BMI, women in the top tertile reported a high daily consumption of offal including liver (2.1 v 1.6g/d), fish (38 v 34g/d), milk (575 v 510g/d), cheese (23 v 20g/d), and soft drinks (193 v 154g/d) but lower daily intake in sugar (6 v 13g/d) than women in the lower tertile (Table 7-12). Women in the top tertile reported higher level of total intake of all food items compared to those in the lower tertile (1682 v 1592g/d, p=0.002).

In women, results of regression models were similar to those in men (Table 7-16). Environmental factors and parental BMI explained 25.3% and 9.6% of BMI variation in separate regression models. Simple linear regression results showed that physical activity is the important environmental factor in predicting BMI. Smoking status however, explained only 1.4% of BMI variation compared to 2.5% explained by physical activity. A model combining both environmental and parental BMI explained 31.4% of BMI variation in women.

Environmental and behavioural factors associated with high BMI by social class

The above analyses were repeated in manual and non-manual groups separately. Comparison was done in three stages separately for men and women: 1. The top tertile was compared with the lower tertile of the manual group; 2. A similar comparison was made in the non-manual group; 3. Finally, subjects in the top tertile in the manual social class were compared to those in the top tertile in the non-manual social class.

1a. Manual men

Manual men in the top tertile had a lower proportion of current smokers (31 v 51%) than men in the lowest tertile (p=0.004). 37% of manual men in the top tertile reported a low level of physical activity compared to 26% in the lowest tertile (p=0.047). There was no significant difference in reported dietary intakes between men's tertiles. Men in the top tertile had significantly higher systolic (137 v 129mmHg, p<0.001) and diastolic (83 v 78mmHg, p<0.001) blood pressure and serum cholesterol level (5.5 v 5.1mmol/l, p<0.0001) than those in the lower tertile but lower level of HDL-cholesterol (1.18 v 1.48mmol/l, p<0.001). 49% of manual men in the top tertile had mid-parental BMI in the top tertile compared to 22% in the lowest tertile (Table 7-17).

BMI in manual men was negatively associated with current smoking status, carbohydrate intake and HDL-cholesterol and positively associated with protein intake, systolic blood pressure, serum cholesterol and mid-parental BMI (Table 7-19). Mid-parental BMI was the main predictor of offspring BMI. Smoking status was the main environmental factor in explaining BMI variation. Dietary factors including reported protein and carbohydrate explained BMI variation to a lesser extent than smoking status. These factors explained 31% of BMI variation in this group.

2a. Non-manual men

Non-manual men in the top tertile had a lower proportion of current (14.5 v 29%) smokers but a higher proportion of former smokers (36 v 19%) than men in the lowest tertile (<0.0001). Non-manual men reported low level of activity (66 v 51%, p=0.006), and had a higher serum cholesterol level (5.6 v 5.2mmol/l, p=0.001), higher systolic (137 v 124mm/Hg, <0.001) and diastolic blood pressure (82 v 74mmHg, <0.001) than men in the lowest tertile. There was no significant different between BMI tertiles in reported dietary intakes except for carbohydrate intake which was lower in the top tertile (284 v 314g/d, p=0.003). 47% of non-manual men had mid-parental BMI in the top tertile compared to 13% in the lowest tertile (Table 7-17).

The main predictors of BMI in non-manual men are shown in Table 7-19. BMI was positively associated with former smokers, systolic blood pressure, serum cholesterol and mid-parental BMI and negatively associated with HDL-cholesterol. These factors together explain 30% of the non-manual men BMI variation. The other determinants were not significantly associated with BMI and were not included in the model. Mid-parental BMI was the strongest predictor of BMI variation. Smoking status was the behavioural factor most significantly associated with BMI in non-manual men. Dietary factors were weaker in predicting BMI in non-manual men.

3a Manual and non-manual men

Comparing men in the top tertile of BMI in the manual and non-manual social classes, there was a higher proportion of current smokers (31 v 15%) and a lower proportion of never smokers (38 v 50%) in the manual social class compared to the non-manual social class (p<0.001). More men in the manual social class reported a high level of physical activity (63 v 34%, p<0.001) and higher levels of reported energy intake (2612 v 2340kcal/day, p<0.001), higher fat (87 v 76g/d, p<0.001), protein (101 v 93g/d, p<0.001) and carbohydrate intakes (325 v 284g/d, p<0.001) compared to the non-manual

group. The effect of parental BMI, systolic and diastolic blood pressure and serum cholesterol seem to be similar in the manual and non-manual groups (See above).

1b. Manual women

Manual women in the top tertile included fewer current smokers (27 v 56%) and more never smokers (42 v 23%) than manual women in the lowest tertile ($p<0.001$). Women in the top tertile had lower levels of reported energy (2014 v 2184kcal/day, $p=0.013$) fat (75 v 83g/d, $p=0.024$) and carbohydrate (245 v 265g/d, $p=0.026$) intakes and higher serum cholesterol level (5.4 v 5.0mmol/l, $p=0.012$), systolic (131 v 119mmHg, $p<0.001$) and diastolic (74 v 70mmHg, $p=0.002$) blood pressure compared to women in the lowest tertile (Table 7-18). 48% of manual women in the top tertile had parental BMI in the top tertile compared to 32% of women in the lowest tertile.

Adjusted results of regression show that BMI of women in the manual social class is negatively associated with HDL-cholesterol and current smoking status while positively associated with high systolic and diastolic blood pressure and mid-parental BMI (Table 7-19). Mid-parental BMI and systolic blood pressure were the main predictors of offspring BMI in linear regression models. Smoking status was the important environmental factor associated with BMI. Although, physical activity was associated with BMI, it explained less than 1% of BMI variation. The combination of all these factors explained 26% of BMI variation.

2b. Non-manual women

Non-manual women in the top tertile were 1.3years older ($p=0.01$) and 1.8cm shorter ($p<0.001$) than women in the lowest tertile. There were fewer current smokers (18 v 24%) and more former smokers (28 v 20%) in the top tertile than in the lowest tertile ($p=0.026$). Non-manual women in the top tertile reported higher level of inactivity (58 v 38%) than women in the lowest tertile. Higher systolic (131 v 119mmHg) and diastolic (74 v 68mmHg) blood pressure and serum cholesterol (5.4 v 4.9mmol/l) were found in

women in the top tertile. Reported dietary intakes were not associated with BMI in women in the non-manual group. 46% of non-manual women in the top tertile had parental BMI in the top tertile compared to 21% non-manual women in the lower tertile (Table 7-18).

Regression results show that factors associated with BMI in non-manual women are similar to those in the manual group and explained 31% of BMI variation. BMI was positively associated with blood pressure, serum cholesterol, and lower level of physical activity and mid-parental BMI but negatively associated with HDL-cholesterol and smoking (Table 7-19). However, physical activity was the main environmental factor explaining BMI variation. Smoking states explained less than 1% of BMI variation in non-manual women.

3b. Manual and non-manual women

Although there were more current and former smokers in the top tertile in the manual group than in the non-manual group, this difference was not significant (p=0.071). Further, manual women in the top tertile reported a higher level of physical activity than non-manual women (74 v 42%, p=0.001). There were no other differences between women in the top tertile in the manual and non-manual groups.

Small percentages of participants were on special diets (9%) and two-thirds of this group were on a diet for personal reasons. There was no difference between manual and non-manual groups in the percentage of those on a special diet (7% v 10%). However, 73% in the non-manual group were on a diet for personal reasons compared to 58% in the manual group (Table 7-22).

Nutrient intake in different social classes

Using macronutrients such as fat, carbohydrate and protein may not give a clear idea about the pattern of food intake in different social classes. This section describes the mean daily consumption in food groups rather than macronutrients.

Comparing those in the top tertile in the manual groups to those in the non-manual groups (Table 7-23), manual people had higher daily consumption of bread (164 v 132 g/d), red meat (61 v 54 g/d), offal including liver (3.1 v 2.1 g/d), potatoes (153 v 125 g/d), sugar (16 v 8 g/d), eggs (27 v 21g/d), butter (14 v 10 g/d), margarine (17 v 13 g/d), vegetable oil (6.6 v 5.7g/d), and alcohol (378 v 265 g/d); but they had lower daily consumption of rice and/or pasta (76 v 85 g/d), fish (33 v 38 g/d), green vegetables (81 v 94 g/d), fruit (105 v 115 g/d) and soft drinks (176 v 199 g/d).

7.4 DISCUSSION

The high prevalence of obesity in the offspring population was partially explained by environmental and behavioural factors and also by familial predisposition.

Although the offspring population had a slightly lower prevalence of obesity than that reported in the Scottish Health Survey, the percentages of obesity and overweight combined were similar. There is a higher prevalence of overweight in men compared to women and a higher prevalence of morbid obesity in women compared to men.

Correlates of high BMI

As obesity results from an imbalance between energy intake and energy expenditure, several factors act on either side or both sides of this formula. Family predisposition, behavioural, lifestyle and environmental factors were investigated in detail and discussed below.

Physical activity

The only measure of physical activity in this study was based on self-reporting, which might be subject to recall bias or inappropriate reporting. Gender and/or social class might also influence reported physical activity (Booth 1996).

Nevertheless, a clear negative relationship was found between the level of reported activity and obesity in both men and women. Lack of physical activity was a strong predictor of an increase in BMI, especially in women, after controlling for all possible confounders. Low physical activity was the main environmental factor associated with obesity in non-manual women.

Another possible indicator of physical activity is car ownership. Different associations were found in men and women. Men without a car were less likely to be obese whereas women were more likely to be obese. One possible explanation is that men without a car

have to walk and use public transport while women who do not have a car avoid going out and so, are more likely to be obese.

Dietary intake

In this study, dietary assessment was based on a 7-day food frequency questionnaire (FFQ). The validity of FFQs is usually assessed by comparing their data with those of a reference method, including repeated 24-h dietary recalls or weighed food records. Most studies indicated an acceptable relative validity of the FFQ. A study comparing FFQ with dietary recall, urinary nitrogen excretion and total energy expenditure (TEE) data, found that energy intake was under-reported when compared with TEE and protein intake was under-reported compared with urinary nitrogen (Kroke et al 1999). The FFQ used in this study was tested by Yarnell et al. They compared the FFQ with 7-day weighted dietary records and found that for major nutrients correlation coefficients of between 0.27 (carbohydrate) and 0.75 (alcohol) were obtained, both, which were statistically significant (Yarnell et al 1983).

Nevertheless, under-reporting is a weakness of food frequency questionnaires. The ratio of energy intake (EI) to estimated basal metabolic rate (BMR) is used to detect suspected under-reporting (Macdiarmid & Blundell 1998). It has been stated that an EI: BMR of 1.27 is the minimum value for survival and not compatible with long term health, thus people with EI: BMR less than 1.2 are classified as under-reporters (Goldberg et al 1991). The prevalence of under-reporting in this study was within the reported range by other studies (Black et al 1991). However, in this study the prevalence of under-reporting was higher in men than women. Consistent with the literature, the obese group had a higher prevalence of under-reporting than the non-obese group (Samaras, Kelly, & Campbell 1999). Further, non-manual men seem to under report more frequently than manual men.

In general, the dietary data used in this study were useful in describing the daily intakes of food groups in different subgroups, and these data were able to detect differences

between men and women, smoking and social class groups. The use of macronutrients was not very helpful in understanding the association with BMI, however it was good enough to detect differences between subgroups such as social classes.

Despite their shortcomings, food frequency questionnaires may be the most practicable method for studying the eating patterns of populations (Barrett-Connor 1991). The daily consumption of food groups was different in men and women. Alcohol and milk intake formed the food groups consumed most by men, followed by potatoes, soft drinks and bread intake. In women, milk intake was the largest food group consumed. Soft drinks intake was the second largest food group consumed by women followed by bread and fruit intake. Alcohol and potato consumption were less in women than men.

Our results are consistent with the Scottish Health Survey that reported an increase in the frequency of fruit consumption, soft drinks intake and potatoes, pasta or rice intake in the Scottish population over a five years period (SHS 1998). Comparing the results of our study to the Scottish Heart Health Study (SHHS) conducted in 1984-86, the offspring population consumes more milk, alcohol, vegetables and fruit and less bread and pudding, but similar cheese and butter intake (Bolton-Smith, Brown, & Tunstall-Pedoe 1991). An outstanding finding is the difference in reported daily consumption of soft drinks between our study and the Scottish Heart Health Study (SHHS). The mean daily intake of soft drinks in this study was almost four times higher that reported in the Scottish Heart Health Study in both men and women across the social groups.

The dietary data also revealed differences in dietary intake between smoking groups although they reported similar amounts. Our findings were consistent with the theory that smokers have unhealthy eating patterns compared to non-smokers (Dallongeville et al. 1998). Smoking was positively associated with alcohol and food groups rich in energy and fat in both men and women. The combination between smoking and unhealthy diet might intensify the effect of smoking on cancer and cardiovascular diseases development (Tarasuk & Brooker 1997).

A consistent finding was the negative association between high BMI and carbohydrate intake and this was supported by the low intake of sugar, bread, cereals and puddings, which are considered the main sources of carbohydrate. Because of the cross-sectional nature of the study, it is difficult to confirm whether this is a true association or was confounded by the high prevalence of under-reporting in this group. The association between reported protein intake and high BMI was found in men and women and remained significant after controlling for other factors. This finding supports the theory that a high level of reported protein intake might reflect the under-reporting of non-protein energy intake (Heitmann & Lissner 1995).

An interesting finding was the difference between reported macronutrients (including protein and carbohydrate) associations with BMI tertiles and BMI as a continuous variable. The association between reported macronutrients and BMI as a continuous variable appears to be more reliable because it is not subject to an arbitrary subdivision of the BMI distribution. Subjects in the top part of BMI distribution are more likely to under report unhealthy foods and so the association of macronutrients would be biased. On the other hand, the association of macronutrients across the BMI spectrum seems to be more reliable than restricting the association to those in the top tertile.

The use of BMI as a continuous variable and in tertiles was used for two reasons. BMI was used as continuous variable to get a general understanding of the associations with environmental, behavioural and familial factors in the whole population. BMI tertiles were used to specifically study the characteristics of those on the top part of BMI distribution compared to those in the lower part of BMI distribution, given the observation of anchoring and skewing reported in chapter six.

Metabolic syndrome precursors

Biological variables were also important factors in explaining the variation of BMI in the offspring population. Higher level of systolic and diastolic blood pressures and serum cholesterol were positively associated with high BMI. Regression results showed

that systolic blood pressure, total cholesterol and HDL-cholesterol explain a substantial part of BMI variation.

This type of relationship was recognised a long time ago, but the causal pathway is not yet clear. It is believed that obesity can induce multiple metabolic abnormalities, which include dyslipidemia (borderline-high cholesterol concentration, high triglyceride and LDL-cholesterol concentrations, and low HDL-cholesterol concentration), raised blood pressure, insulin resistance and glucose intolerance, and abnormalities in the coagulation system (procoagulant state). The cluster of these factors was observed and termed Syndrome X, the Insulin Resistance Syndrome, or the Multiple Metabolic Syndrome. It is believed that the metabolic syndrome is the precursor of cardiovascular disease and type 2 diabetes mellitus.

Finally, obesity is usually observed with high blood pressure. One of the hypotheses that explain this association is the discrepancy between the increased body mass and the unchanged filtration surface area, which leads to the development of hypertension. Another hypothesis emphasises the role of hyperinsulinemia caused by obesity. Studies assert that insulin resistance may affect the kidney by one or more of the following mechanisms: increasing sodium ion retention, activating the sympathetic nervous system, increasing vascular sensitivity to the vasoconstrictor effect and causing proliferation of arterial smooth muscle cells.

Results from genetic epidemiology studies have suggested that the various phenotypes associated with causes and manifestations of the metabolic syndrome are influenced by genetic factors. Whether shared genetic and/or environmental factors could be responsible for the clustering of metabolic syndrome is still under investigation by researchers.

Familial predisposition

Parental BMI is a key factor associated with high BMI in offspring. Men were three times more likely to be in the top tertile if they had parents in the top tertile of BMI compared to those in the lower tertile and women were almost twice as likely to be in the top tertile if they had parents in the top tertile.

In a univariate analysis, parental BMI explained 13% and 10% of men and women's BMI variations and remained a significant predictor of raised BMI after adjusting for other confounding factors. Further investigations of the familial resemblance of body mass index are presented in chapter eight.

Social class

Social class was an important determinant of high BMI in both men and women. A higher proportion of manual occupation and a lesser proportion of non-manual occupations were found in those with higher BMI. This observation was clearer for women. Social class and high BMI association is similar to that found in the parent generation (see Chapter Four) and consistent with the Scottish Health Study 1998 findings. Attitude and practices concerning weight control might explain this difference between social classes in women. In this study the proportion of women on a special diet was twice that among the men, and mainly they are on the diet for personal reasons. In the non-manual group, three individuals out of four reported being on a diet compared to one out of two in the manual group. These findings support the idea that lower prevalence of obesity in higher social class groups might be the result of higher frequency of weight control, as also reported in a study on British adults (Wardle & Griffith 2001).

Obesity was also influenced by paternal social class- i.e., social class during their childhood- especially in women. This supports the theory that childhood social class predicts the development of obesity in adult life (Stunkard & Sorensen 1993). The

strongest evidence supporting this theory is the adoption study in Denmark, in which there was a negative correlation between the social class of adoptive parents and the BMI of adoptees, but no relationship between the BMI of the adoptive parents and that of the adoptees (Teasdale, Sørensen, & Stunkard 1990). It is important to note that this conclusion is based on the assumption that paternal social class indicates the childhood condition, although, in this study, paternal social class was based on paternal occupation and was measured at one point in time.

The relationship of obesity and social class appears to be bidirectional, obesity influencing social class and vice versa (Stunkard & Sorensen 1993). However, there is the possibility of the influence of a common factor or factors that mediate or modify the relationship between obesity and social class. Heredity is one of the suspected factors. Results from the Danish adoptees studies suggested that socioeconomic status of biological parents influences the socioeconomic status of offspring through genetic contribution of IQ (Teasdale, Sørensen, & Stunkard 1990).

The nature of a cross-sectional survey limits the ability to determine the ways in which these factors are related. Both theories (obesity influences social class and social class influencing obesity) are supported in our study.

Social class differences in BMI correlates

Several studies have reported a higher obesity prevalence in manual groups, especially in women. The findings suggest gender specific associations and a complex relationship between lifestyle and behavioural factors in different social classes.

Similar to observations in of the general population, individuals in the top tertile of the BMI distribution had a family predisposition, were more likely to be never or former smokers and have a low level of physical activity in addition to the abnormal blood pressure and cholesterol profile.

Although smoking was the main behavioural factor associated with high BMI of men in both manual and non-manual social groups, current smoking status was negatively associated with BMI in men and former smoking status was positively associated with BMI in non-manual men. Although, macronutrients were not associated with BMI, daily food groups consumption show that manual men consumed large amounts of alcohol and this was highest in the smoking group. This implies that despite the fact that smoking is associated with low BMI, other lifestyle factors with which it is associated, promotes obesity or high BMI. Further, the manual occupation group itself has changed in the last few decades and involves less level of physical activity, which might promote increase in individual BMI.

In non-manual men, on the other hand, former smokers were more likely to have high BMI. Even though manual men have higher levels of daily food intake, dietary intakes were associated with the BMI of non-manual group but not the manual one.

Manual men in the top part of the BMI distribution have reported a higher level of physical activity and high energy, fat, protein and carbohydrate intakes than non-manual men in the top BMI tertile. It seems plausible that this may not reflect a genuine difference. Manual men may consider themselves more physically active as manual jobs involve more physical activity than non-manual jobs and this might explain the reporting of higher levels of physical activity in the manual group. Further, using car ownership as an index of sedentary lifestyle, non-manual men with a car were more likely to have high BMI compared to manual men with a car.

The effect of mid-parental BMI on offspring BMI was similar for women in both social groups. However, environmental factors were different between manual and non-manual women. Current smoking was the main factor associated with low BMI as in manual women. Physical inactivity was the main factor associated with high BMI in non-manual women. The only difference between manual and non-manual women in the top part of

BMI distribution was the high level of physical activity by manual women. There was no difference in dietary intake between the two groups.

7.5 Summary

The main findings in this chapter are listed below.

- The prevalence of obesity (BMI≥30kg/m^2) in the offspring generation was 18% in men and women. Moreover, two out of three men and one out of two women were overweight and/or obese (BMI≥25kg/m^2).

- The highest prevalence of obesity was found in former smokers and in the manual group, while the lowest prevalence was found in current smokers and in the non-manual group.

- Although dietary data were based on a reported food frequency questionnaire, which has the weakness of under reporting, the dietary data were sufficient to describe different food patterns in population subgroups.

- In general men reported high intakes of energy-dense food groups while women reported high intakes of healthier food elements.

- Dietary patterns were different between smoking and social class groups. Current smokers and the manual group reported high intakes of energy-dense foods. Alcohol was associated with smoking in men (especially manual men) and women.

- Mid-parental BMI was an important factor in predicting which men and women would be in the top tertile of the BMI distribution. Environmental factors affecting BMI were different in men and women. Smoking was the main factor affecting BMI in men while physical activity and smoking were the main factors affecting BMI in women. Reported nutrient intakes were associated with BMI as a continuous variable but not when divided into tertiles of BMI. Further, both men and women in the top tertile of BMI distribution reported high intakes of meat and fish, green vegetables and fruits, milk and cheese as well as soft drinks and low intake of sugar.

- There is a gender-specific and highly complex relation between lifestyle and behaviour in different social classes and obesity.

- Mid-parental BMI and smoking were the main correlates of BMI distribution in manual and non-manual men. However, manual men compared to non-manual men in the top tertile had higher levels of physical activity and macronutrient intake.

- In women, mid-parental BMI was the main determinant of BMI in manual and non-manual women. While smoking was the second main determinant of BMI in manual women, reported level of physical activity was the second main determinant of BMI in non-manual women. Manual women in the top tertile reported higher level physical activity than non-manual women in the top tertile.

- Although this study has included the main factors reported to be affecting obesity, other factors need to be investigated in longitudinal studies to be able to understand the mechanism by which these factors influence the social differences in obesity.

Table 7-1: Characteristics of Family Study population (number, %)

		Female	Male	Total
		1298	1040	2338
	Mean (SD)	45.2±6.1	44.9±6.3	
		62	56	118
Age groups	30-34	4.8%	5.4%	5.0%
		180	160	340
	35-39	13.9%	15.4%	14.5%
		337	266	603
	40-44	26.0%	25.6%	25.8%
		407	322	729
	45-49	31.4%	31.0%	31.2%
		225	172	397
	50-54	17.3%	16.5%	17.0%
		87	64	151
	55-59	6.7%	6.2%	6.5%
Smoking habit	Never	642	459	1101
		49.5%	44.1%	47.1%
	Former	330	317	647
		25.4%	30.5%	27.7%
	Current (1-14/day)	142	75	217
		10.9%	7.2%	9.3%
	Current (15-24/day)	140	113	253
		10.8%	10.9%	10.8%
	Current (>24/day)	44	76	120
		3.4%	7.3%	5.1%
Social class	Non-manual	1000	608	1608
		77.0%	58.5%	68.8%
	Manual	298	432	730
		23.0%	41.5%	31.2%

Table 7-2: Prevalence of BMI categories in men and women (number, %)

		Male	Female	Total
N	BMI	1040	1281	2321
Obesity groups	<18.5	9	20	29
		.9%	1.6%	1.2%
	18.5-24.9	385	624	1009
		37.0%	48.7%	43.5%
	25-29.9	460	405	865
		44.2%	31.6%	37.3%
	≥30	186	232	418
		17.9%	18.1%	18.0%

Table 7-3: Prevalence of morbid obesity by sex (number,%)

		Male	Female	Total
N	BMI	1040	1281	2321
Obesity groups	30-34.9	152	160	312
		14.6%	12.5%	13.4%
	35-39.9	27	54	81
		2.6%	4.2%	3.5%
	≥40	7	18	25
		.7%	1.4%	1.1%

Table 7-4: Prevalence of obesity (BMI≥30kg/m^2) in different age groups by sex (number, %)

		Male	Female
Total		186	232
Age groups	30-34	9	12
		16.1%	21.1%
	35-39	17	33
		10.6%	19.3%
	40-44	49	63
		18.4%	18.8%
	45-49	72	71
		22.4%	17.5%
	50-54	30	37
		17.4%	16.4%
	55-59	9	16
		14.3%	18.6%

Figure 7-1: Distribution of obesity prevalence in men and women by age groups

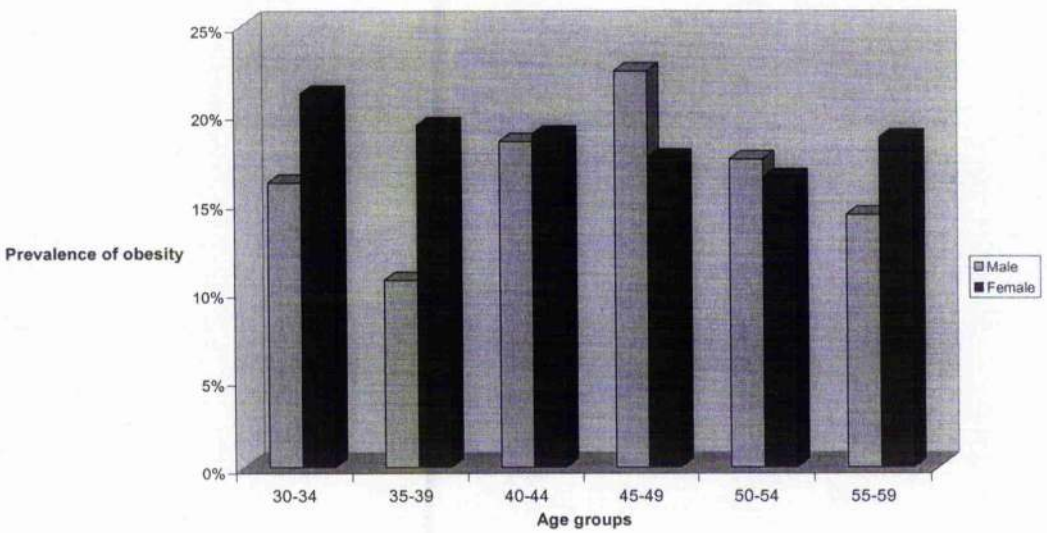


Table 7-5: Prevalence of obesity (BMI≥30kg/m^2) in different smoking groups by sex (number, %)

		Male	Female
		186	232
Smoking habit	Never smoker	77	120
		16.8%	19.0%
	Former smoker	68	64
		21.5%	19.6%
	Current smoker	41	48
		15.5%	14.9%

Figure 7-2: Distribution of obesity (BMI≥30kg/m^2) prevalence in men and women by smoking groups (number, %)

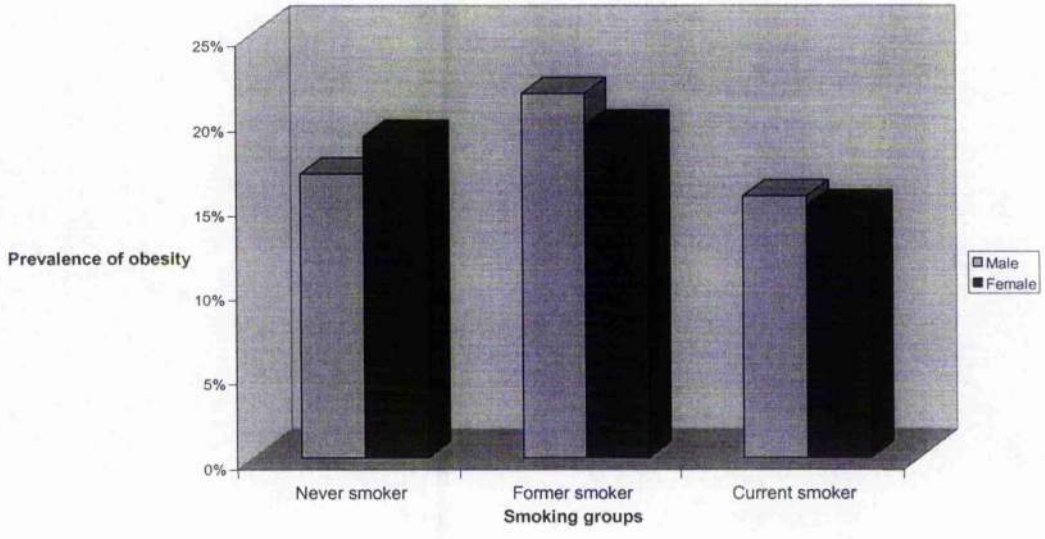


Table 7-6: Prevalence of obesity (BMI≥30kg/m^2) in social class groups by sex (number, %)

		Male	Female
		186	232
Social class	Non-manual	98	164
		16.1%	16.6%
	Manual	88	68
		20.4%	23.1%

Figure 7-3: Distribution of obesity or overweight prevalence (BMI≥25kg/m^2) in men and women by social class

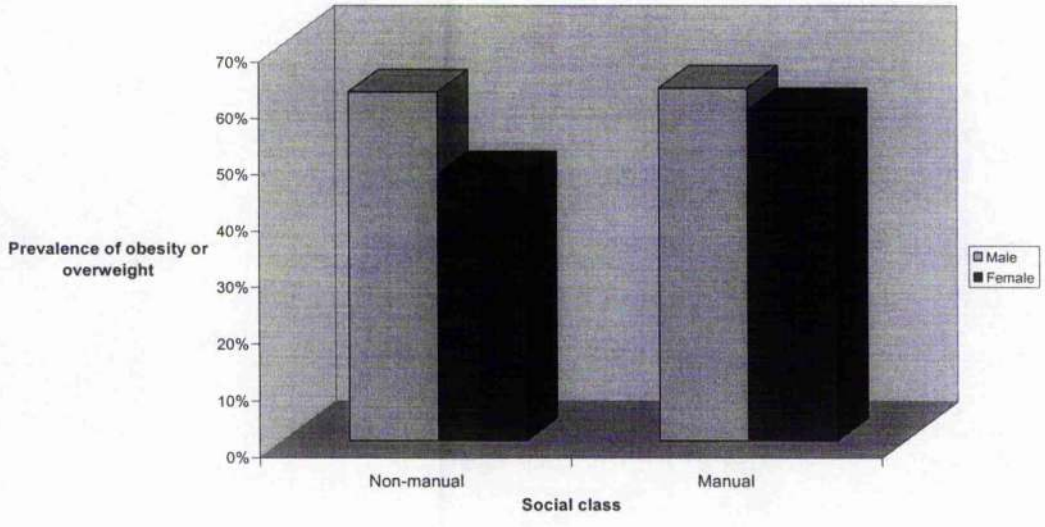


Table 7-7: Mean (SD) of daily consumption of food groups (g/d) in men and women

		Male	Female	p-value
Bread	Mean	155.6	124.6	0.000
	SD	86.8	68.0	
Cereals	Mean	21.0	23.6	0.002
	SD	19.2	20.0	
Rice/pasta	Mean	79.3	85.6	0.004
	SD	50.3	53.8	
Red meat	Mean	59.2	50.6	0.000
	SD	31.9	30.5	
Poultry	Mean	39.7	42.2	0.008
	SD	21.3	22.9	
Offal	Mean	2.3	1.7	0.000
	SD	4.6	3.8	
Fish	Mean	33.7	36.4	0.005
	SD	22.4	24.6	
Potatoes	Mean	187.6	85.8	0.000
	SD	79.7	38.8	
Green vegetables	Mean	79.5	95.8	0.000
	SD	41.2	44.4	
Root vegetables	Mean	46.3	54.2	0.000
	SD	31.2	35.4	
Sugar	Mean	21.1	8.4	0.000
	SD	30.9	20.1	
Pudding	Mean	67.3	66.4	0.670
	SD	51.2	47.6	
Fruits	Mean	102.3	119.0	0.000
	SD	78.1	70.1	
Egg	Mean	26.1	19.6	0.000
	SD	18.9	15.2	
Milk	Mean	559.9	551.9	0.603
	SD	393.7	350.6	
Cheese	Mean	19.0	21.3	0.002
	SD	17.0	18.2	
Butter	Mean	11.6	11.0	0.310
	SD	14.9	13.2	
Margarine	Mean	14.2	13.1	0.074
	SD	15.1	13.5	
Oil	Mean	5.4	7.3	0.000
	SD	4.2	6.8	
Soft drinks	Mean	172.2	171.2	0.819
	SD	106.9	104.5	
Alcohol	Mean	559.7	69.6	0.000
	SD	623.6	118.8	
Total	Mean	2260.3	1648.7	<0.001
	SD	761.0	457.3	

Table 7-8: Mean (SD) of daily consumption of food groups (g/d) by smoking status

		Male				Female			
		Never	Former	Current	P-value	Never	Former	Current	p-value
Bread	Mean	149.8	156.8	163.9	0.104	126.2	122.5	123.4	0.690
	SD	79.7	92.9	90.5		64.5	68.5	74.1	
Cereals	Mean	23.3	20.6	17.6	0.001	24.8	24.2	20.7	0.008
	SD	19.1	19.4	18.8		20.5	20.5	18.1	
Rice/pasta	Mean	84.4	78.9	71.1	0.003	85.8	86.5	84.1	0.839
	SD	50.6	48.7	50.8		53.9	50.2	57.0	
Red meat	Mean	54.6	58.2	68.4	0.000	47.8	47.5	59.2	0.000
	SD	30.5	29.7	34.9		29.6	27.6	33.4	
Poultry	Mean	42.3	39.7	35.4	0.000	43.2	44.8	37.5	0.000
	SD	21.3	20.7	21.4		22.4	23.5	22.5	
Offal	Mean	1.7	2.2	3.5	0.000	1.5	1.4	2.5	0.000
	SD	3.5	4.1	6.4		3.5	3.2	4.8	
Fish	Mean	33.9	33.8	33.1	0.893	36.4	39.5	33.3	0.006
	SD	23.0	21.2	22.9		24.0	27.3	22.6	
Potatoes	Mean	180.6	183.4	204.6	0.000	83.2	86.0	90.5	0.021
	SD	80.8	73.2	83.1		35.3	43.2	40.0	
Green vegetables	Mean	79.3	84.4	73.9	0.009	96.7	98.0	91.8	0.165
	SD	40.8	42.0	40.3		44.0	46.1	43.5	
Root vegetables	Mean	44.7	49.3	45.6	0.116	54.0	55.4	53.2	0.714
	SD	29.5	33.4	31.4		35.4	37.0	33.9	
Sugar	Mean	12.1	19.8	38.3	0.000	5.1	4.8	18.8	0.000
	SD	20.8	28.1	40.3		13.7	13.3	30.5	
Pudding	Mean	71.8	65.7	61.3	0.024	72.8	63.3	56.9	0.000
	SD	52.0	49.3	51.6		49.8	41.4	47.3	
Fruits	Mean	111.7	108.8	78.2	0.000	127.1	123.3	98.8	0.000
	SD	82.0	79.5	63.5		73.1	66.1	64.1	
Egg	Mean	21.5	27.5	32.3	0.000	17.5	19.0	24.5	0.000
	SD	17.3	18.7	19.6		14.1	14.5	17.1	
Milk	Mean	585.6	597.3	470.4	0.000	552.0	561.8	541.7	0.764
	SD	377.0	376.8	428.0		337.7	326.6	396.6	
Cheese	Mean	17.5	20.1	20.4	0.034	20.4	21.8	22.4	0.253
	SD	14.3	19.9	17.4		18.3	18.1	18.0	
Butter	Mean	9.2	12.0	15.3	0.000	10.4	9.9	13.4	0.001
	SD	12.1	14.1	18.8		12.2	12.4	15.4	
Margarine	Mean	12.8	13.3	17.6	0.000	12.0	13.7	14.8	0.006
	SD	11.9	13.4	20.4		11.9	13.2	16.4	
Oil	Mean	4.9	5.5	6.1	0.001	7.0	7.2	8.1	0.045
	SD	3.9	4.2	4.5		6.4	6.5	7.8	
Soft drinks	Mean	193.0	169.3	139.6	0.000	174.4	174.9	161.2	0.136
	SD	104.8	106.8	102.6		101.2	102.7	112.0	
Alcohol	Mean	484.0	566.9	682.6	0.000	56.0	74.5	91.4	0.000
	SD	555.5	566.7	766.7		81.0	106.1	176.4	
Total	Mean	2220.4	2335.7	2260.3	0.138	1648.8	1675.8	1619.3	0.330
	SD	715.7	725.6	762.1		448.4	428.3	503.1	

Table 7-9: Mean (SD) of daily consumption of food groups (g/d) by social class

		Male			Female		
		Non-manual	Manual	p-value	Non-manual	Manual	p-value
Bread	Mean	142.0	174.7	<0.001	123.4	128.5	0.210
	SD	78.6	93.9		67.7	69.2	
Cereals	Mean	21.3	20.6	0.582	23.4	24.3	0.509
	SD	18.5	20.2		20.1	19.7	
Rice/pasta	Mean	83.3	73.8	0.003	87.2	80.1	0.046
	SD	48.9	51.8		52.4	57.8	
Red meat	Mean	55.9	63.9	<0.001	48.4	57.7	<0.001
	SD	30.5	33.2		28.9	34.3	
Poultry	Mean	41.1	37.8	0.015	43.2	38.7	0.003
	SD	20.9	21.8		22.5	23.9	
Offal	Mean	1.8	3.1	<0.001	1.6	2.2	0.017
	SD	3.6	5.7		3.5	4.7	
Fish	Mean	33.5	33.8	0.838	37.0	34.5	0.122
	SD	21.9	23.2		24.1	26.3	
Potatoes	Mean	179.5	198.9	<0.001	82.9	95.4	<0.001
	SD	76.4	83.0		36.5	44.4	
Green vegetables	Mean	83.2	74.3	0.001	98.3	87.3	<0.001
	SD	41.4	40.4		44.4	43.6	
Root vegetables	Mean	44.9	48.3	0.078	54.0	54.7	0.761
	SD	30.0	32.9		34.7	37.6	
Sugar	Mean	16.5	27.6	<0.001	7.3	12.4	<0.001
	SD	28.1	33.3		18.9	23.5	
Pudding	Mean	66.7	68.0	0.678	65.9	67.9	0.519
	SD	51.5	50.9		46.1	52.5	
Fruits	Mean	104.1	99.8	0.378	123.1	105.3	<0.001
	SD	79.6	76.0		72.0	61.8	
Egg	Mean	22.7	30.8	<0.001	18.5	23.3	<0.001
	SD	17.8	19.3		14.9	15.7	
Milk	Mean	594.5	511.3	0.001	553.8	545.5	0.720
	SD	371.3	418.8		343.4	374.0	
Cheese	Mean	18.4	19.9	0.154	21.4	21.0	0.742
	SD	15.5	18.9		17.8	19.5	
Butter	Mean	10.1	13.8	<0.001	10.6	12.5	0.032
	SD	13.3	16.6		12.6	14.9	
Margarine	Mean	12.4	16.7	<0.001	11.9	17.2	<0.001
	SD	13.5	16.7		11.9	17.4	
Oil	Mean	4.7	6.3	<0.001	7.0	8.3	0.004
	SD	3.7	4.6		6.5	7.5	
Soft drinks	Mean	182.8	157.4	<0.001	172.6	166.6	0.382
	SD	104.5	108.7		104.1	105.8	
Alcohol	Mean	487.5	661.3	<0.001	69.0	71.5	0.758
	SD	564.2	686.5		109.4	146.3	
Total	Mean	2200.4	2348.3	0.004	1655.4	1625.0	0.345
	SD	726.3	802.4		450.1	481.9	

Table 7-10: Characteristics of men in tertiles[1] of their BMI distribution.

		Low	Medium	High	L-M	L-H	M-H
BMI (mean)		**22.1**	**26.1**	**30.9**			
Age (mean (SE))		44.0 (0.4)	44.7 (0.31)	45.6 (0.31)	0.185	**0.001**	**0.032**
Height (mean (SE))		175.3(4.1)	175.1(3.1)	174.7(3.4)	0.735	0.28	0.388
Waist (mean(SE))		82.1 (0.35)	91.2 (0.24)	103.8 (0.43)	**<0.0001**	**<0.0001**	**<0.0001**
Social class (%)	Non-manual	57.3	62.5	55.2	0.192	0.629	**0.02**
	Manual	42.7	37.5	44.8			
Smoking status (%)	Never smoker	41.6	45.7	44.3	**<0.0001**	**<0.0001**	0.78
	Former smoker	19.8	34.4	33.7			
	Current smoker	38.5	19.9	22.0			
Biological measurements	Systolic blood pressure (mmHg)	118.7 (0.63)	123.8 (0.76)	130.6 (0.63)	**<0.0001**	**<0.0001**	**<0.0001**
	Diastolic blood pressure (mmHg)	68.3 (0.44)	70.9 (0.47)	74.1 (0.51)	**<0.0001**	**<0.0001**	**<0.0001**
	Serum cholesterol (mmol/l)	5.1 (0.9)	5.4 (0.96)	5.6 (1.0)	**0.002**	**<0.0001**	**0.004**
	HDL-cholesterol	1.60 (0.017)	1.49 (0.019)	1.37 (0.018)	**<0.0001**	**<0.0001**	**<0.0001**
Paternal social class	Non-manual	35.0	31.6	29.6	0.208	0.088	0.299
		65.0	68.4	70.4			
Mid-parental tertiles[2] (%)	Low	53.8% (141)	35.5% (139)	18.4% (71)	**<0.0001**	**<0.0001**	**<0.0001**
	Medium	29.4% (77)	37.1% (145)	33.5% (129)			
	High	16.4% (44)	27.4% (107)	48.1% (185)			

[1] Low tertile: BMI<24.6 kg/m2, medium: BMI 24.6-27.8 kg/m2, high: BMI >27.8 kg/m2
[2] Low tertile: BMI <24.6 kg/m2, medium: BMI 24.6-27.0 kg/m2, high: BMI >27.0 kg/m2

Table 7-11: Physical activity and dietary intake of men in tertiles[1] of their BMI distribution

		Low	Medium	High	L-M	L-H	M-H
Physical activity (%)	Very physical active	11.5	7.7	6.5	0.106	**0.009**	**0.022**
	Fairly physical active	48.1	45.2	40.5			
	Not very physically active	32.8	41.1	43.4			
	Not at all physical active	7.6	6.1	9.6			
Car ownership (%)	None	18.7	10.7	8.5	0.003	**<0.001**	0.184
	One or more	81.3	89.3	91.5			
Nutrient intake	Energy intake, kcal/day (SE)	2520.2 (38.3)	2439.6 (32.2)	2462 (29.9)	0.109	0.232	0.601
	Total fat intake (g/d)	81.6 (1.6)	78.1 (1.3)	80.9 (1.3)	0.099	0.75	0.129
	Total protein intake (g/d)	92.8 (1.4)	90.8 (1.1)	96.1 (1.1)	0.247	0.068	**0.001**
	Total carbohydrate intake (g/d)	320.3 (5.5)	301.7(4.0)	302.6 (4.2)	**0.005**	**0.01**	0.88
	Alcohol	22.3 (1.3)	25.4 (1.3)	24.4 (1.15)	0.119	0.246	0.563
Special diet		6.1	3.6	5.4	**0.033**	0.442	0.218
On diet to lose weight		21.5	42.9	75.0	0.300	**<0.0001**	0.580
Diet recommended by	Myself	37.5	50.0	38.1	0.865	0.261	**0.007**
	Medical staff	56.3	42.9	47.6			

[1] Low tertile: BMI<24.6 kg/m2, medium: BMI 24.6-27.8 kg/m2, high: BMI >27.8 kg/m2

Table 7-12: Mean (SD) daily consumption by food groups for men and women

		Male				Female			
		1	2	3	p-value	1	2	3	p-value
Bread	Mean	156.9	151.3	159.0	0.764	121.6	123.2	129.2	0.098
	SD	84.6	85.9	89.1		66.5	67.3	70.5	
Cereals	Mean	21.8	20.8	20.7	0.457	24.0	23.7	22.6	0.317
	SD	20.7	19.2	18.1		20.0	19.6	20.2	
Rice/pasta	Mean	78.5	80.7	78.5	0.998	83.2	89.6	84.1	0.805
	SD	49.6	51.0	50.3		52.6	55.1	53.8	
Red meat	Mean	58.4	57.0	62.1	0.148	50.0	51.1	51.7	0.412
	SD	34.0	31.4	30.8		32.1	30.6	27.9	
Poultry	Mean	37.0	39.6	41.7	0.006	41.3	42.8	42.7	0.380
	SD	21.2	21.4	21.2		23.0	21.8	24.0	
Offal	Mean	2.2	1.9	2.9	0.090	1.6	1.6	2.1	0.056
	SD	4.3	4.0	5.4		3.4	3.3	4.7	
Fish	Mean	35.1	32.6	33.8	0.499	34.5	36.7	38.2	0.033
	SD	24.3	20.7	22.9		24.2	22.3	27.2	
Potatoes	Mean	194.3	185.4	185.2	0.168	85.6	86.0	86.4	0.741
	SD	87.6	75.6	78.2		39.5	37.5	39.2	
Green vegetables	Mean	75.5	79.2	82.6	0.030	92.8	100.3	95.4	0.386
	SD	37.6	42.2	42.3		44.4	44.8	44.3	
Root vegetables	Mean	45.4	45.4	47.9	0.312	50.7	57.9	54.9	0.067
	SD	30.6	31.5	31.5		33.6	36.9	36.1	
Sugar	Mean	33.0	18.1	16.1	<0.001	13.3	4.6	6.0	<0.001
	SD	39.7	26.1	26.0		25.1	13.9	16.7	
Pudding	Mean	70.7	65.2	66.9	0.374	65.1	67.3	66.8	0.611
	SD	60.6	47.9	47.4		48.2	44.2	50.3	
Fruits	Mean	93.3	104.0	106.7	0.028	117.8	121.2	116.4	0.755
	SD	63.7	82.0	82.6		74.6	68.9	64.4	
Egg	Mean	28.7	24.2	26.2	0.109	18.5	19.9	20.7	0.034
	SD	20.3	18.8	17.6		15.4	14.6	15.6	
Milk	Mean	452.3	568.8	624.0	<0.001	510.1	580.5	574.5	0.007
	SD	404.5	371.6	393.7		367.8	341.9	331.7	
Cheese	Mean	17.9	18.4	20.5	0.073	19.9	20.9	23.5	0.005
	SD	18.8	15.5	17.2		14.7	15.5	24.0	
Butter	Mean	12.3	10.6	12.1	0.839	11.4	10.5	11.1	0.761
	SD	14.1	14.7	15.5		13.1	12.9	13.7	
Margarine	Mean	13.7	13.7	15.0	0.260	13.7	12.0	13.5	0.883
	SD	15.2	15.6	14.4		14.7	13.0	12.0	
Oil	Mean	5.3	5.6	5.2	0.600	7.5	7.6	6.9	0.204
	SD	4.1	4.3	4.1		7.1	6.9	6.2	
Soft drinks	Mean	147.7	173.5	187.6	<0.001	154.4	169.8	193.4	<0.001
	SD	103.5	107.1	106.4		102.5	105.1	102.3	
Alcohol	Mean	524.0	592.1	551.0	0.575	76.6	68.5	63.8	0.138
	SD	613.3	660.1	591.5		143.4	97.8	102.7	
Total	Mean	2100.0	2293.6	2346.0	<0.001	1591.6	1689.5	1681.8	0.002
	SD	760.1	753.7	753.8		474.3	442.4	435.9	

Table 7-13: Characteristics of women in tertiles[1] of their BMI distribution.

		Low	Medium	High	L-M	L-H	M-H
BMI (mean)		**21.2**	**24.9**	**31.4**			
Age (mean (SE))		44.6 (0.27)	46 (0.29)	45.6 (0.31)	**<0.0001**	**0.014**	0.322
Height (mean (SE))		162 (2.6)	160.9 (2.8)	160.5 (3.1)	**0.007**	**0.0001**	0.315
Waist (mean(SE))		70.4 (0.23)	79.4 (0.30)	93.6 (0.53)	**<0.0001**	**<0.0001**	**<0.0001**
Social class (%)	Non-manual	80.4	78.5	71.1	0.502	**0.001**	**0.01**
	Manual	19.6	21.5	28.9			
Smoking status(%)	Never smoker	49.5	48.4	50.3	**0.006**	**0.001**	0.72
	Former smoker	20.4	28.5	29.1			
	Current smoker	30.1	23.0	20.6			
Biological measurements	Systolic blood pressure (mmHg)	126.4 (0.96)	129.0 (0.68)	136.8 (0.66)	**0.023**	**<0.0001**	**<0.0001**
	Diastolic blood pressure (mmHg)	75.6 (0.66)	78.7 (0.51)	82.5 (0.56)	**0.002**	**<0.0001**	**<0.0001**
	Serum cholesterol (mmol/l)	4.9 (0.89)	5.3 (0.98)	4.5 (0.92)	**<0.0001**	**<0.0001**	0.15
	HDL-cholesterol	1.41 (0.023)	1.30 (0.018)	1.19 (0.016)	**<0.0001**	**<0.0001**	**<0.0001**
Paternal social class	Non-manual	34.3	31.9	24.4	0.250	**0.001**	**0.012**
	Manual	65.7	68.1	75.6			
Mid-parental tertiles[2] (%)	Low	45.5% (232)	27.4% (104)	21.6% (84)	**<0.0001**	**<0.0001**	**0.022**
	Medium	31.2% (159)	35.8% (136)	32.0% (124)			
	High	23.3% (119)	36.8% (140)	46.4% (180)			

[1] Low tertile: BMI<23.2 kg/m2, medium: BMI 23.2-26.9 kg/m2, high: BMI >26.9 kg/m2
[2] Low tertile: BMI <24.6 kg/m2, medium: BMI 24.6-27.0 kg/m2, high: BMI >27.0 kg/m2

Table 7-14: Physical activity and dietary intake of women in tertiles[1] of their BMI distribution

		Low	Medium	High	L-M	L-H	M-H
Physical activity(%)	Very physical active	9.2	3.7	4.9	**0.003**	**<0.001**	0.204
	Fairly physical active	55.2	55.0	43.8			
	Not very physically active	31.3	34.0	41.8			
	Not at all physical active	4.3	7.3	9.5			
Car ownership (%)	None	14.9	12.6	19.6	0.187	**0.038**	**0.005**
	One or more	85.1	87.4	80.4			
Nutrient intake	Energy intake, kcal/day	2104 (21.5)	1995.1 (23.5)	2015 (24.9)	0.54	0.97	0.545
	Total fat intake (g/d)	72.6 (1.0)	71.3 (1.2)	73.1 (1.2)	0.41	0.78	0.305
	Total protein intake (g/d)	82.4 (0.81)	84.4 (0.98)	85.6 (1.0)	0.12	**0.015**	0.404
	Total carbohydrate intake (g/d)	250.3 (2.9)	244.2 (3.2)	245.9 (3.4)	0.163	0.321	0.722
	Alcohol	8.1 (0.36)	8.9 (0.41)	7.8 (0.45)	0.145	0.549	0.061
Special diet		6.9	11.3	20.1	**0.006**	**<0.0001**	**<0.0001**
On diet to lose weight		28.6	76.7	91.0	**<0.0001**	**<0.0001**	**<0.0001**
Diet recommended by	Myself	54.3	83.7	78.2	**0.002**	**0.002**	0.91
	Medical staff	42.9	14.0	19.2			

[1] Low tertile: BMI<23.2 kg/m2, medium: BMI 23.2-26.9 kg/m2, high: BMI >26.9 kg/m2

Table 7-15: Regression results for BMI in men using different predictors

Best-fit model including environmental predictors in men

BMI	β	95% CI	P-value	R^2 (univariate model)
Age	0.00	(-0.04_0.04)	0.934	0.5%
Smoking: never				
Former	0.76	(0.22_1.31)	0.006	2.7%
Current	-1.43	(-2.03_-0.84)	<0.001	
Manual social class	0.89	(0.38_1.40)	0.001	0.5%
Physical activity: very active				
Fairly active	0.70	(-0.17_1.57)	0.115	2.0%
Not very active	1.27	(0.36_2.19)	0.006	
Not at all active	1.19	(0.02_2.36)	0.046	
Protein	0.04	(0.03_0.06)	<0.001	1.5%
Carbohydrate	-0.01	(-0.01_-0.01)	<0.001	1.0%
Systolic blood pressure	0.07	(0.05_0.09)	<0.001	9.7%
Cholesterol	0.43	(0.16-0.69)	0.002	2.7%
HDL-cholesterol	-3.89	(-4.61_-3.17)	<0.001	7.2%
R^2=25.6%				

Best-fit model including parental BMI predictors in men

BMI	β	95% CI	P-value
Age	0.03	(0.00_0.07)	0.072
Mid-parental BMI	0.47	(0.40_0.55)	<0.001
R^2= 12.7%			

Best-fit model including environmental and parental BMI predictors in men

BMI	β	95% CI	P-vlaue
Age	-0.01	(-0.05_0.02)	0.510
Smoking: never			
Former	0.54	(0.02_1.07)	0.042
Current	-1.40	(-1.96_-0.83)	<0.001
Manual social class	0.71	(0.22_1.20)	0.004
Physical activity: very active			
Fairly active	0.47	(-0.36_1.31)	0.266
Not very active	0.97	(0.09_1.84)	0.030
Not at all active	1.14	(0.03_2.26)	0.045
Protein	0.04	(0.02_0.05)	<0.001
Carbohydrate	-0.01	(-0.01_0.00)	<0.001
Systolic blood pressure	0.07	(0.05_0.08)	<0.001
Cholesterol	0.46	(0.21_0.72)	<0.001
HDL-cholesterol	-3.56	(-4.25_-2.87)	<0.001
Mid-parental BMI	0.35	(0.27_0.43)	<0.001
R^2=32.4%			

Table 7-16: Regression results predicting BMI in women using different predictors

Best-fit model including environmental predictors in women				
BMI	**β**	**95% CI**	**P-value**	**R^2 (univariate model)**
Age	-0.07	(-0.11_-0.03)	0.002	0.1%
Smoking: never				
Former	0.44	(-0.16_1.04)	0.149	1.4%
Current	-1.80	(-2.42_-1.17)	<0.001	
Manual social class	0.81	(0.20_1.41)	0.009	1.0%
Fathers social class	0.88	(0.33-1.42)	0.002	1.0%
Physical activity: very active				
Fairly active	0.14	(-0.91_1.20)	0.790	2.5%
Not very active	1.40	(0.31_2.50)	0.012	
Not at all active	1.49	(0.09_2.88)	0.036	
Protein	0.04	(0.02_0.05)	<0.001	1.0%
Carbohydrate	-0.01	(-0.02_-0.01)	<0.001	0.04%
Systolic blood pressure	0.09	(0.07_0.10)	<0.001	11.1%
Cholesterol	0.87	(0.59_1.15)	<0.001	4.2%
HDL-cholesterol	-4.01	(-4.70_-3.31)	<0.001	7.5%
R^2=25.3%				

Best-fit model including parental BMI predictors in women			
BMI	**β**	**95% CI**	**P-value**
Age	0.02	(-0.03_0.06)	0.422
Mid-parental BMI	0.53	(0.44_0.61)	<0.001
R^2=9.6%			

Best-fit model including environmental and parental BMI predictors in women			
BMI	**β**	**95% CI**	**P-value**
Age	-0.08	(-0.12_-0.04)	<0.001
Smoking: never			
Former	0.46	(-0.11_1.04)	0.115
Current	-1.85	(-2.45_-1.25)	<0.001
Manual social class	0.60	(0.02_1.19)	0.043
Fathers social class	0.59	(0.06-1.11)	0.028
Physical activity: very active			
Fairly active	0.24	(-0.77_1.26)	0.637
Not very active	1.52	(0.46_2.57)	0.005
Not at all active	1.76	(0.43_3.10)	0.010
Protein	0.02	(0.01_0.04)	0.006
Carbohydrate	-0.01	(-0.01_0.00)	0.004
Systolic blood pressure	0.08	(0.07_0.10)	<0.001
Cholesterol	0.87	(0.59_1.14)	<0.001
HDL-cholesterol	-3.74	(-4.41_-3.07)	<0.001
Mid-parental BMI	0.42	(0.34_0.51)	<0.001
R^2=31.4%			

Table 7-17: Characteristics of sons in tertiles[1] of their BMI distribution in manual and non-manual groups.

	Manual				Non-manual				
	Low	Medium	High	L-H	Low	Medium	High	L-H	M-NM
	112	147	173		150	245	213		
BMI	21.7	25.6	30.9		22.1	25.5	30.4		
Age	44.8(0.64)	45.4(0.52)	46.1(0.46)	0.086	43(0.52)	44.2(0.39)	45.2(0.41)	0.007	0.155
Height	173.7(5.9)	174.2(4.8)	173.3(4.9)	0.63	176.5(5.4)	175.7(4.1)	1758(4.6)	0.38	**<0.001**
Smoking %									
Never	28.6	34.0	37.6	**0.004**	51.3	52.7	49.8	**<0.001**	**<0.001**
Former	20.5	39.5	31.2		19.3	31.4	35.7		
Current	50.9	26.5	31.2		29.3	15.9	14.5		
Physical activity									
Highly active	74.1	78.2	62.8	**0.047**	48.7	37.5	34.3	**0.006**	**<0.001**
Not active	25.9	21.8	37.2		51.3	62.5	65.7		
Car ownership %	26.8	21.8	13.9	**0.006**	12.7	4.1	4.2	**0.003**	**0.001**
	73.2	78.2	86.1		87.3	95.9	95.8		
Energy	2629(59.4)	2679(54.7)	2612(48.3)	0.84	2443(49.1)	2296(36.6)	2340(35.1)	0.082	**<0.001**
Fat	86.8(2.6)	85.5(2.2)	87.0(2.3)	0.95	77.8(2.1)	73.7(1.6)	75.9(1.5)	0.452	**<0.001**
Protein	96.9(2.3)	96.2(1.8)	100.5(1.8)	0.22	89.8(1.7)	87.6(1.2)	92.6(1.4)	0.21	**<0.001**
Carbohydrate	329(8.4)	324(6.9)	325(7.1)	0.74	314(7.1)	288(4.8)	284(4.7)	**0.003**	**<0.001**
Systolic blood pressure	129.1(1.7)	129.2(1.1)	136.7(1.1)	**<0.001**	124.4(1.1)	128.9(0.9)	136.8(1.1)	**<0.001**	0.966
Diastolic blood pressure	77.5(1.1)	78.7(0.79)	82.7(0.83)	**<0.001**	74.2(0.78)	77.9(0.65)	82.3(1.1)	**<0.001**	0.736
Cholesterol	5.1±0.9	5.4±1.0	5.5±0.94	**<0.001**	5.2±0.89	5.4±0.90	5.6±1.04	**0.001**	0.361
HDL-cholesterol	1.48(0.05)	1.37(0.04)	1.18(0.02)	**<0.001**	1.35(0.03)	1.26(0.02)	1.19(0.02)	**<0.001**	0.646
Mid-parental tertiles2									
Low	50.9	34.3	14.0	**<0.001**	56.0	36.3	22.1	**<0.001**	0.087
Medium	26.8	25.6	36.6		31.3	38.0	31		
High	22.3	30.1	49.4		12.7	25.7	46.9		

1 Low tertile: BMI<24.6 kg/m2, medium: BMI 24.6-27.8 kg/m2, high: BMI >27.8 kg/m2
2 Low tertile: BMI <24.6 kg/m2, medium: BMI 24.6-27.0 kg/m2, high: BMI >27.0 kg/m2

Table 7-18: Characteristics daughters in tertiles[1] of their BMI distribution in manual and non-manual groups.

	Manual				Non-manual				
	Low	**Medium**	**High**	**L-H**	**Low**	**Medium**	**High**	**L-H**	**M-NM**
	100	82	112		411	300	276		
BMI	21.3	25.7	32.1		21.7	25.4	31.8		
Age	45.2(0.75)	46.5(0.65)	45.8(0.59)	0.544	44.5(0.29)	45.9(0.33)	45.8(0.36)	**0.01**	0.745
Height	160.4(5.2)	160.5(6.9)	160.4(6.7)	0.998	162.4(2.9)	161.1(3.1)	160.6(3.7)	**<0.001**	0.797
Smoking %									
Never	23.0	39.0	42.0	**<0.001**	56.0	51.0	53.6	**0.026**	**0.071**
Former	21.0	26.8	31.2		20.2	29.0	28.3		
Current	56.0	34.2	26.8		23.8	20.0	18.1		
Physical activity									
Highly active	73.0	72.0	64.3	0.173	62.3	55.0	42.4	**<0.001**	**0.001**
Not active	27.0	28.0	35.7		37.7	45.0	57.6		
Car ownership %	32.0	24.4	29.5	0.401	10.7	9.3	15.6	**0.039**	**0.002**
	68.0	75.6	70.5		89.3	90.7	84.4		
Energy	2184(55.4)	2104(63.4)	2014(41.2)	**0.013**	1974(22.3)	1965(24.1)	2017(30.9)	0.25	0.952
Fat	82.7(2.7)	78.2(3.3)	74.8(2.3)	**0.024**	70.2(1.1)	69.4(1.2)	72.4(1.4)	0.22	0.356
Protein	87.0(2.1)	87.4(2.7)	86.0(1.8)	0.715	81.3(0.87)	83.6(1.0)	85.4(1.3)	0.006	0.816
Carbohydrate	265(7.5)	248(7.9)	245(5.4)	**0.026**	247(3.1)	243(3.4)	246(4.2)	0.94	0.799
Systolic blood pressure	119.4(1.3)	124.2(1.9)	130.9(1.5)	**<0.001**	118.6(0.71)	123.7(0.82)	130.5(0.95)	**<0.001**	0.818
Diastolic blood pressure	69.6(0.89)	70.9(1.1)	73.5(0.89)	**0.002**	68.0(0.49)	70.9(0.52)	74.4(0.62)	**<0.001**	0.413
Cholesterol	5.0±1.0	5.4±1.1	5.4±1.0	**0.012**	4.9±0.85	5.3±0.96	5.4±0.88	**<0.001**	0.459
HDL-cholesterol	1.48(0.03)	1.42(0.04)	1.33(0.03)	**0.001**	1.63(0.02)	1.51(0.02)	1.39(0.02)	**<0.001**	0.096
Mid-parental tertiles2									
Low	40.4	22.0	18.8	**0.002**	46.7	28.9	22.8	**<0.001**	0.072
Medium	27.3	40.2	33.0		32.1	34.6	31.5		
High	32.3	37.8	48.2		21.2	36.5	45.7		

1 Low tertile: BMI<23.2 kg/m2, medium: BMI 23.2-26.9 kg/m2, high: BMI >26.9 kg/m2
2 Low tertile: BMI <24.6 kg/m2, medium: BMI 24.6-27.0 kg/m2, high: BMI >27.0 kg/m2

Table 7-19: Regression results predicting BMI in men by social class

Non-manual men				
BMI	**β**	**95% CI**	**P-value**	**R^2 (univariate model)**
Age	-0.06	(-0.15_0.02)	0.145	0.4%
Never smoker				
Former smoker	1.71	(0.37_3.04)	0.013	2.6%
Current smoker	-1.21	(-2.91_0.48)	0.159	
Systolic blood pressure	0.07	(0.04_0.10)	<0.001	10.9%
Cholesterol	0.63	(-0.01_1.27)	0.054	2.3%
HDL-cholesterol	-2.48	(-4.43_-0.53)	0.013	5.2%
Mid-parental BMI	0.25	(0.06_0.43)	0.010	13.5%
R^2=30.3%				
Manual men				
BMI	**β**	**95% CI**	**P-value**	**R^2 (univariate model)**
Age	-0.01	(-0.07_0.05)	0.790	0.4%
Never smoker				
Former smoker	0.31	(-0.52_1.15)	0.461	2.5%
Current smoker	-2.01	(-2.99_-1.03)	<0.001	
Protein	0.06	(0.03_0.09)	<0.001	1.0%
Carbohydrate	-0.01	(-0.02_-0.01)	<0.001	0.2%
Systolic blood pressure	0.07	(0.05_0.10)	<0.001	7.9%
Cholesterol	0.47	(0.05_0.89)	0.027	2.8%
HDL-cholesterol	-3.15	(-4.44_-1.86)	<0.001	9.3%
Mid-parental	0.34	(0.21_0.47)	<0.001	11.3%
R^2=30.7%				

Table 7-20: Regression results predicting BMI in women by social class

Non-manual women				
BMI	**β**	**95% CI**	**P-value**	**R^2 (univariate model)**
Age	-0.07	(-0.12_-0.02)	0.004	0.03%
Never smokers				
Former smokers	0.50	(-0.12_1.12)	0.111	0.6%
Current smokers	-1.24	(-1.92_-0.55)	<0.001	
Very physically active				
Fairly physically active	1.09	(-0.07_2.25)	0.064	3.8%
Not physically active	2.36	(1.17_3.54)	<0.001	
Not active at all	3.23	(1.73_4.73)	<0.001	
Systolic blood pressure	0.08	(0.06_0.10)	<0.001	11.2%
Cholesterol	0.93	(0.62_1.23)	<0.001	4.3%
HDL-cholesterol	-3.53	(-4.24_-2.82)	<0.001	7.8%
Mid-parental BMI	0.43	(0.34_0.52)	<0.001	9.1%
R^2=31.1%				
Manual women				
BMI	**β**	**95% CI**	**P-value**	**R^2 (univariate model)**
Age	-0.04	(-0.12_0.05)	0.399	0.2%
Never smokers				
Former smokers	0.51	(-0.51_1.52)	0.325	6.2%
Current smokers	-1.63	(-2.84_-0.42)	0.008	
Very physically active				
Fairly physically active	1.27	(-0.58_3.13)	0.178	0.4%
Not physically active	1.96	(0.05_3.87)	0.044	
Not active at all	4.22	(1.66_6.77)	0.001	
Systolic blood pressure	0.06	(0.03_0.09)	<0.001	9.8%
Cholesterol	0.98	(0.46_1.50)	<0.001	2.9%
HDL-cholesterol	-3.89	(-5.04_-2.74)	<0.001	4.3%
Mid-parental	0.43	(0.28_0.58)	<0.001	9.3%
R^2=26.4%				

Table 7-21: Percentages of men and women on special diet and how recommended

		Female	Male	Total
		1298	1040	2338
Are you on special diet	Yes	156	51	207
		12.0%	4.9%	8.9%
	No	1142	989	2131
		88.0%	95.1%	91.1%
	P<0.001			
Diet recommended by	Myself	116	21	137
		76.3%	45.7%	69.2%
	Medical staff	36	25	61
		23.7%	54.3%	30.8%
	P<0.001			

Table 7-22: Percentages of men and women on special diet and how recommended by social class

		Non-manual	Manual	Total
		1608	730	2338
Are you on special diet	Yes	154	53	207
		9.6%	7.3%	8.9%
	No	1454	677	2131
		90.4%	92.7%	91.1%
	P=0.039			
		Non-manual	**Manual**	**Total**
		148	50	198
Diet recommended by	Myself	108	29	137
		73.0%	58.0%	69.2%
	Medical staff	40	21	61
		27.0%	42.0%	30.8%
	P=0.037			

Table 7-23: Mean daily consumption by food groups by social class

		Non-manual				Manual				
		1	2	3	p-value	1	2	3	p-value	M-NM
Bread	Mean	129.2	129.7	132.3	0.769	145.0	155.8	164.2	0.054	<0.001
	SD	70.8	72.3	75.1		84.0	89.1	88.3		
Cereals	Mean	23.8	22.1	21.6	0.149	21.8	22.6	21.8	0.893	0.874
	SD	19.9	19.1	19.5		21.3	20.5	18.8		
Rice/pasta	Mean	85.5	86.7	84.5	0.792	71.4	81.1	75.8	0.171	0.024
	SD	51.4	50.5	51.6		50.9	59.1	52.7		
Red meat	Mean	49.1	51.2	54.4	0.014	62.7	60.9	61.0	0.824	0.003
	SD	30.3	29.2	29.4		37.6	34.6	30.0		
Poultry	Mean	41.6	42.9	42.8	0.594	35.1	37.2	41.2	0.009	0.364
	SD	21.8	21.4	22.6		23.5	21.6	22.7		
Offal	Mean	1.5	1.5	2.1	0.006	2.6	2.3	3.1	0.250	0.009
	SD	3.2	3.2	4.2		4.8	4.5	6.3		
Fish	Mean	34.2	34.9	37.9	0.026	36.2	33.8	32.8	0.306	0.006
	SD	22.7	21.1	26.3		27.9	22.6	23.0		
Potatoes	Mean	109.4	125.6	125.4	<0.001	156.9	161.8	153.3	0.536	<0.001
	SD	72.1	71.6	72.4		86.8	86.0	86.7		
Green vegetables	Mean	90.2	94.2	93.6	0.261	78.5	78.6	81.1	0.732	<0.001
	SD	43.4	43.9	44.5		40.7	44.8	41.3		
Root vegetables	Mean	47.6	51.8	52.3	0.041	52.1	51.0	49.9	0.792	0.353
	SD	30.8	35.2	33.8		37.0	34.0	34.5		
Sugar	Mean	15.4	8.4	8.1	<0.001	32.1	18.6	16.1	<0.001	<0.001
	SD	29.1	19.3	18.7		36.7	26.2	27.0		
Pudding	Mean	66.9	66.1	65.4	0.876	67.2	66.8	69.3	0.828	0.282
	SD	52.1	44.2	48.1		54.7	50.2	50.1		
Fruits	Mean	115.5	115.5	115.2	0.997	93.7	105.2	105.2	0.134	0.072
	SD	72.6	79.4	73.9		68.2	67.8	74.3		
Egg	Mean	19.4	19.7	21.4	0.105	28.7	27.6	27.0	0.617	<0.001
	SD	16.5	15.8	16.2		19.5	18.4	17.3		
Milk	Mean	511.1	593.7	606.2	<0.001	435.9	529.2	587.0	<0.001	0.478
	SD	373.9	336.1	345.5		396.0	399.8	395.5		
Cheese	Mean	19.0	19.3	22.8	<0.001	19.7	20.5	20.7	0.834	0.183
	SD	13.2	14.1	22.8		22.2	18.6	17.1		
Butter	Mean	10.9	9.8	10.4	0.382	13.9	12.3	13.7	0.499	0.002
	SD	12.2	13.5	12.9		16.0	14.4	17.0		
Margarine	Mean	11.9	11.5	12.9	0.176	18.3	15.9	16.6	0.328	<0.001
	SD	12.4	13.5	11.6		19.3	16.1	15.5		
Oil	Mean	6.3	6.5	5.7	0.101	8.0	7.0	6.6	0.032	0.032
	SD	5.8	6.0	5.3		7.4	5.3	5.4		
Soft drinks	Mean	156.3	176.8	199.1	<0.001	141.0	159.5	175.9	0.002	0.003
	SD	101.0	105.7	102.1		107.0	106.2	106.6		
Alcohol	Mean	178.8	248.3	265.1	0.001	359.1	537.0	378.3	0.003	0.003
	SD	322.7	458.4	443.5		615.9	659.9	551.7		
Total	Mean	1726.5	1925.1	1962.4	<0.001	1865.0	2169.0	2112.9	0.001	0.001
	SD	571.9	641.9	657.5		770.5	767.5	764.4		

Table 7-24: The proportion of under-reporting using the energy intake ratio

		Total	BMI≥30	BMI<30	Manual	Non-manual
Men	<1.1*	21.6% (209)	30.9% (54)	19.5% (155)	13.2% (53)	27.5% (156)
	>1.1	78.4% (760)	69.1% (121)	80.5% (639)	86.8% (348)	72.5% (412)
				P=0.001		P<0.001
	<1.28φ	46.1% (447)	65.7% (115)	41.8% (332)	32.7% (131)	55.6% (316)
	>1.28	53.9% (522)	34.3% (60)	58.2% (462)	67.3% (230)	44.4% (252)
				P<0.001		P<0.001
Women	<1.1	13.4% (161)	24.9% (54)	10.9% (107)	12.7% (35)	13.6% (126)
	>1.1	86.6% (1040)	75.1% (163)	89.1% (877)	87.3% (241)	86.4 (799)
				P<0.001		P=0.687
	<1.28	36.3% (436)	56.7% (123)	31.8% (313)	32.6% (90)	37.4% (346)
	>1.28	63.7% (765)	43.3% (94)	68.2% (671)	67.4% (186)	62.6% (579)
				P<0.001		P 0.146

* Goldberg et al.

φWHO criteria

CHAPTER 8

FAMILIAL PREDISPOSITION TO OBESITY AND RAISED BODY MASS INDEX

8.1 INTRODUCTION

It was shown in Chapter 6 that the offspring whose parents have raised BMI are more likely to have raised BMI themselves. Further, the results in Chapter 7 showed that 48% of men and 46% of women in the top third of the BMI distribution had parents in the top tertile of mid-parental BMI compared with 16% of men and 23% of women in the lowest tertile of the BMI distribution. This chapter describes first, the individual and population attributable risks of obesity associated with a family history of raised BMI, and second, the estimation of familial correlations and heritability of BMI using multilevel modelling.

Heritability

The level of heritability is defined as the fraction of the population variation in the trait that can be explained by genetic transmission (Bouchard 1997). The level of heritability of BMI has been investigated in a large number of twin, adoption and family studies. The heritability level estimates arising from these studies depend on how the study was conducted and on the kinds of family relationships upon which they were based (Bouchard 1998). Since families share behaviours and environments as well as genes, these estimates of heritability cannot be attributed wholly to genetic effects.

The observed heritability of obesity is highest in twin studies, intermediate in studies of nuclear families and lowest in adoption studies (Bouchard 1994a). Heritability estimates of 25-40% of the individual age-adjusted variance in BMI or body fat have been reported from two studies from Norway and Quebec (Tambs et al. 1991). These results are similar to those in the Danish adoption study, which reported a heritability factor of 34% (Bouchard 1994b;Bouchard 1997).

The risk of becoming obese

Several studies have reported that obese children are more likely than non-obese children to have obese parents. Nearly 30% (range of 5 to 45%) of obese children have

two obese parents. Further, it has been estimated that 25 to 35% of obese children had normal weight parents. The risk of becoming obese when one or two of the parents are overweight or obese has been estimated using the lambda coefficient (λ_R) (Risch 1990a;Risch 1990b;Risch 1990c). λ_R is defined as the ratio of the risk of being obese when a biological relative is obese compared with the risk in the population at large. The risk of obesity has been estimated to be two to three times higher for an individual with a family history of obesity (having an obese relative) and increases with the severity of the history of obesity (Allison, Faith, & Nathan 1996).

Below is a review of the different studies estimating BMI heritability and correlations of BMI between relatives.

Twin studies

The twin design has been used extensively to study the genetics of obesity. Most twin studies have found evidence for genetic factors in the aetiology of obesity. Reported levels of heritability vary between 0.50 and 0.90 (Maes, Neals, & Eaves 1997).

Estimates from samples of adolescent twins tend to be higher than those from studies of adults (0.67 to 0.93 in adolescence compared to 0.51 to 0.84 in adults). Results from the Finnish Twin Registry found that heritability is significantly higher in males (0.74) than in females (0.69). Similar estimates for heritability were found for males and females in the Swedish Twin study. The Danish Twin Registry (DTR) and Norwegian Twin Panel (NTP) have reported different heritability estimates for men (0.46 in DTR and 0.71 in NTP) and women (0.61 in DTR and 0.79 in NTP) (Maes, Neals, & Eaves 1997).

Evidence for genetic determinants of BMI has been found in studies of twins reared apart, in which the observed heritability estimates were in the same range as those reported for twins reared together (Maes, Neals, & Eaves 1997).

Adoption studies

Adoption studies are based on comparing the correlation of BMI between adoptees and their adoptive parents and biological parents. This provides direct estimates of the cultural and genetic transmission of obesity.

Correlations of BMI between adopted children and their adoptive parents are lower and insignificant compared with the correlations observed with biological parents. In the Danish and Canadian Adoption studies, data were based on adoptees in childhood. Only one study from Iowa reported similar findings in adoptees who had reached adulthood.

Familial studies

The Quebec Family Study (QFS), the Canada Fitness Survey (CFS), the Trøndelag Study in Norway, the Framingham Heart Study and other studies have investigated BMI and obesity in families. These studies have investigated many types of relationship between family members. The most commonly studied relationships are parent-offspring and sibling relationships. Most studies report correlations; few estimate heritability.

The correlations of BMI between parents and their adult offspring varied between 0.17 and 0.27, in results obtained from the Framingham Heart study (Heller et al. 1984), and studies from Jerusalem (Friedlander et al. 1988) and Iowa (Maes, Neals, & Eaves 1997). Correlations in black and white subjects were reported in the Princeton School District Family study, where parent-offspring correlations varied between 0.01 and 0.11 in white pairs and between 0.03 and 0.37 in black pairs (Khoury et al. 1983).

More than ten studies have investigated the correlations between parents and their children or adolescent offspring. There were no clear trends observed in the parent-offspring correlations by gender of parents or offspring. The range of maternal correlations was 0.03 to 0.38, compared to 0.12 to 0.39 for the paternal correlations. Correlations between parents and their daughters ranged from 0.01 to 0.39; those with parents and their sons, between 0.01 and 0.37(Maes, Neals, & Eaves 1997).

Observed correlations of BMI between siblings range from 0.15 to 0.55 for both adult and adolescent siblings. Correlations were higher between brothers than between sisters, between blacks than whites and between siblings close in age than between siblings aged further apart.

Correlations of BMI between spouses have been investigated in many studies, in which the correlations varied between 0.10 and 0.19. A higher correlation was observed between black (0.20-0.44) than between white (0.09-0.14) spouses.

Results from the Victorian Family Heart Study showed interesting correlations between anthropometric variables. Correlations of height between different categories of first-degree relatives were similar, suggesting that the familial co-variation in height was mostly due to genetic factors (Harrap et al. 2001). However, correlations between weight and body mass index in first-degree relatives varied considerably suggesting a role for shared environmental factors such as diet and physical activity (Harrap et al 2001).

8.2 METHOD

Obesity clustering in families

The prevalence of obesity was investigated in offspring according to paternal, maternal and mid-parental BMI categories (using WHO criteria). The analysis included 2388 offspring and 2954 parents (1477 fathers and mothers). Similar analyses, confined to one offspring per family, were repeated to control for families with more than one offspring.

The proportion of cases of obesity in offspring attributable to raised mid-parental BMI was estimated on the basis of the 9.2% prevalence of obesity in offspring with mid-parental BMI values in the range 20.0 –24.9 kg/m^2.

The population attributable fraction (PAF) was calculated separately for men and women. Using the following formula: -

$PAF = [(P_T - P_O)/P_T] \times 100\%$

Where

P_T = prevalence in total population

P_O = prevalence in unexposed population

The lambda coefficient (λ_R) is defined as $[P(A|R)]/[P(A)]$, where $P(A)$is the probability of being affected (the prevalence of obesity in the population under study) and $P(A|R)$ is the probability of being affected given that one's relative of degree R is affected. The lambda coefficient (λ_R) was estimated for each percentile cut-off above the 50th by increments of 5 using the MlwiN package. The lambda coefficient (λ_R) was also estimated for each percentile cut-offs below the 50th to assess the pattern in extreme leanness.

8.3 Familial aggregation of BMI

Age adjustment

The log of body mass index was adjusted for age separately in each of the sex-by-generation groups by running regression models. The resulting age-adjusted and standardised residuals were used as the phenotypes in the familial analyses.

Familial correlation model

Familial correlations were estimated and used to assess the degree of familial resemblance for BMI. The familial patterns of BMI were analysed using multilevel modelling fitted using the MLwiN statistical package (Rasbash et al 2000). Models were fitted to family data under the assumption that BMI phenotypes in families follow a multivariate normal distribution.

Genetic epidemiologists usually model continuous data using special programs such as Fisher or Generalised Estimating Equation (GEE4). However, familial correlations can be estimated by the multilevel modelling using the MlwiN package.

Colleagues investigated differences and similarities between the MlwiN and Fisher packages using FEV1 variable (unpublished work by Upton M and McConnachie A). Estimates of familial correlations for FEV1 in the two packages were similar with accuracy to the third decimal place.

In univariate studies, analyses of four types of family member (father, mother, son and daughter) led to eight correlations within three familial classes (one spouse [fm], four parent-offspring [fs, fd, ms, md] and three sibling [ss, dd, sd]). A general model and several null hypotheses were estimated (Table 8-10). The null hypotheses was tested using the likelihood ratio test (the difference in minus twice the log likelihood [-2 ln L] obtained under two models), which is distributed approximately as a χ^2 with the degree of freedom being the difference in the number of parameters estimated in the two

models. Each null hypothesis was compared with the general model for these likelihood ratio tests.

Maximum heritability includes both genetic and familial environmental sources of variance and is adjusted for the degree of spouse resemblance was calculated using the following equation:

$$\text{Maximum heritability} = ([r_{\text{sibling}} + r_{\text{parent-offspring}}][1+r_{\text{spouse}}]/[1+r_{\text{spouse}}+2\, r_{\text{spouse}}\, r_{\text{parent-offspring}}])$$

8.4 RESULTS

Mid-parental BMI as marker of family susceptibility

Table 8-1 show the distribution of offspring BMI categories by the parental BMI categories. The percentages of normal weight and obese offspring show a stepwise change and follow the stepwise changes in categories for the parents. A gradient effect was found from two "obese" parents to one "obese" parent to neither "obese" parent (Figure 8-1).

The patterns formed by the two extremes represent almost mirror images. 64% of normal weight offspring had normal weight fathers and mothers and 63% of obese offspring had obese fathers and mothers (Table 8-1).

Mid-parental BMI $\geq$30kg/m^2 has the effect of dividing obese fathers and mothers into a 39-46% subgroup married to an obese partner and a 53-60% subgroup married to an overweight partner (Table 8-2). 85% of the mothers in the mid-parental $\geq$30 kg/m^2 were personally obese while only 54% of the fathers in this group were also obese.

Table 8-3 shows the distribution of father and mother BMI categories combinations. There was only one couple with an obese father and normal weight mother and one couple with an obese mother and normal weight father who were misclassified in mid-parental BMI <25. Further 100% of both obese fathers and mothers and similarly 100% of normal weight fathers and mothers where classified in the obese category of mid-parental BMI.

Familial aggregation of body mass index

The prevalence of obesity (BMI$\geq$30kg/m^2) was 9% in sons of parents with normal weight (mid-parental BMI<25 kg/m^2), 20% in sons of overweight parents (BMI 25-29.9 kg/m^2) and 44% in sons who were obese (BMI$\geq$30 kg/m^2). The corresponding figures for daughters were 9%, 20% and 42% respectively. Similar patterns were observed between sons and daughters and their fathers and mothers (Table 8-4).

Converse patterns were seen in relation to the familial aggregation of individuals with BMI <25 kg/m^2. Just less than 20% of obese sons and daughters had mid-parental BMI values below 25 kg/m^2, while less than 5% of sons and daughters with BMI values below 25 kg/m^2 had mid-parental BMI values of 30 kg/m^2 or above (Table 8-4). Similar results were found when confining the analyses to the oldest offspring per family (Table 8-5).

The prevalence of obesity (BMI≥30 kg/m^2) was four times higher in the sons of fathers who were obese compared to those whose fathers had BMI levels below 25. The prevalence of obesity was only twice as high in daughters whose fathers were obese. However, the prevalence of obesity was about three times higher in both sons and daughters with an obese mother compared with offspring whose mothers had BMI levels below 25 (Table 8-4).

Mid-parental BMI showed a strong, graded relationship with the prevalence of obesity in adult offspring (Table 8-6). 49% of cases of obesity in offspring were associated with mid-parental BMI levels above 24.9 kg/m^2. The population attributable fraction from mid-parental BMI ≥25 was 49% in all offspring (51% in men and 48% in women). However, the estimated population attributable fraction from mid-parental BMI ≥30 on offspring obesity was 13%. It was as high as 12.8% in women and as low as 4% in men.

Table 8-7 shows the prevalences of offspring obesity, overweight and normal weight, percentages of families and the population attributable fractions in different mid-parental BMI categories. The prevalence of obesity was 18% in all families, 24% in the 61% of families with mid-parental BMI≥25kg/m^2, 31% in the 27% of families with mid-parental BMI≥27.5kg/m^2 and 43% in the 8% of families with mid-parental BMI ≥30 kg/m^2. The prevalence of obesity was highest in offspring with mid-parental BMI ≥30 kg/m^2 and the prevalence of obesity decreases in offspring with lower mid-parental BMI. However, the population attributable fraction is lowest in offspring with mid-parental BMI ≥30kg/m^2 and increases with increasing mid-parental BMI.

The estimated risk of becoming obese, based on the lambda coefficient, increases as the percentile cut-off for defining obesity increases. The lambda coefficient almost doubles

in parent-offspring pairs at the 85th percentile and in sibling pairs at the 90th percentile compared to the lambda value for the 50th percentile. A similar pattern was found for lambda values for leanness. High lambda values were found in those in the 10th percentile in parent-offspring pairs and 5th percentile in the sibling pairs (Table 8-8).

Familial correlation of BMI

The correlation coefficients of different family pairings are shown in Table 8-9. The lowest correlation was between spouses (0.148) and the highest between sex-like sibs (0.347 between sons and 0.304 between daughters). Correlations were higher between sex-like parent-offspring (0.273 between father-son and 0.298 between mother-daughter) than between opposite sexes (0.181 between father-daughter and 0.255 between mother-son).

The estimate of maximum heritability, including both shared genetic and environmental factors of variance, and adjusted for the degree of spouse resemblance, was 56.9%.

A general model and null hypotheses were estimated (Table 8-10). All null hypotheses were rejected except two. The models of no sex difference in offspring and a mitochondrial pattern of inheritance (i.e. maternal effect) were not rejected. This excludes the hypothesis that the correlations between sibling and mother-offspring pairs were equal because mitochondria are inherited primarily from the mother via cytoplasmic rather than nuclear sources. The model of no spouse correlation was rejected ($p<0.001$) indicating the magnitude of the assortative mating and shared environment. The models of no difference in offspring or parents ($p<0.05$), no sex or generation difference ($p<0.01$), no sibling correlations ($p<0.001$), no parent-offspring correlations ($p<0.001$), no familial resemblance at all ($p<0.001$) were all significant.

8.5 DISCUSSION

The data presented in this chapter show the importance of familial determinants of obesity and raised body mass index. Familial factors include both genetic predisposition and shared environments. Although this observation is well established and has been reported in several studies, these findings are specific to this population. Because different populations have different degrees of genetic and environmental variability, any familial clustering found may be due to genetic factors to a greater or lesser extent in one population compared to another. In MIDSPAN Family study, the familial component associated with obesity, measured by BMI, was found to be slightly higher compared to other populations.

A limitation of this study is the lack of twin data, which help to explain to what extent the observed variation in obesity, measured by BMI, is explained by genetic factors. Because twins (monozygote twin) have the same genes, any phenotypic variation between twins may be attributed to environmental effects.

Although the correlation between spouses was relatively small, the null hypothesis of there being no between-spouse correlation was rejected. The degree of correlation between spouses reported in this study was similar to that in the Framingham Heart Family Study and much smaller than that reported in the Victorian Family Heart Study. The significant between-spouse correlation can be explained either by assortative mating or by shared environment.

Assortative mating is the tendency for like to marry like. It has been suggested that a higher rate of assortative mating in obese people has an impact through both genetic and non-genetic mechanisms and so contributes to the recent rise in obesity (Hebebrand et al. 2000). This was found to be true in extremely obese children. One theory suggests that the increase in stigmatisation of obese individuals is a powerful driving force to increase the rate of assortative mating.

The findings show that correlations between family members of the same sex were higher than correlations between family members of different sexes. Similar results were reported in the Framingham Heart Family Study and Jerusalem Lipid Research Clinic Study. However, the difference between mother-son and mother-daughter correlations was not as large as the difference between father-offspring correlations.

Consistently, estimates using BMI as a continuous variable were similar to estimates using BMI categories, BMI $\geq 30 kg/m^2$. Similar results were found in the effect of parental obesity on offspring obesity, where obese sons are four times likely to have an obese father, while obese daughters are twice as likely to have an obese father.

The correlations between siblings were the highest of all estimated familial correlations. Correlations between sons were especially higher than correlations between opposite sexes. The Framingham Heart Family Study has reported a similar observation, while the Jerusalem Lipid Research Clinic Study reported a higher correlation between daughters. In general, the sibling-sibling correlations found in this study were similar to those reported in Jerusalem Lipid Research Clinic and the Victorian Family Heart Studies.

Different methods have been used in different studies to estimate BMI heritability in families. The maximum heritability of 57% found in this study is higher than that reported in other family studies. A possible explanation is that in this study, offspring and parents were studied at similar ages. Twin and sibling studies suggest that in addition to environmental factors, genetic factors that only "switch on" at particular ages may account for variation in BMI (Maes, Neals, & Eaves 1997) and so the correlations may be reduced and heritability underestimated, if parents and offspring had different ages.

The findings of this study are potentially important for two reasons. First, from a genetic epidemiology perspective, the results provide a basis for further genetic research testing genes and phenotype associations. The findings provide evidence of familial clustering of obesity, measured by BMI. The Lambda coefficient can be used as the first step to identify the sample size for genetic mapping (Allison, Faith, & Nathan 1996). Results

from lambda provide the opportunity of looking at both genes causing and genes protecting from obesity by targeting the groups at high risk of obesity and leanness.

Most of the research on obesity has focused on the upper part of BMI distribution and little attention has been given to the lower part of the BMI distribution. It has been suggested that focusing on the extremely lean group would help identifying candidate genes that confer resistance to obesity (Bulik & Allison 2001).

Second, from a public health perspective, these findings highlight a susceptible group, which might be targeted to prevent obesity. 49% of obesity cases could be prevented if offspring of overweight parents were targeted, 17% of cases with mid-parental BMI>27.5kg/m^2 and 13% of the cases could be prevented if offspring with obese parents were targeted. Intervention programmes targeting these susceptible groups would be more effective than intervention programmes to the whole population regardless of their susceptibility. Chapter nine describes the different environmental and behavioural factors associated with obesity and the role of these factors in offspring with different familial susceptibilities (see Chapter Nine).

The use of mid-parental BMI showed an added value as a marker for family susceptibility compared to the values from using one parental marker on its own (Figure 8-1). High mid-parental BMI include families with at least one parent with high individual BMI while the other might not have high individual BMI value. However, when both parents have high individual BMI values this results in high mid-parental BMI and so have high combined effect on offspring.

The mid-parental BMI group 25-29.9 is the largest group compared to the normal weight and obese groups. This is because if one of the parents is in the obese group while the other is in the overweight or normal weight group, the obese parent will be pulled into the other group unless the BMI values was very high and so pulls the other parent into the obese group.

8.6 SUMMARY

The results in this chapter show the importance of familial susceptibility in obesity development. Familial susceptibility was investigated in two ways. First, using BMI as continuous variable to estimate the heritability in the participating families. Second, using obesity with BMI>30kg/m^2 in parents (using mid-parental BMI) to estimate the population attributable faction and the risk of becoming obese in the offspring population. These findings provide the basis for sample selection for further research at the molecular level. At the same time, these finding highlight high risk groups which could be targeted in prevention programs.

Table 8-1: Distribution of offspring BMI categories by parent BMI categories

Father	Mother	No. Offspring	Offspring (%) <25	25-29.9	>30
<25	<25	448	63.6%	27.2%	9.2%
	25-29.9	321	50.5%	37.1%	12.5%
	≥30	82	36.6%	36.6%	26.8%
25-29.9	<25	508	48.2%	39.6%	12.2%
	25-29.9	495	37.2%	41.4%	21.4%
	≥30	197	27.9%	47.2%	24.9%
≥30	<25	80	35.0%	45.0%	20.0%
	25-29.9	109	37.6%	32.1%	30.3%
	≥30	76	7.9%	28.9%	63.2%

Figure 8-1: Distribution of offspring BMI categories by parent BMI categories

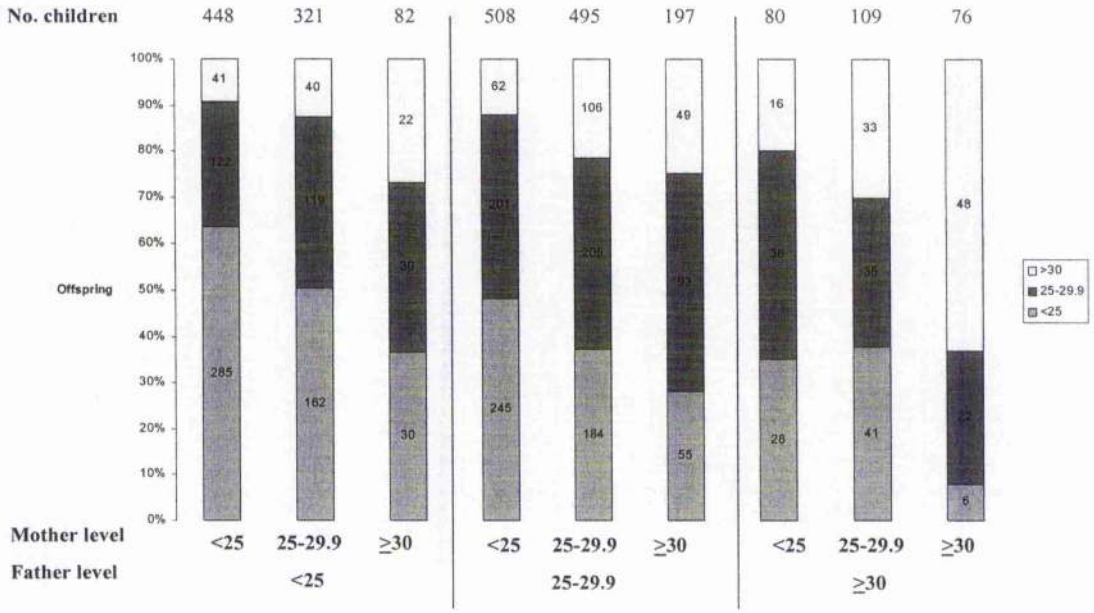


Table 8-2: The distribution of father and mother BMI categories across mid-parental BMI categories

		Mid-parental obesity		
		Normal weight	Overweight	Obese
Father obesity	**Normal**	395	153	5
		71.4%	27.7%	.9%
		68.3%	19.7%	4.2%
	Overweight	182	526	50
		24.0%	69.4%	6.6%
		31.5%	67.7%	42.0%
	Obese	1	98	64
		.6%	60.1%	39.3%
		.2%	12.6%	53.8%
Mother obesity	**Normal**	473	201	0
		70.2%	29.8%	.0%
		81.8%	25.9%	.0%
	Overweight	104	459	18
		17.9%	79.0%	3.1%
		18.0%	59.1%	15.1%
	Obese	1	117	101
		.5%	53.4%	46.1%
		.2%	15.1%	84.9%

Table 8-3: The distribution of father and mother BMI categories by mid-parental BMI categories

		Mid-parental categories					
		Normal weight		Overweight		Obese	
Father	**Mother**	**N**	**%**	**N**	**%**	**N**	**%**
Normal	Normal	290	100.0				
	Overweight	104	50.5	102	49.5		
	Obese	1	1.8	51	89.5	5	8.8
Overweight	Normal	182	55.0	149	45.0		
	Overweight			311	100.0		
	Obese			66	56.9	50	43.1
Obese	Normal	1	1.9	52	98.1		
	Overweight			46	71.9	18	28.1
	Obese					46	100.0

The distribution of the nine groups, resulting from the combination of mother and father, BMI categories in mid-parental BMI categories.

Table 8-4: Offspring BMI categories distribution within father, mother and mid-parental BMI categories.

	Son BMI categories				Daughter BMI categories			
	<25 Kg/m^2	25-29.9 Kg/m^2	≥30 Kg/m^2	P- value	<25 Kg/m^2	25-29.9 Kg/m^2	≥30 Kg/m^2	P-value
Father BMI categories	394	459	185		643	405	232	
< 25 kg/m^2	200 (52.5%)	146 (38.3%)	35 (9.2%)	<0.0001	278 (58.9%)	126 (26.7%)	68 (14.4%)	<0.0001
	50.8%	31.7%	18.9%		43.2%	31.2%	29.3%	
25-29.9 kg/m^2	168 (31.5%)	264 (49.5%)	101 (18.9%)		316 (47.4%)	235 (35.2%)	116 (17.4%)	
	42.6%	57.4%	54.6%		49.1%	58.2%	50.0%	
≥ 30 kg/m^2	26 (20.8%)	50 (40.0%)	49 (39.2%)		49 (35.0%)	43 (30.7%)	48 (34.3%)	
	6.6%	10.9%	26.5%		7.6%	10.6%	20.7%	
Mother BMI categories								
< 25 kg/m^2	226 (47.1%)	200 (41.7%)	54 (11.3%)	<0.0001	333 (59.7%)	160 (28.7%)	63 (11.6%)	<0.0001
	57.4%	43.6%	29.2%		51.8%	39.5%	28.0%	
25-29.9 kg/m^2	140 (34.4%)	186 (45.7%)	81 (19.9%)		247 (47.7%)	173 (33.4%)	98 (18.9%)	
	35.5%	40.5%	43.8%		38.4%	42.7%	42.2%	
≥ 30 kg/m^2	28 (18.5%)	73 (48.3%)	50 (33.1%)		63 (30.9%)	72 (35.3%)	69 (33.8%)	
	7.1%	15.9%	27.0%		9.8%	17.8%	29.7%	
Mid-parental BMI categories								
< 25 kg/m^2	213 (53.7%)	150 (37.8%)	34 (8.6%)	<0.0001	309 (64.8%)	124 (26.0%)	44 (9.2%)	<0.0001
	54.1%	32.7%	18.4%		48.1%	30.7%	19.0%	
25-29.9 kg/m^2	168 (30.4%)	272 (49.3%)	112 (20.3%)		304 (44.1%)	244 (35.4%)	141 (20.5%)	
	42.6%	59.3%	60.5%		47.4%	60.4%	60.8%	
≥ 30 kg/m^2	13 (14.6%)	37 (41.6%)	39 (43.8%)		29 (25.9%)	36 (32.1%)	47 (42.0%)	
	3.3%	8.1%	21.1%		4.5%	8.9%	20.3%	

Table 8-5: Offspring BMI categories distribution within parents and mid-parental BMI categories (using the oldest offspring)

	Son BMI categories			Daughter BMI categories		
	<25 Kg/m^2	25-29.9 Kg/m^2	≥30 Kg/m^2	<25 Kg/m^2	25-29.9 Kg/m^2	≥30 Kg/m^2
Father BMI categories	**253**	**276**	**122**	**399**	**277**	**142**
< 25 kg/m^2	127 (53.4%)	88 (37.0%)	23 (9.7%)	184 (58.4%)	91 (28.9%)	40 (12.7%)
	50.2%	31.9%	18.9%	46.1%	32.9%	28.2%
25-29.9 kg/m^2	113 (33.2%)	160 (47.1%)	67 (19.7%)	186 (45.1%)	160 (38.8%)	66 (16.0%)
	44.7%	58.0%	54.9%	46.6%	57.8%	46.5%
≥ 30 kg/m^2	13 (17.8%)	28 (38.4%)	32 (43.8%)	29 (31.9%)	26 (28.6%)	36 (39.6%)
	5.1%	10.1%	26.2%	7.3%	9.4%	25.4%
Mother BMI categories						
< 25 kg/m^2	155 (49.8%)	119 (38.3%)	37 (11.9%)	220 (60.8%)	104 (28.7%)	38 (10.5%)
	61.3%	43.3%	30.3%	55.0%	37.5%	26.8%
25-29.9 kg/m^2	84 (34.1%)	107 (43.5%)	55 (22.4%)	145 (43.8%)	126 (38.1%)	60 (18.1%)
	33.2%	38.9%	45.1%	36.3%	45.5%	42.3%
≥ 30 kg/m^2	14 (15.1%)	49 (52.7%)	30 (32.3%)	35 (27.8%)	47 (37.3%)	44 (34.9%)
	5.5%	17.8%	24.6%	8.8%	17.0%	31.0%
Mid-parental BMI categories						
< 25 kg/m^2	139 (53.3%)	99 (37.9%)	23 (8.8%)	203 (64.0%)	87 (27.4%)	27 (8.5%)
	54.9%	36.0%	18.9%	50.9%	31.4%	19.0%
25-29.9 kg/m^2	108 (32.0%)	154 (45.6%)	76 (22.5%)	185 (42.7%)	168 (38.8%)	80 (18.5%)
	42.7%	56.0%	62.3%	46.4%	60.6%	56.3%
≥ 30 kg/m^2	6 (11.8%)	22 (43.1%)	23 (45.1%)	11 (16.2%)	22 (32.4%)	35 (51.5%)
	2.4%	8.0%	18.9%	2.8%	7.9%	24.6%

Table 8-6: Association of mid-parental BMI with the prevalence of obesity in adult offspring

Parents			Offspring		
BMI groups	**Families (N)**	**Offspring (N)**	**Obese (N)**	**Obesity (%)**	**Non-attributable cases[1]**
<20.0	12	22	0	0	
20.0-25.0	566	852	78	9.2%	78
25.0-27.5	506	805	144	17.9%	74.6
27.5-30.0	271	436	109	25.0%	40.1
30-32.5.0	84	139	54	38.8%	12.8
32.5-35.0	23	40	19	47.5%	3.4
35.0-37.5	9	18	9	50.0%	1.7
37.5-40.0	3	4	4	100.0%	0.4
Total	1474	2316	417		211.0

PAF=[(0.182-0.092)/0.182]x100%, PFA=49.2%

Males					
BMI groups	**Families (N)**	**Offspring (N)**	**Obese (N)**	**Obesity (%)**	**Non-attributable cases[2]**
<20.0	8	12	0	0	
20.0-25.0	312	285	34	8.8%	34
25.0-27.5	284	364	62	17.0%	32.0
27.5-30.0	157	190	50	26.3%	16.7
30-32.5.0	47	58	25	43.1%	5.1
32.5-35.0	11	22	8	54.5%	1.9
35.0-37.5	6	6	4	50.0%	0.5
37.5-40.0	2	3	3	33.3%	0.3
Total	827	1040	186		90.5

PAF=[(0.181-0.088)/0.181]x100%, PFA=51.4%

Females					
BMI groups	**Families (N)**	**Offspring (N)**	**Obese (N)**	**Obesity (%)**	**Non-attributable cases[3]**
<20.0	8	10	0	0	
20.0-25.0	364	474	44	9.3%	44
25.0-27.5	348	454	82	18.1%	42.2
27.5-30.0	181	249	59	23.7%	23.2
30-32.5.0	60	83	31	37.3%	7.7
32.5-35.0	16	19	12	63.2%	1.8
35.0-37.5	7	8	3	37.5%	0.7
37.5-40.0	1	1	1	100%	0.1
Total	985	1298	232		119.7

PAF=[(0.180-0.093)/0.180]x100%, PFA=48.4%

[1]Assuming the baseline 9.2% of obesity in offspring with mid-parental BMI in range 20.0-25.0kg/m^2.
[2]Assuming the baseline 8.8% of obesity in offspring with mid-parental BMI in range 20.0-25.0kg/m^2.
[3]Assuming the baseline 9.3% of obesity in offspring with mid-parental BMI in range 20.0-25.0kg/m^2.

Table 8-7: Target population recommended for prevention programmes

Targeted categories of mid-parental BMI	Families	PAF	Offspring		
			Prevalence of obesity	Prevalence of overweight	Prevalence of normal weight
≥30	8.1%	13%	42.8%	36.3%	20.9%
			(86)	(73)	(42)
≥27.5	26.5%	17%	30.6%	39.1%	30.3%
			(195)	(249)	(193)
≥25	60.8%	49%	23.5%	10.8%	35.6%
			(339)	(589)	(514)
All	100%	100%	18.0%	37.3%	44.7%
			(418)	(865)	(1038)

Table 8-8: Empirical lambda values

Percentile cut-off	Siblings	Parent-offspring
Obesity		
≥50	1.21	1.14
≥55	1.25	1.19
≥60	1.27	1.24
≥65	1.33	1.23
≥70	1.41	1.44
≥75	1.51	1.58
≥80	1.71	1.85
≥85	1.70	2.43
≥90	2.02	2.83
≥95	2.16	4.03

Percentile cut-off	Siblings	Parent-offspring
Leanness		
≥50	1.21	1.14
≥45	1.17	1.21
≥40	1.22	1.26
≥35	1.28	1.30
≥30	1.35	1.38
≥25	1.50	1.49
≥20	1.76	1.72
≥15	1.86	1.96
≥10	1.93	2.10
≥5	2.25	2.30

Table 8-9: Correlation estimates (using z- score)

Relationship	Estimate	SD
Spouse:		
Father-mother	0.148	0.026
Parent-offspring:		
Father-son	0.273	0.032
Father-daughter	0.181	0.029
Mother-son	0.255	0.032
Mother-daughter	0.298	0.030
Sibling:		
Son-son	0.347	0.060
Daughter-daughter	0.304	0.052
Son-daughter	0.279	0.052
Parents-offspring	0.254	0.019
Sibling-sibling	0.352	0.033

Maximum heritability includes both genetic and familial environmental sources of variance and is adjusted for the degree of spouse resemblance was 56.9%

Table 8-10: Univariate familial correlation models

Model	DF*	Parameter reductions	χ^2	P-value
General	8	All 8 correlations estimated	28526.29	
No sex differences in offspring	4	Fs=fd. Ms=md, ss=dd=sd	8.82	NS
No differences in offspring or parents	5	Fs=fd=ms=md, ss=dd=sd	12.08	<0.05
No sex or generation differences	6	Fs=fd=ms=md=ss=dd=sd	15.45	<0.01
A mitochondrial pattern if inheritance* was tested by equating all mother and sibling correlations	4	Ms=md=ss=dd=sd	3.45	NS
All the correlations were equated	7	Fm=fs=fd=ms=md=ss=dd=sd	30.6	<0.001
No sibling correlations	3	Ss=dd=sd=0	223.36	<0.001
No parent-offspring correlations	4	Fs=fd=ms=md=0	237.63	<0.001
No spouse correlation	1	Fm=0	32.38	<0.001
No familial resemblance at all	8	Fm=fs=fd=ms=md=ss=dd=sd=0	371	<0.001

*Mitochondria are inherited primarily from the mother via cytoplasmic rather than nuclear sources and play a central role in the production of ATP at the cellular level.

CHAPTER 9

GENE-ENVIRONMENT INTERACTIONS

9.1 INTRODUCTION

In previous chapters, environmental, behavioural and familial factors were found to be associated with the high prevalence of obesity and raised BMI in the offspring generation. Mid-parental BMI was identified as an important factor associated with offspring obesity.

These findings are consistent with the hypothesis that mid-parental BMI>30kg/m^2 is a useful indicator of "familial susceptibility" to obesity. This chapter explores and tests this hypothesis in several ways.

First, the environmental and behavioural correlates of raised mid-parental BMI are described, in order to identify possible non-genetic aspects of the familial aggregation of obesity.

Second, mid-parental BMI is investigated as a potential determinant of increased susceptibility to the effect of environmental factors on BMI and obesity in offspring.

Third, environmental and behavioural factors are compared in offspring with contrasting familial predisposition to obesity, in order to determine possible non-genetic explanations of their different obesity profiles.

Finally, a case-control analysis is used to estimate the possible magnitude of gene-environment interactions and their effects on obesity in offspring

Gene-environment Interactions

The fact that everyone is not obese within our current environment suggests either that many people are able to maintain a relatively high level of energy expenditure, though regular physical activity, or that they are able to restrict their energy intake in line with their low rate of energy expenditure (Hill & Melanson 1999).

For example, some individuals appear to be relatively insensitive (low response) to dietary interventions, whereas others are quite sensitive (high response). There is strong evidence that variability in the response to diet is partly determined by genetic factors, especially for lipid and lipoprotein phenotypes. Direct evidence comes from the fact that the phenotypic response to diet is determined partly by the baseline value of the phenotype that is itself affected by genetic factors (Pérusse & Bouchard 2000). For example, some 50% of the population variance in fasting serum cholesterol is genetically determined (Hopkins 1992).

The study of gene-environment interactions is still a relatively new subject and there have been few studies investigating this issue. The available literature is mainly from twin studies, rather than studies of the general population (Samaras et al. 1998).

A gene-environment interaction is defined as "a different effect of an environmental exposure on disease risk in persons with different genotypes" or as "a different genotype on disease risk in persons with different environmental exposure" (Ottman 1990). Different models have been postulated to help investigate the relationships between genetic predisposition and associated risk factors and disease in an epidemiologic framework. A summary of these models is shown in Figure 9-1.

Gene-environment interaction effects could be important in the aetiology of obesity at two levels:

First, they could be involved in determining susceptibility to gaining fat in response to environmental risk factors such as a high fat diet or low physical activity. Second, they could be involved in determining the susceptibility of obese individuals and families to the development of co-morbidities associated with obesity (such as diabetes, hyperlipideamia etc) or in their responses to treatment (Pérusse & Bouchard 2000).

Pérusse et al studied dietary fat intake and weight gain over a 6-year period in 361 women, with and without family history of obesity (defined as having at least one obese parent). High dietary fat intake was associated with a significant increase in BMI and the development of obesity, but only in women with a familial predisposition (Pérusse et al. 2000).

9.2 METHODS

The BMI of offspring and parent generations were divided into three groups according to the WHO Criteria; <25 kg/m^2 as normal weight, 25-29.9 kg/m^2 as overweight and ≥30 kg/m^2 as obese. Offspring BMI categories were then cross-tabulated across parental BMI categories, giving nine groups of offspring, based on parent and offspring obesity categories. Contrasting offspring groups (e.g. normal weight offspring with obese parents verses obese offspring with obese parents) were compared in their behavioural and environmental factors. Multinomial logistic regression was used to test differences in environmental and behavioural variables between offspring in different categories, using normal weight offspring as the reference group. Linear regression was used to test the same association using offspring BMI as a continuous variable. Statistical procedures were performed using STATA (StataCorp 1999).

Although this is not a case-control study, the data allow the calculation of odds ratios. Odds ratios and interactions were estimated using the two-by-four table (Table 9-1), suggested by Botto et al(Botto & Khoury 2001). Cases were defined as offspring with BMI≥30kg/m^2 while controls were defined as offspring with BMI<25kg/m^2. Environmental and behavioural factors were the exposures and parental obesity was used as the potential marker of genetic susceptibility. A positive family history was defined as mid-parental BMI≥30 kg/m^2 and a negative family history as mid-parental BMI <25 kg/m^2.

9.3 RESULTS

Correlates of high mid-parental BMI

Parents in the mid-parental BMI range ≥30kg/m^2 include more in manual occupations (71% of the fathers and 60% of the mothers) and fewer current smokers (45% of the fathers and 29% of the mothers, Table 9-2). Regression analysis showed that smoking was negatively associated with mid-parental BMI in fathers ($p<0.001$) and mothers ($p<0.001$). Paternal, but not maternal, social class was significantly associated with high mid-parental BMI ($p=0.027$).

Characteristics of offspring across mid-parental BMI categories

In this population, 38% of mid-parental BMI values were below 25 kg/m^2, 54% were in the range 25-29.9 kg/m^2 and 9% were 30 kg/m^2 or above (Table 9-3).

The offspring of obese parents were more likely to be in manual occupations (39 v 26%) and to be current smokers (31 v 25%) than offspring of parents with BMI <25 kg/m^2. There were no significant differences between these groups of offspring in levels of physical activity or reported intakes of energy, fat or carbohydrate. Offspring of obese parents reported higher intakes of protein. Similar characteristics of obese and normal weight offspring were found when father's and mother's BMI categories were used instead of mid-parental BMI.

Results based on analyses of variance showed differences between offspring across mid-parental BMI categories in social class ($p=0.035$) and levels of reported protein intake ($p<0.001$). There were no significant differences between offspring of obese and normal weight parents in smoking ($p=0.258$), physical activity ($p=0.372$), or reported intakes of fat ($p=0.61$) or carbohydrate ($p=0.187$).

Interactions of physical activity, smoking behaviour and social class with mid-parental BMI

In offspring reporting high levels of physical activity, the proportion with BMI less than 25 was 64% in offspring of parents with normal weight, 43% in offspring of overweight parents and 24% in offspring of obese parents (Table 9-4 and Figure 9-2). In offspring reporting low levels of physical activity, the proportion with BMI $\geq$30 kg/m^2 was 12% in offspring of parents with BMI<25 kg/m^2, 26% in offspring of overweight parents and 19% in offspring of obese parents. Similar patterns were observed between offspring in different categories of mid-parental BMI with respect to the associations of offspring social class and smoking status with offspring obesity (Figure 9-3 and Figure 9-4).

Almost one in five offspring in this population are obese. However, the obese offspring are not a homogenous group, as described below.

Correlates of obesity in offspring with obese parents

The offspring of obese parents (mid-parental BMI ≥30 kg/m^2) included 86 who were obese and 42 with normal BMI. Comparing these groups, obese offspring reported fewer current smokers (29 v 45%), more former smokers (31 v 21%), more in manual occupations (42 v 33%), fewer having a car (20 v 14%), and less physically active (52 v 64% "very" or "fairly" active) than offspring with normal BMI. They also had higher serum cholesterol level(5.5 v 4.6 mmol/l) and higher intakes of total protein (97 v 92 g/d). There were no significant differences in total intakes of energy, fat or carbohydrate (Table 9-4).

Obese offspring with obese parents had higher levels of reported daily intakes of almost all food groups except for fish, green vegetables, and sugar, which were higher in the normal weight offspring with obese parents (Table 9-5).

The associations of environmental and behavioural factors with obesity were compared in offspring BMI groups, using the normal weight group as the reference group. Regression models showed that none of the environmental or behavioural factors included in the model were associated with obesity compared to normal weight. However, physical activity and reported protein intake were weakly and positively associated with offspring BMI as a continuous variable.

Correlates of obesity in offspring with normal weight parents

The offspring of parents with normal BMI (mid-parental BMI <25 kg/m^2) included 78 who were obese and 522 with normal BMI (<25 kg/m^2). Comparing these groups, obese offspring reported fewer current smokers (13 v 31%), more former smokers (36 v 20%), more in manual occupations (35 v 25%), more with a manual father, and less physical activity (41 v 60% "very" or "fairly" active) than offspring with normal body weight. There were no significant differences in serum cholesterol (5.0 v 5.1 mmol/l) or in reported intakes of total energy, fat, protein or carbohydrate (Table 9-4)

Obese offspring with normal weight parents had higher levels of reported daily intakes of bread (148 v138g/d), red meat (58 v 52g/d), root vegetables (52 v 48g/d), eggs (24 v 21g/d), potatoes (133 v 128g/d), milk (587 v 497g/d) and alcohol (321 v

267g/d) than normal weight offspring. Furthermore, obese offspring had lower reported intakes of breakfast cereals (17 v 24g/d), rice and/or pasta (78 v 82g/d), green vegetables (81 v 88g/d), and soft drinks (191 v 152g/d) than normal weight offspring (Table 9-5).

Regression analysis showed that the obese group with normal weight parents was positively associated with manual social class ($p=0.003$), physical inactivity ($p<0.001$), reported protein intake ($p=0.026$) and negatively associated with reported intakes of fat ($p=0.026$) and carbohydrate ($p=0.004$). Similar associations were found with offspring BMI except that individual social class was no longer significant. However, paternal social class was positively associated with offspring BMI ($p=0.003$).

Characteristics of obese offspring with contrasting family predisposition

The next set of comparisons compared the obese offspring of obese parents with the obese offspring of parents with normal weight. Only 9% of offspring with normal weight parents were obese while 43% of offspring of obese parents were obese. Comparing these groups, offspring with a family predisposition (i.e. mid-parental BMI >30) included more current smokers (29 v 13%), fewer never smokers (40 v 51%), more in manual occupations (42 v 35%), fewer with a manual father (71 v 78%), more physically active (52 v 41%), and higher reported intake of energy, fat, protein, and carbohydrate compared with the obese offspring without family disposition.

The reported daily intakes of food groups were higher in obese offspring with a family predisposition except for alcohol intake, which was higher in obese offspring without family predisposition (Table 9-5).

Characteristics of normal weight offspring with contrasting family predisposition

The next analysis compares the normal weight offspring of normal weight parents with the normal weight offspring of obese parents. There were 60% of normal weight offspring with mid-parental BMI<25 kg/m^2 compared to 21% of normal weight offspring with mid-parental BMI>30 kg/m^2. Comparing the two groups, those with

mid-parental BMI>30 kg/m^2 included more current smokers (45 v 31%), fewer never smokers (33 v 49%), more in manual occupations (33 v 25%), more with manual fathers (75 v 61%), higher reported levels of energy, fat and protein intake and lower levels of serum cholesterol compared to offspring with mid-parental BMI <25 kg/m^2. There was no significant difference in reported physical activity or carbohydrate intake between the two groups.

There were no major differences in dietary intake between normal weight offspring with and without family predisposition. Normal weight offspring with family predisposition had higher reported intakes of poultry (51 v 40g/d), fish (46 v 35g/d), butter (14 v 12g/d) and soft drinks (171 v 152g/d) and low reported intakes of rice and/or pasta (76 v 82g/d), milk (468 v 497g/d) and alcohol (250 v 267g/d) compared with normal weight offspring without family predisposition (Table 9-5).

Testing for gene-environment interactions

A test for gene-environment interaction was carried out for categorical variables including smoking, social class, father's social class, physical inactivity and mid-parental BMI as a putative marker of familial susceptibility: where BMI <25kg/m^2 indicating the absence of familial susceptibility and mid-parental BMI ≥30kg/m^2 indicating the presence of familial susceptibility.

The odds ratios for familial effects were high, regardless of the exposure factors. The odds ratios for offspring with obese parents was 15.7 in never smokers, 7.2 in the non-manual group, 33.3 for offspring with non-manual fathers and 16.3 for physically active offspring. These findings are consistent with the finding reported in previous chapters that family predisposition has a major role in the development of obesity in this population.

Smoking as a behavioural exposure fits a synergetic multiplicative model. The odds ratio for the familial factor (mid-parental BMI≥30kg/m^2) was 15.7 and the odds ratio for the smoking factor was 0.4. The odds ratio for combined familial and environmental factors was 8.5 (Table 9-6). However, the odds ratio for former smoking and familial factors was 19.4, which was higher than the odd ratio for familial effect only (15.7) and former smoking (1.74) on their own.

Individual social class also fits the synergetic additive interaction model. The odds ratio of combined gene and environmental exposures was 10.3. The odds ratio summarising the relation between the risk factors was 1.36 within cases and 0.78 within controls.

The odds ratio for the combination of familial effect and fathers manual social class effect was less than the odds ratio of the familial effect on its own. The odds ratios were 22.2 for gene-environment exposures and 33.3 for the gene factor. The gene-environment interaction follows an antagonistic model because the odds ratio of combined exposure was less than the odds ratio of gene only and environment only combined together.

It is not clear whether the model of gene-environment interaction for physical activity follows the multiplicative or the additive scale. The odds ratios of the risk factors within the cases and controls were less than one (Table 9-6).

9.4 Discussion

The findings of this chapter show the complicated inter-relationships of risk factors for obesity. The availability of parental data provided the chance to study the interaction between family predisposition and different environmental and behavioural factors.

Family susceptibility appears to be the strongest factor associated with offspring obesity (see Chapter Eight). Familial susceptibility reflects shared genes and shared environment. The influence parental environment and behaviour seems to be minor. Offspring population are more likely to be in the non-manual social and less likely to be current smoker unlike their parents (see Chapter Six).

This study supports the theory of gene-environment interactions that either enhance or reduce the risk of obesity development in this population. Smoking alone protects from weight gain and further protects those with family predisposition. A contrary effect was found in former smokers. Stopping smoking increases the risk for obesity development and is increased further in the presence of family predisposition.

Individual social class was not associated with the obesity development in this population (odds ratio of 0.8). However, the presence of family predisposition in offspring in the manual group increases the risk of obesity development. Similarly, father's social class was not associated with offspring obesity, but the influence of family predisposition is reduced if offspring had a manual father. These two observations are hard to interpret. Although social class, as measured by father's social class during childhood and by individual social class in adult life, might show significant independent effect in regression analysis, it appears that in this population social class works on obesity development in association with other factors. Further research investigating the effect of social mobility on obesity development is required to understand how environmental and behavioural factors interact and change as individuals move from one social class to another.

The risk of obesity associated with physical inactivity increases if offspring have a family predisposition. Some studies have reported that physical activity aggregates in families either because of common genes or shared environments (Braxton 2003;

(Moore et al. 1991). In addition, in a cross-sectional study, parents inactivity was a strong and positive predictor of inactivity in their offspring (Fogelholm et al. 1999). However, this observation was not confirmed in other studies (Aarnio et al. 1997).

The methods used to test for gene-environment interaction have some limitations. The method is oversimplified, by assuming that exposure variables and family predisposition are dichotomous variables. Family predisposition was based on combined parental BMI. However, as shown in previous chapters, mid-parental BMI is a good marker of family susceptibility.

Only the extreme categories (normal weight and obese) were included in the calculation of odds ratios and the overweight group was excluded. However, the extreme groups are the most and least likely to show genetic effects.

Finally, this study lacked twin data which would be helpful in quantifying the separate genetic and environmental effects on obesity development.

The method used provides estimates of the odds ratios for each factor separately, which can be combined to assess departure from specified interaction models. Moreover, this method provides the distribution of exposure among controls (normal weight offspring) and helps to evaluate the independence of the distribution of the genetic and environmental factors in the underlying population.

Further, the characteristics of offspring with contrasting family predisposition within this population supported the gene-environment hypothesis. Normal weight offspring with obese parents were more likely to be current smokers, to be more physically active and to have manual parents. Normal weight offspring with obese parents reported less consumption of almost all food groups except fish and vegetables, when compared with obese offspring with similar family predisposition. This observation might explain why they have normal weight despite their predisposition.

On the other hand, obese offspring with normal weight fathers were more likely to be former or never smokers, to be less physically active and to have a manual father. The eating habits of this group are interesting because they reported high intakes of energy-dense and high protein foods and low intakes of rice and vegetables, which are considered as healthier foods. It appears that the quality rather than the quantity of

food affects obesity development in offspring with no family predisposition. Similar findings have been reported in young girls aged 5 and 9 years old. This study found that girls with a family predisposition tended to consume more snacks (snacks are used as a measure of unhealthy eating) in front of the TV compared with girls without a family predisposition (Francis, Lee, & Birch 2003).

This finding is very important for intervention programmes. Normal weight offspring with a family predisposition eat similar types of food but in smaller quantities, while obese offspring without a family predisposition tend to eat relatively unhealthy food. This finding seems clear, notwithstanding the possibility of under-reporting in obese individual (see Chapter Seven).

People are obese for various reasons and the individual response to these factors differ accordingly. For example, obese offspring with a family predisposition show a combination of behavioural and environmental factors. Higher proportions of such offspring are current smokers and have higher levels of reported physical activity. These factors are usually associated with a lower prevalence of obesity, i.e. their effect is insufficient to protect against obesity when mid-parental BMI is high. At the same time, a high proportion of such offspring are also in the manual social class, are less likely to have a manual father and have higher levels of reported macronutrients and food intake all factors which are usually associated with obesity.

These factors appear to act differently in normal weight offspring with and without a family predisposition. Normal weight offspring with a family predisposition are more likely to be current smokers, to be in the manual social class, with manual fathers, and to have a higher level of reported intakes of macronutrients. i.e. normal weight may be due to combination of current smoking and insensitivity to the effect of social class and increased food intake.

Identification of individuals at risk of obesity, the development of complications associated with obesity, and the identification of those likely to be resistant to dietary intervention and hence requiring, perhaps, more drastic or better-adjusted prescription.

9.5 SUMMARY

The results of this chapter explain part of the variation in individual BMI. Familial susceptibility appears to promote or restrict the influence of different environmental and behavioural factors. Individuals with a family predisposition to obesity are at higher risk of becoming obese if they are former smokers, in the manual social class and physically inactive. They are less likely to be obese if they are current smokers or have a manual father.

The characteristics of individuals with contrasting family susceptibility were described in this chapter and support the previous observation. Normal weight offspring with family susceptibility are current smokers and more physically active. Obese offspring with no family susceptibility are either former or never smokers, and less physically active.

Familial susceptibility, defined by mid-parental obesity, is the main factor associated with offspring obesity identified for the studies population. Offspring with familial susceptibility will become obese whatever their behaviour. However the extent of familial susceptibility effect depends on the environmental and behavioural factors.

Table 9-1: Layout of a case-control study assessing the effect of a genotype and an environmental factor

G*	E*	Cases	Controls	OR		Contrast
+	+	a	b	ah/bg	A	A v D
+	-	c	d	ch/dg	B	B v D
-	+	e	f	eh/fg	C	C v D
-	-	g	h	1	D	Reference
Other measures			OR	Main information		
Case only odds ratio			ag/ce	Departure from multiplicative model of interaction		
Control only odds ratio			bh/df	Independence of factors in the population		
Multiplicative interaction			A/(BxC)	Deviation from multiplicative model of interaction		
Additive interaction			A-(B+C-1)	Deviation from additive model of interaction		

*G, genotype; E, environmental factor.

Table 9-2: The characteristics of parents across mid-parental BMI

		Mid-parental BMI		
		<25	**25-29.9**	**>30**
Father	BMI (mean (SD))	23.8 (2.5)	27.0 (2.6)	30.1 (3.1)
	Never smoker	100	183	28
		17.3%	23.6%	23.5%
	Former smoker	121	237	38
		20.9	30.5	31.9%
	Current smoker	357	357	53
		61.8%	30.5%	44.5%
	Non-manual	219	241	35
		38.2%	31.3%	29.4%
	Manual	355	530	84
		61.8%	68.7%	70.6%
Mother	BMI (mean (SD))	22.7 (2.5)	27.0 (2.9)	33.9 (4.7)
	Never smoker	215	394	73
		37.2%	50.7%	61.3%
	Former smoker	32	73	11
		5.5%	9.4%	9.2%
	Current smoker	331	310	35
		57.3%	39.9%	29.4%
	Non-manual	271	315	47
		49.4%	41.7%	40.5%
	Manual	278	440	69
		50.6%	58.3%	59.5%

Table 9-3: Characteristics of offspring in different parental obesity categories.

	BMI categories								
	Mid-parental			Father			Mother		
	<25	25-29.9	≥30	<25	25-29.9	≥30	<25	25-29.9	≥30
	879 (37.7%)	1253 (53.7%)	201 (8.6%)	856 (36.7%)	1214 (51.9%)	265 (11.3%)	1046 (44.8%)	934 (40.0%)	355 (15.2%)
Obesity (BMI≥30)	8.9% (78)	20.4% (253)	42.8%*** (86)	12.1 (103)	18.1 (218)	36.6*** (97)	11.5 (119)	19.4 (179)	33.5*** (119)
Smoking									
Never	49.4% (434)	47.0% (589)	38.3% (77)	47 (488)	47.1 (407)	47.1 (197)	50.3 (526)	44.6 (417)	44.5 (158)
Former	25.3% (222)	28.7% (360)	30.3% (61)	22.3 (231)	32.4 (280)	31.6 (132)	25.9 (271)	28.9 (270)	29.0 (103)
Current	25.4% (223)	24.3% (304)	31.3% (63)	30.7 (319)	20.6 (178)	21.3 (89)	23.8 (249)	26.4 (247)	26.5 (94)
Manual social class	26.2% (236)	32.9% (412)	39.3%** (79)	27.4 (284)	33.1 (28.6)	37.3 (156)	26.9 (281)	33.6 (314)	37.2** (132)
Physical activity									
Fairly – very physically active	56.2% (494)	54.7% (685)	56.8% (114)	58.1 (497)	53.8 (652)	55.1 (146)	56.1 (586)	53.5 (500)	58.6 (208)
Not physically active	43.8% (3850	45.3% (567)	43.3% (87)	41.9 (359)	46.2 (561)	44.9 (119)	43.9 (459)	46.5 (434)	41.4 (147)
Total energy intake (kcal/day)	2227 (564)	2184 (570)	2312 (583)	2224 (588)	2195 (554)	2253 (591)	2212 (566)	2205 9576)	2228 (562)
Total fat intake (g/d)	75.6 (23)	74.9 (24)	81 (26)	75.9 (24)	75 (23)	77.5(25)	75.1 (23)	75.8 (24)	77.5 (25)
Total protein intake (g/d)	86.8 (20)	88.0 (21)	94.0 (21)***	87.9 (22)	88 (20)	91.2(22)**	87.2 (20)	88 (24)**	91.1 (22)
Total carbohydrate intake(g/d)	276.8 (79)	270 (80)	281 (79)	275 (80)	271 (79)	277 (82)	275.5 (79)	271 (80)	274 (97)

***p<0.001, **p<0.01, *p<0.05 level of significance assessed using linear regression controlling age, sex and other known confounders.

Table 9-4: Characteristics of normal weight, overweight and obese offspring in different parental obesity categories

Mid-parental	<25 kg/m^2			25-29.9 kg/m^2			≥30 kg/m^2		
Offspring	<25	25-29.9	≥30	<25	25-29.9	≥30	<25	25-29.9	≥30
	59.7 (522)	31.4 (274)	8.9 (78)	38.0 (472)	41.6 (516)	20.4 (253)	20.9 (42)	36.3 (73)	42.8 (86)
Smoking %									
Never	258 (59.9)	133 (30.8)	40 (9.3)	216 (37.0)	244 (41.9)	123 (21.1)	14 (18.2)	29 (37.7)	34 (44.1)
	49.4	48.5	51.3	45.8	47.3	28.6	33.3	39.7	39.5
Former	104 (47.0)	89 (40.3)	28 (12.7)	116 (32.5)	165 (46.2)	76 (21.3)	9 (14.8)	25 (41.0)	27 (44.3)
	19.9	32.5	35.9	24.6	32.0	30.0	21.4	34.2	31.4
Current	160 (72.1)	52 (23.4)	10 (4.5)	107 (46.5)	107 (35.5)	54 (17.9)	19 (30.2)	19 (30.2)	25 (39.7)
	30.7	19.0	12.8	29.7	20.7	21.3	45.2	26.0	29.1
Manual social class%	131(55.5)	78 (33.1)	27 (11.4)	138 (33.8)	178 (43.6)	92 (22.5)	14 (17.7)	29 (36.7)	36 (45.6)
	25.1	28.9	34.6	29.2	34.5	36.4	33.3	39.7	41.9
Fathers manual class %	318 (57.6)	173 (31.3)	61 (11.1)	322 (36.3)	376 (42.4)	188 (21.2)	33 (22.6)	52 (356)	61 (41.8)
	61.4	63.4	78.2	69.0	73.3	74.9	78.6	71.2	70.9
Physical activity %									
Fairly – very physically active	313 (63.9)	145 (29.6)	32 (6.5)	290 (42.8)	282 (41.6)	106 (15.6)	27 (23.7)	42 (36.8)	45 (39.5)
	60.0	52.9	41.0	61.4	54.7	42.1	64.3	57.5	52.3
Not physically active	209 (54.4)	129 (33.6)	46 (12.0)	182 (32.4)	234 (41.6)	146 (26.0)	15 (17.2)	31 (35.6)	41 (47.1)
	40.0	47.1	59.0	38.6	45.3	57.9	35.7	42.5	47.7
Car ownership%	82 (63.1)	36 (27.7)	12 (9.2)	72 (45.0)	47 (29.4)	41 (25.6)	6 (18.2)	10 (30.3)	17 (51.5)
	15.7	13.1	15.4	15.3	9.1	16.2	14.3	13.7	19.8
Total energy intake kcal/day (SD)	2219(559)	2247(557)	2209(634)	2159(590)	2197(575)	2216(520)	2295 (625)	2306(611)	2324(545)
Total fat intake (g/d)	75(23)	76(23)	76(27)	75(27)	74(23)	76(21)	81(24)	80(30)	83(24)
Total protein intake (g/d)	86(20)	88(20)	89(26)	86(21)	88(22)	91(20)	92(22)	92(21)	97(21)
Total carbohydrate intake(g/d)	279(80)	275(77)	269(83)	269(80)	271(82)	270(75)	276(84)	283(77)	282(79)
Serum cholesterol	5.1 (0.93)	5.5(1.1)	5.5(0.94)	5.04(0.92)	5.41(0.92)	5.43(0.96)	4.62(0.89)	5.35(0.92)	5.52(0.98)

Table 9-5: Mean daily intake of food groups in normal weight, overweight and obese offspring with and without family predisposition

Means	<25			25-29.9			>30		
	<25	25-29.9	>30	<25	25-29.9	>30	<25	25-29.9	>30
Bread	138.0	135.0	148.4	131.5	138.3	144.1	138.3	139.8	156.4
Cereals	23.6	21.0	17.4	23.0	20.7	22.4	28.1	23.7	25.7
Rice/pasta	81.7	83.9	77.5	82.2	83.4	84.7	76.3	81.8	83.4
Red meat	51.5	56.5	58.0	54.3	54.0	55.8	49.0	64.1	59.5
Poultry	39.6	41.1	40.6	40.2	41.4	43.5	50.5	43.0	40.6
Offal	1.8	2.1	2.0	1.8	2.2	2.1	1.7	2.2	3.5
Fish	34.7	32.7	34.1	35.2	34.8	36.9	45.6	30.7	41.6
Puddings	64.3	65.1	63.6	69.3	67.9	65.7	60.4	73.6	68.5
Root vegetables	47.8	49.6	52.3	51.1	49.8	51.7	49.3	57.3	61.7
Green vegetables	88.4	87.7	81.2	88.0	88.2	92.1	91.1	89.6	88.8
Egg	21.1	22.9	24.3	22.4	22.9	22.2	24.7	23.6	24.8
Sugar	20.4	12.9	8.8	15.2	11.7	8.3	18.3	12.7	9.8
Fruits	108.8	105.4	103.6	114.2	112.8	114.8	111.4	111.3	113.7
Oil	6.8	6.2	6.0	6.4	6.0	6.5	6.7	7.3	7.3
Milk	497.3	536.3	587.0	527.3	599.7	617.2	468.0	587.5	646.7
Cheese	19.1	21.0	17.3	18.5	21.0	21.7	22.1	23.8	24.5
Butter	11.8	10.8	11.8	11.7	10.3	10.7	13.8	10.7	14.8
Margarine	12.7	12.7	12.3	14.3	14.0	13.1	11.9	15.8	16.9
Soft drinks	152.3	192.7	190.8	154.9	178.0	194.1	170.8	173.1	186.3
Potatoes	127.6	141.4	133.4	123.0	135.5	129.1	129.4	146.8	139.3
Alcohol	267.0	374.2	321.1	233.1	328.9	277.2	249.6	284.6	264.4

Table 9-6: Odds ratios for gene, environment and gene-environment interactions in the offspring generation

Parental obesity	Smoking	Cases	Controls		OR	Exposure frequency in controls %	Main interaction
+ (Obese)	+ (Current)	25	19	OR ge	8.48	4.2	Cases only OR=2.94
+ (Obese)	- (Never)	34	14	OR g	15.66	3.1	Controls only OR=2.19
- (Non-Obese)	+ (Current)	10	160	OR e	0.4	35.5	Multiplicative interaction 1.35
- (Non-Obese)	- (Never)	40	258	Reference	1	57.2	Additive interaction 6.58
Parental obesity	Former smoker	Cases	Controls		OR		
+ (Obese)	+ (former)	27	9	OR ge	19.35	2.3	Cases only OR=1.36
+ (Obese)	- (never)	34	14	OR g	15.66	3.6	Controls only OR=0.78
- (Non-Obese)	+ (former)	28	104	OR e	1.74	27.0	Multiplicative interaction 1.76
- (Non-Obese)	- (never)	40	258	Reference	1	72.1	Additive interaction 3.33
Parental obesity	Social class	Cases	Controls		OR		
+ (Obese)	+ (M)	36	14	OR ge	10.29	3.7	Cases only OR=1.36
+ (Obese)	- (NM)	50	28	OR g	7.14	7.4	Controls only OR=0.78
- (Non-Obese)	+ (M)	27	131	OR e	0.82	34.7	Multiplicative interaction 1.76
- (Non-Obese)	- (NM)	51	204	Reference	1	54.1	Additive interaction 3.33
Parental obesity	Fathers social class	Cases	Controls		OR		
+ (Obese)	+ (M)	61	33	OR ge	22.18	5.9	Cases only OR=1.34
+ (Obese)	- (NM)	25	9	OR g	33.3	1.6	Controls only OR=2.35
- (Non-Obese)	+ (M)	31	318	OR e	1.1	56.4	Multiplicative interaction 0.61
- (Non-Obese)	- (NM)	17	204	Reference	1	36.2	Additive interaction 11.22
Parental obesity	Physical activity	Cases	Controls		OR		
+ (Obese)	+ (PIA)	41	15	OR ge	26.74	2.7	Cases only OR=0.63
+ (Obese)	- (PA)	45	27	OR g	16.3	4.8	Controls only OR=0.83
- (Non-Obese)	+ (PIA)	46	209	OR e	2.15	37.1	Multiplicative interaction 0.76
- (Non-Obese)	- (PA)	32	313	Reference	1	55.5	Additive interaction 9.29

Gene in this table refers to familial susceptibility (there is not any genetic measurements included).
OR ge, joint genotype and environmental factors, OR g, genotype alone, OR e, environmental factor alone.
M, manual group. NM, non-manual group
PIA, physically inactive. PA, physically active.

Figure 9-1: Hypothetical models describing the relationship between genetic susceptibility to disease and risk factors for disease in an epidemiologic framework, adopted from (Ottman 1990)

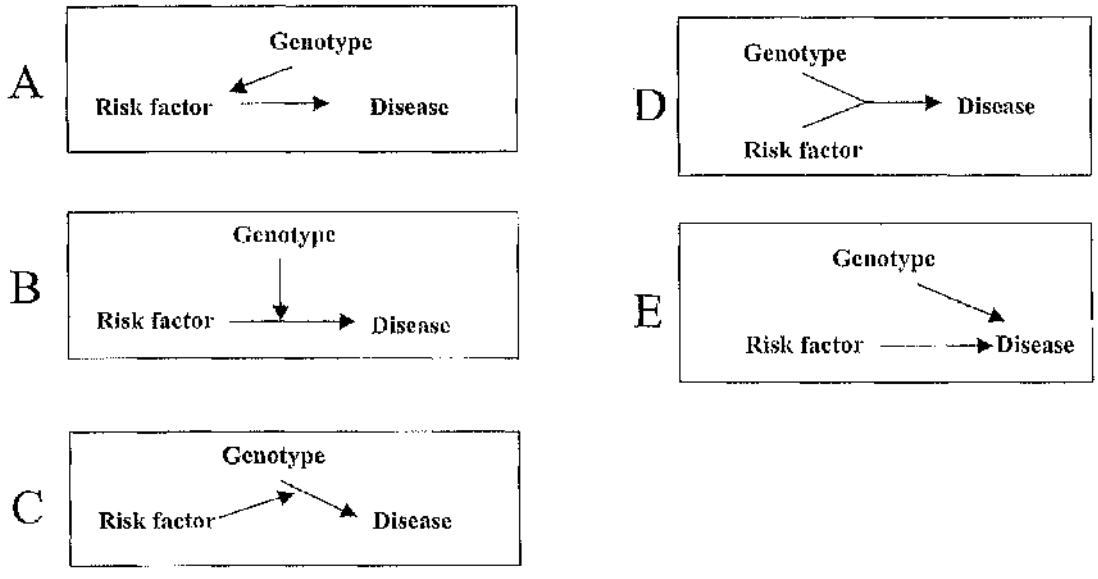


Figure 9-2: Prevalence of obesity and normal weight in offspring with high and low physical activity by their parent's BMI categories.

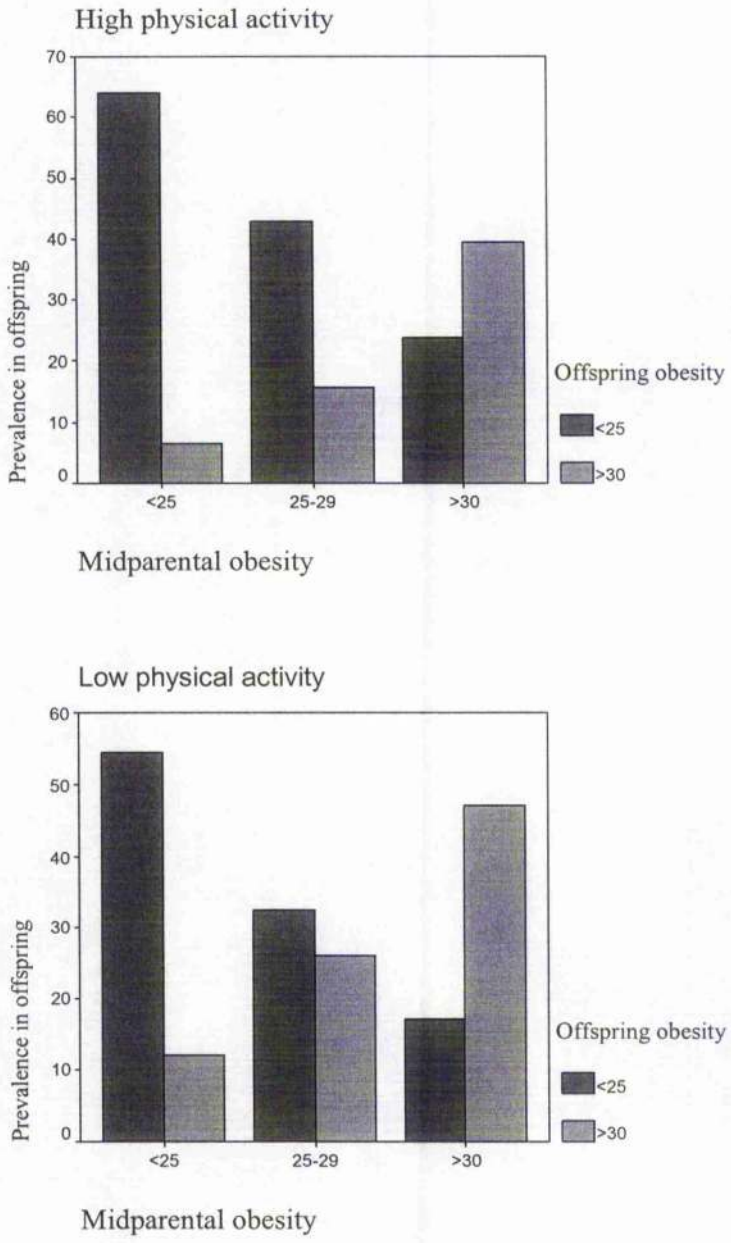


Figure 9-3: Prevalence of obesity and normal weight in offspring smoking groups by their parent's BMI categories.

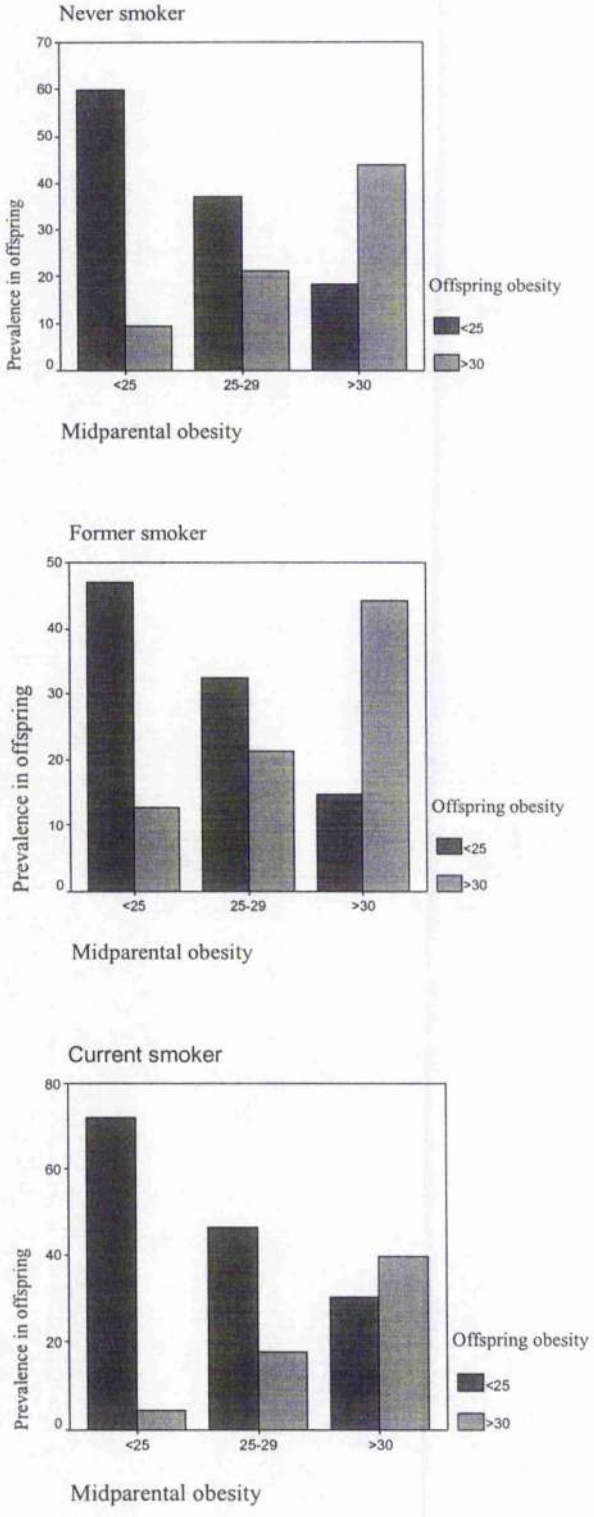
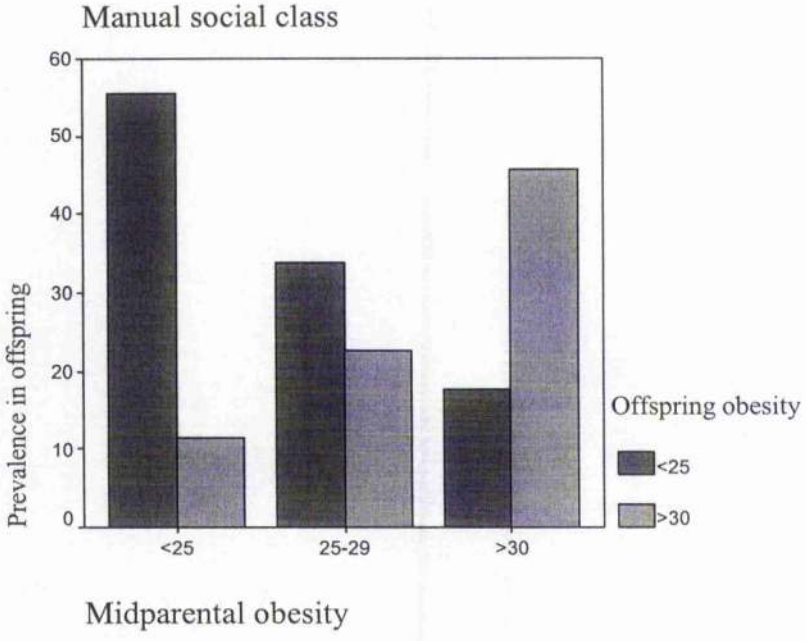
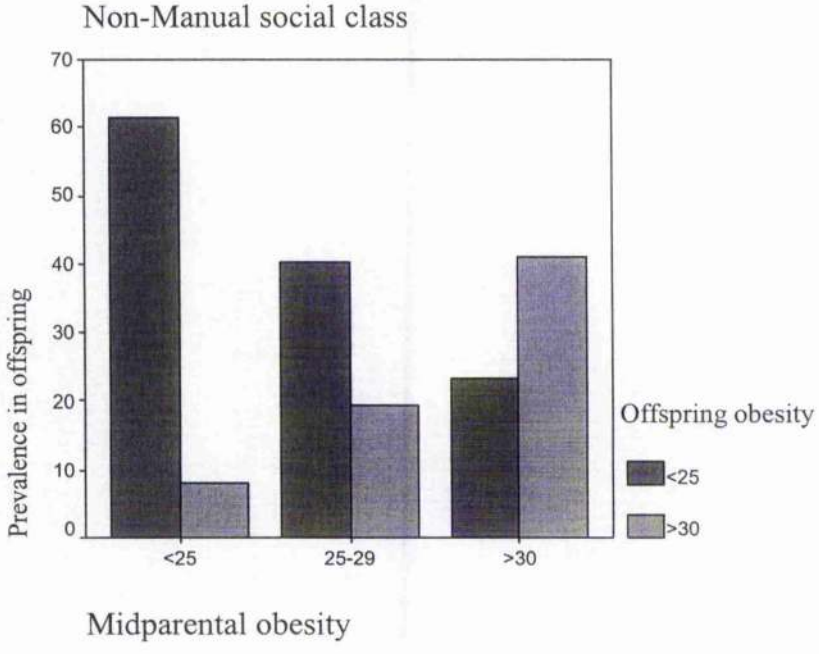


Figure 9-4: Prevalence of obesity and normal weight in offspring social class groups by their parent's BMI categories.





CHAPTER 10

GENERAL DISCUSSION AND CONCLUSIONS

10.1 Introduction

This chapter summarises the main findings of the thesis, concerning the major health complications of obesity, changes in the prevalence of obesity between parent and offspring generations, and the role of mid-parental BMI as a marker for offspring obesity and their implications for policy and practice.

10.2 Methodological Considerations

Family study population

The participating offspring and their parents had undertaken similar screening surveys at overlapping age ranges with a 20 year interval between surveys.

Participants in the Renfrew and Paisley study were representative of the general population, aged 45-64, of these two towns. Participants in the offspring study could only be compared with the study population of the Scottish Health Survey (SHS). Offspring were not representative of the SHS population and had a generally better health profile (see Chapter Three). Participating offspring were more likely to be never smokers, less likely to be in the manual social class, and had lower blood pressure, serum cholesterol and BMI than SHS participants.

However, they were representative of all offspring eligible to take part in the Family Study, who were defined as the offspring of couples who took part in the Renfrew and Paisley Survey, who lived locally in 1996 and were aged between 30 to 59 years. There were no significant differences between participant and non-participant offspring with respect to their age, paternal social class or parental obesity.

The characteristics of the study populations allowed the study of obesity aggregation in families and the heritability of BMI. It is important to note, however, that the estimated heritability in this study was a component of both genetic and non-genetic factors, since families tend to share not only genes, but also behaviours and environments. Additional twin data would help in explaining to what extent the variation in BMI is explained by genetic factors, but such data were not available. Because monozygote twins have the same genes, any variation in the genotype is attributable to behavioural and environmental effects.

Analyses were mainly performed at the level of individuals, rather than families. The number of sibs was insufficient to study differences within families. A practical consequence (in chapter 9 for example) is that obese and normal weight offspring with mid-parental BMI$\geq$30kg/m^2 may not be related. The same is true for those with mid-parental BMI<25kg/m^2.

However, controlling for familial clustering was included in the analyses of changes in obesity prevalence and BMI. Familial clustering did not affect the main findings of the study.

Body mass index

In this thesis, the prevalence of obesity, its correlates and health impact were studied using a definition of obesity based on body mass index. This is the most commonly used measure of body fatness, independent of body height. The cut-off points of BMI between 25-29.9kg/m^2 to define overweight and BMI≥30kg/m^2 to define obesity were defined by the World Health Organisation based on the associated increased risk of mortality (World Health Organisation 1998). The definition of these cut-off points was helpful in comparing the prevalence of obesity between and within populations.

Both the Renfrew and Paisley (MIDSPAN) general population study and the follow up study of offspring involved BMI measurements, which provided the opportunity, therefore, to study trends in the prevalence of obesity and in mean BMI between parents and offspring.

Waist circumference was measured in offspring but not in parents and was rejected therefore, as a basis for comparing obesity in the two generations. Waist circumference is a measure of abdominal fat, as well as the total body fat (Han et al 1996;Han et al 1995;Han et al. 1997). The focus of this study is general obesity and total body fat, and for this purpose, BMI is the established measure. Although, waist circumference is a better measure of body fat in the elderly, the populations in this study were not old.

Dietary data

Participating offspring completed food frequency questionnaires, which were then converted into estimates of the intakes of food groups and nutrients. This questionnaire had been tested and validated by Yarnell (Yarnell et al 1983).

One limitation of food frequency questionnaires is the possibility of under-reporting. The prevalence of under-reporting was estimated in this study using the ratio of

energy intake (EI) to the basal metabolic rate (BMR). More under-reporting was found in men, and in non-manual and obese groups.

The results of analyses of dietary data were interpreted with caution, therefore, especially the associations between dietary data and BMI in obese people. Estimated under-reporting of certain food groups influenced estimates of fat, carbohydrate, and protein intake and thus influenced the observed associations with BMI. In general, there was no association between estimated intakes of macronutrients and BMI, except for protein intake. The dietary data were helpful, nevertheless in describing differences in nutrient intake between men and women, and between social class groups.

Physical activity

The only measure of physical activity was based on self-reporting. Participants were asked to classify themselves as very physically active, fairly active, not very active and not active at all. Self-reported physical activity might be subject to recall bias or inappropriate reporting (Booth 1996).

Nevertheless, a low level of reported physical activity was strongly associated with offspring obesity, especially in women. Physical activity was negatively associated with high BMI, after controlling for possible confounders.

10.3 Main findings

Health complications of obesity

The Renfrew and Paisley population is characterised by high levels of deprivation and mortality. Consistent with previous studies, the risk of death was high in the two ends of the BMI distribution. High mortality in individuals with low BMI was not confounded by previous illness or smoking status. The risk of mortality was higher in the manual social class and in smokers with high BMI.

The observed pattern of association between BMI and all cause mortality might be explained by the combination of a positive association between BMI and cardiovascular causes of mortality and a negative association with respiratory causes of mortality. It is preferable, therefore, to analyse cause specific mortality data.

Mortality data can be confounded by other underlying factors, because mortality represents the accumulation of many different factors. However, data on site-specific cancers provide strong evidence of the association between BMI and the risk of cancer. In this study, BMI was positively associated with breast cancer and was negatively associated with lung cancer.

Several studies have investigated the relationship between obesity and breast cancer. Results generally suggest that the risk of breast cancer starts to increase in post-menopausal obese women while pre-menopausal obese women are at a lower risk of breast cancer. Most women in this study were post-menopausal and our results are consistent with previous studies.

The relationship between BMI and lung cancer found in this study has been reported previously, and is thought to be confounded by smoking or previous illness. However, these explanations were not supported in this study.

The association between BMI and the risk of lung cancer did not change after excluding cases identified in the first years of follow-up, or using second measurements of BMI after 2 to 4 years of the first screening. Furthermore, in those who survived 20 years after the first screening, individuals with low BMI still had a higher risk or lung cancer than those with high BMI.

Controlling for smoking was difficult because most of the cases were smokers. However, we managed to compare lung cancer cases with cancer-free individuals with low BMI and high BMI in the smoking group. The rate of lung cancer was higher in individuals with low BMI compared to those with high BMI. In addition, we investigated the association between BMI and smoking-related cancers. There was no clear pattern between BMI and smoking related cancers. Finally, we tested for statistical interactions between smoking and BMI and found none (i.e. the association between BMI and the risk of lung cancer was similar in all smoking groups).

Finally, the association between BMI and the risk of lung cancer was not specific for the Renfrew and Paisley population. This association was found in another cohort, the collaborative occupational study, screened at similar time as Renfrew and Paisley cohort. Participants of this cohort were recruited from the central belt of Scotland, and had measurements similar to the Renfrew and Paisley survey.

Changes in the prevalence of obesity and mean BMI

The prevalence of obesity (BMI$\geq$30kg/m^2) was 18% in men and women in the offspring generation. Compared with the prevalence of obesity in the parent generation, the prevalence of obesity doubled in male offspring. The prevalence of obesity in female women offspring was slightly higher than that in the mother's generation.

These findings show first, that the prevalence of obesity has increased in the population as a whole. Second, that the prevalence of obesity in men is catching up with the prevalence of obesity in women. The difference in prevalence of obesity between mothers and daughters was small because the prevalence of obesity in the mother's generation was already high in the 1970s.

However, the increase in the prevalence of obesity was not accompanied by a shift in the overall distribution of BMI in the offspring population. Instead, only the top part of the BMI distribution in offspring was different from the BMI distribution in parents. The lower parts of both distributions were similar.

This finding could be explained by the observed difference between the two generations being the result of missing data from migrants who had left the study area or from non-participants. This possibility was rejected for two reasons. First, there was no difference between participants and non-participants or between participant and migrant offspring in their age, paternal social class or the prevalence of obesity in parents. Second, similar observations have been reported in studies in the United States and France. We cannot compare this observation with other studies because most studies report changes in the prevalence of obesity and in mean BMI. Few studies have investigated changes in the distribution of BMI between generations. The observation of skewing and anchoring was found in men and women, in smoking groups and in manual and non-manual social groups. However, the points where skewing starts were different in each group. The non-manual group showed, in addition to the observation of skewing, an overall shift in BMI distribution, with higher offspring BMI values at each centile point compared with the corresponding values in the parent generation.

Possible explanations of the observed "anchoring and skewing", in the lower and upper part of the BMI observations respectively, include an increased prevalence of adverse behaviours or environments in a substantial minority of the population and/or increased susceptibility to the effects of such behaviours and environments on BMI.

Offspring included more never and former smokers, fewer current smokers and fewer in manual groups when compared with the parent generation. These differences in smoking and social class groups, and their associations with BMI, were insufficient, however, to explain the observed increase in the prevalence of obesity.

More variables were collected from offspring than from parents. For example offspring reported levels of physical activity and food frequency intake were used to investigate the increased prevalence of obesity in the offspring generation.

Recent studies have attributed the increase in obesity prevalence to changes in the surrounding environment, and in particular the greater availability of energy-dense foods and the increase in sedentary lifestyles. The report of the National Audit Office

(NAO) showed that average household energy intake has decreased since 1970, while eating outside the home is increasing. Food eaten outside the home tends to be higher in fat than food consumed in the home (The National Audit Office 2001). Further, the level of physical activity has decreased through reductions in occupational exercise, the use of the cars, and increasing use of energy-saving devices such as escalators in public places (The National Audit Office 2001).

Environmental and behavioural factors, in addition to familial susceptibility, were studied to explain the increase in mean BMI. Consistent with previous studies, high BMI was positively associated with physical inactivity, reported protein intake, former smoking, manual social class, paternal social class and parental obesity (mid-parental BMI $\geq$30kg/m^2) and was negatively associated with smoking and reported carbohydrate intake.

Parental obesity was the factor most strongly associated with high BMI in offspring. However, the observed strength of the associations between high BMI and environmental and behavioural factors differed between subgroups such as gender and social class. Smoking was the main correlate of low BMI in men and physical inactivity was the main correlate of high BMI in women. We found that there is a complex relationship between lifestyle factors and BMI in different social classes. In addition to parental obesity, smoking was the main correlate of high BMI in manual and non-manual men. In women, parental obesity and smoking were the main correlates of high BMI in the manual group while parental obesity and physical inactivity were the main correlates in the non-manual group.

The association between obesity and social class has been reported previously. However, the relationship between obesity and environmental and behavioural factors within social groups has not been reported previously.

Mid-parental BMI as a predictor for offspring obesity

The main finding in this thesis is the important role of parental obesity, measured by mid-parental BMI $\geq$30kg/m^2, as a marker for offspring obesity. Mid-parental BMI showed a strong graded relationship with the prevalence of obesity in adult offspring. The prevalence of obesity was 9% in sons with normal weight parents (mid-parental

BMI<25kg/m^2), 20% in sons of overweight parents (mid-parental BMI 25-29.9kg/m^2) and 44% in sons of obese parents (mid-parental BMI≥30kg/m^2). The corresponding figures for daughters were 9%, 20% and 42% respectively.

Similar pattern was found using the fathers and mothers BMI categories. The percentage of normal weight and obese offspring show a stepwise change, and follow the stepwise changes in categories for the parents (see Figure 8-1). A similar observation was reported in the Tecumseh Study for relative weight, height, blood pressure and cholesterol (Deuscher, Frederick, & Kjelsberg 1966).

The use of mid-parental BMI had added value as a marker for family susceptibility compared to using one parental marker on its own. 85% of the mothers in the mid-parental BMI≥30kg/m^2 were personally obese while only 54% of the fathers in this group were also obese. Further 100% of both obese father and mother were classified in the obese category in mid-parental BMI categories. Similarly 100% of both normal weight father and mother were in the normal weight category. High mid-parental BMI include families with high susceptibility because it includes at least one parent with high BMI while the other might not have high individual BMI value. But when both parents have high individual BMI values this results in high mid-parental BMI and so have high combined effect on offspring.

Mid-parental BMI was the strongest factor predicting high BMI (defined by the percentage of offspring in the top tertile) in offspring compared with other environmental and behavioural factors studied in this thesis (see Chapter Seven). Men were three times more likely to be in the top part of the BMI distribution if they had parents in the top part of the BMI distribution compared to those in the lower part of the BMI distribution. Women were almost twice likely to be in the top part of the BMI distribution if they had parents in the top part of the BMI distribution.

The influence of familial susceptibility on offspring obesity was closely associated with the presence of environmental and behavioural factors. For example, the risk of offspring with obese parents becoming obese increased if they were former smokers, in the manual social class and were physically inactive and decreased if they were smokers and had a manual father.

Differences in the prevalence of obesity between individuals within groups with and without familial susceptibility are, mainly, attributable to behavioural factors. For example normal weight offspring with obese parents are more likely to be current smokers and physically active compared with the obese offspring of obese parents. On the other hand, the obese offspring of normal weight parents are more likely to be never or former smokers, and to be less physically active compared with the normal weight offspring of normal weight parents.

To summarise, the prevalence of obesity has increased the offspring population, especially in men. However, this increase in obesity prevalence was accompanied with little or no change in mean BMI. The difference in BMI distributions between parent and offspring showed anchoring at the lower part of the distribution and skewing at the upper part. This observation is not a result of selection or participation bias and it has been reported in other populations. There are two possible explanations for this observation either there is an increase in the prevalence of adverse behaviour and/or an increase susceptibility to such factors in the presence of familial susceptibility determined by mid-parental obesity.

Mid-parental BMI is a useful indicator of familial susceptibility to obesity. The prevalences of obesity show a graded relationship with mid-parental categories. Familial susceptibility is the strongest factor associated with offspring obesity and offspring will become obese whatever their behaviour. However, the extent of familial susceptibility effect depends on the environmental and behavioural factors. Individual behaviour is an important factor explaining obesity variation between individuals.

10.4 Significance of the findings

Implications for policy and practice

From this thesis we conclude that the prevalence of obesity has increased. This is likely to lead in time to health complications, mainly cardiovascular disease and cancer. The reported increase in obesity and the expected increase in its complications in the near future will result in increases in the cost of treating obesity and its complications.

It is of public health importance to develop intervention programmes to prevent and reverse weight gain. Minor changes in energy balance have potential major long-term effects on the prevalence of obesity and its complications including ostcoarthritis (Visscher & Seidell 2001).

Intervention programmes should focus on the balance between energy intake and physical activity. Obesity is a multifactorial disease. It results from small daily changes in energy intake and physical activity over time. Hill et al have suggested that food availability and portion size are important determinants of obesity. They have also suggested making the environment more conducive to physical activity (Hill & Peters 1998).

In this study we found that about 49% of the obesity cases were attributable to parental BMI≥25kg/m^2. These results suggest several preventive approaches depending on the targeted group. Targeting offspring with obese parents (mid-parental BMI≥30kg/m^2) would prevent 13% of the obesity cases, and targeting offspring with mid-parental BMI≥27.5 kg/m^2 would prevent 17% of the cases. But these come from 27% of the families. However, targeting offspring with overweight parents, this includes 61% of the families, would prevent about 50% of obesity cases. Although these number may not be impressive, prevention programmes targeting specific groups might be more effective than targeting the whole population regardless of their susceptibilities.

There has been little research on the effectiveness of prevention programmes, but there is indirect evidence that prevention programmes should be effective in tackling

the increasing prevalence of obesity. There are still low rates of obesity in some countries, and the rate of obesity varies within the same country between sexes and social class. These variations suggest environmental conditions as well as genetic factors, which increases the susceptibility to weight gain.

BMI is routinely measured in general practice and collating information about parental BMI could be useful in highlighting susceptible groups. This approach might also be useful if similar information was collected for school children.

It is possible that different educational messages could be targeted at these different groups. For example, the normal weight offspring with a family susceptibility eat similar types of food but in smaller amounts than obese offspring with a family susceptibility. On the other hand, obese offspring without a family susceptibility tend to eat relatively unhealthy food and to have low levels of physical activity compared to normal weight offspring without a family susceptibility.

Although this study was based on adults, recent studies have reported an increase in obesity prevalence in children and adolescents. Thus, prevention programmes should be directed at all age groups, including adulthood, adolescence and childhood.

Several guidelines have been published to prevent, manage and treat obesity. These include the Scottish Intercollegiate Guideline Network (Scottish Intercollegiate Guideline Network 1996), *Tackling obesity: a toolbox for local partnership action* (Davis, Giles, & Rona 1999) and *The Practical Guide: identification, evaluation, and treatment of obesity in adults* (National Institutes of Health: National Heart 1998).

Implications for research

Further research is needed to investigate the association of leanness and lung cancer in longitudinal studies. Several measurements of BMI are needed to be able to exclude those whose weight loss is caused by sub-clinical illness. These studies should include sufficient numbers of never and former smokers to control for the confounding effect of smoking. Clinical samples, biopsies, and hormonal measurements would be needed to understand the patho-physiological causes of the negative relationship between leanness and lung cancer incidence.

As discussed earlier, the focus of this study was to study general obesity and total body mass using BMI as a measurement tool. Because BMI and waist circumference measurements are highly correlated, it may be expected to find similar results for abdominal obesity. Further research is needed to investigate changes in the prevalence of abdominal obesity.

Throughout the thesis, we found accumulating evidence of the importance of parental obesity in the risk of offspring obesity. This supports the importance of a role for genes. However, identification of genes will be difficult because the expression of obesity may depend on many factors. The obesity gene map reveals that assumed loci affecting obesity-related phenotypes can be found on all chromosomes except chromosome Y (Perusse et al 2001, obesity gene map).

Our findings help planning further research to overcome this problem. We have addressed the questions "Why are certain offspring obese?" and "Why are certain offspring not obese?". By studying informative groups, that is where both offspring and parents have high BMI or both have low BMI. These are the families in which genetic effects are most and least likely to be found (Bulik & Allison 2001;Lee, Reed, & Price 1997).

In designing genetic studies of obesity, estimates of statistical power are important. Risch has shown that models of inheritance can be examined by computing a risk ratio. Risk ratios compare the prevalence of a trait in relatives with the prevalence of the trait in the population (Allison, Faith, & Nathan 1996). This ratio can be calculated for both obesity and leanness.

Understanding the aetiology of obesity well help in its treatment if not prevention. Further research is needed to investigate the pathophysiology of obesity using biomarkers such as leptin, leptin receptor or resistin in offspring with and without family susceptibility.

Finally, the pattern of familial aggregation observed for BMI is also true for height, blood pressure and serum cholesterol. Similar approaches could be used, therefore, to investigate the epidemiology of familial and non-familial factors associated with these traits.

APPENDICES

Appendix A: Chapter Five Tables

Table 1: Relative hazard ratios for all cause mortality in different BMI categories

	No	<18.5	18.5-25	25-30	>30	Linear trend
Total	7939	1.45	1	1.00	1.23	0.001
		(1.23-1.72)**		(0.95-1.05)	(1.15-1.31)**	
Men	4318	1.28	1	0.99	1.15	0.1585
		(0.93-1.75)		(0.93-1.06)	(1.04-1.27)**	
Women	3621	1.58	1	1.02	1.30	0.0011
		(1.29-1.92)***		(0.95-1.10)	(1.19-1.43)***	

Table 2: Relative hazard ratios (95% confidence interval) for mortality for all cause and specific cause of death by equal groups of BMI, by social class

		BMI equal groups									
Cause of death	**No of death**	**Group1**	**Group2**	**Group3**	**Group4**	**Group5**	**Group6**	**Group7**	**Group8**	**Group9**	***p*-trend**
All causes											
Class I.II	1245	1.18	0.97	0.898	0.85	1	0.88	1.07	0.98	1.44	0.077
		(0.93-1.49)	(0.77-1.22)	(0.71-1.14)	(0.67-1.08)		(0.69-1.12)	(0.85-1.34)	(0.77-1.25)	(1.14-1.82)**	
Class IIINM, IIIM	3853	1.1	1.02	0.9	0.89	1	0.95	0.98	1.14	1.17	0.03
		(0.96-1.26)	(0.89-1.16)	(0.79-1.04)	(0.78-1.02)		(0.83-1.1)	(0.85-1.12)	(0.99-1.3)	(1.03-1.34)**	
Class IV,V	2841	1.51	1.2	1.12	1	1	1.04	1.19	1.2	1.36	0.58
		(1.29-1.77)***	(1.02-1.42)	(0.95-1.33)	(0.84-1.19)		(0.88-1.23)	(1.02-1.4)*	(1.02-1.4)*	(1.17-1.59)***	

Table 3: relative hazard ratios (95% confidence interval) for mortality for all cause and specific cause of death by equal groups of BMI (after excluding the first five years of follow-up) by smoking status

	Cause of death	No	Group1	Group2	Group3	Group4	Group5	Group6	Group7	Group8	Group9	P-value
All causes	Non smoker	3018	1.07 (0.89-1.3)	0.85 (0.69-0.98)*	0.84 ((0.72-0.99)*	0.82 (0.7-0.96)*	1	0.94 (0.8-1.08)	1.01 (0.88-1.17)	0.98 (0.85-1.13)	1.29 (1.13-1.5)***	<0.0001
	Smoker	4002	1.34 (1.18-1.5)***	1.27 (1.1-1.4)***	1.09 (0.95-1.25)	1.05 (0.9-1.2)	1	1.05 (0.9-1.2)	1.15 (0.99-1.3)	1.26 (1.1-1.45)**	1.2 (1.05-1.4)**	0.07
All cancer	Non smoker	784	0.7 (.48-1.02)	0.56 (0.39-0.79)**	0.77 (0.57-1.04)	0.72 (0.54-0.95)*	1	0.87 (0.67-1.13)	0.97 (0.76-1.3)	0.72 (0.54-0.94)*	0.95 (0.73-1.23)	0.011
	Smoker	1286	1.3 (1.05-1.7)*	1.4 (1.12-1.76)**	1.2 (0.93-1.5)	1.13 (0.89-1.44)	1	1.1 (0.86-1.4)	1.2 (0.9-1.5)	1.1 (0.85-1.4)	1.02 (0.78-1.3)	0.004
Lung cancer	Non smoker	91	0.64 (0.21-1.9)	0.722 (0.29-1.77)	0.6 (0.25-1.5)	0.77 (0.35-1.7)	1	0.53 (0.24-1.23)	1.3 (0.66-2.5)	0.67 (0.31-1.5)	0.29 (0.1-0.79)*	0.55
	Smoker	583	1.5 (1.1-2.1)**	1.6 (1.12-2.2)**	1.2 (0.86-1.7)	1.9 (0.76-1.6)	1	1.09 (0.75-1.6)	1.2 (0.85-1.8)	0.82 (0.54-1.3)	0.72 (0.46-1.13)	<0.0001
Colorectal cancer	Non smoker	116	0.46 (.2-1.4)	0.21 (0.1-0.71)*	0.56 (0.25-1.23)	0.73 (0.37-1.4)	1	0.4 (0.18-0.88)*	0.81 (0.43-1.5)	0.68 (0.35-1.3)	0.99 (0.54-1.8)	0.28
	Smoker	102	0.74 (0.3-1.8)	1.8 (0.84-3.8)	1.1 (0.47-2.5)	1.03 (0.44-2.4)	1	1.06 (0.44-2.5)	1.12 (0.46-2.7)	1.13 (0.46-2.8)	0.94 (0.36-2.5)	0.73
IHD	Non smoker	1011	1.1 (0.78-1.5)	0.92 (0.68-1.2)	0.77 (0.57-1.05)	0.83 (0.63-1.1)	1	1.04 (0.8-1.5)	1.18 (0.92-1.5)	1.18 (0.9-1.5)	1.6 (1.27-1.03)***	<0.0001
	Smoker	1218	1.06 (0.8-1.3)	1.15 (0.9-1.5)	0.96 (0.75-1.2)	1.01 (0.79-1.3)	1	1.1 (0.86-1.4)	1.1 (0.83-1.4)	1.2 (0.9-1.5)	1.4 (1.06-1.75)	0.082
Stroke	Non smoker	443	1.33 (0.8-2.1)	0.85 (0.53-1.3)	0.98 (0.65-1.4)	0.95 (0.63-1.4)	1	0.96 (0.66-1.4)	0.88 (0.59-1.3)	0.91 (0.62-1.33)	1.4 (1.002-2)*	0.25
	Smoker	464	1.3 (0.9-1.99)	1.5 (0.98-2.2)	1.5 (1.04-2.3)*	0.97 (0.6-1.5)	1	1.08 (0.69-1.7)	1.28 (0.8-1.98)	1.9 (1.3-2.9)**	1.15 (0.72-1.8)	0.94
Respiratory	Non smoker	239	2.09 (1.22-3.6)	1.25 (0.74-2.12)	0.92 (0.53-1.6)	0.93 (0.56-1.6)	1	0.67 (0.39-1.2)	0.86 (0.5-1.4)	0.72 (0.43-1.2)	0.88 (0.54-1.45)	0.0016
	Smoker	415	2.9 (1.9-4.4)***	1.7 (1.1-2.7)**	1.4 (0.89-2.26)	1.3 (0.82-2.1)	1	0.8 (0.46-1.4)	1.5 (0.9-2.4)	1.7 (1.05-2.8)*	1.4 (0.8-2.4)	<0.0001
Digestive	Non smoker	84	0.66 (0.18-2.4)	0.4 (0.11-1.5)	0.48 (0.15-1.6)	0.72 (0.27-1.9)	1	0.91 (0.38-2.2)	1.3 (0.57-2.9)	1.6 (0.74-3.5)	1.4 (0.61-3.1)	0.0014
	Smoker	116	0.99	0.74	1.3	0.92	1	0.94	1.4	1.7	1.6	0.048
Other causes	Non smoker	450	1.2 (0.75-1.99)	1.11 (0.7-1.7)	1.9 (0.7-1.6)	0.82 (0.53-1.3)	1	1 ((0.68-1.5)	0.92 (0.62-1.4)	1.2 (0.86-1.8)	1.4 (1.04-2.11)*	0.083
	Smoker	500	1.3 (0.91-1.8)	0.96 (0.67-1.4)	0.69 (0.47-1.02)	0.88 (0.6-1.3)	1	0.9 (0.62-1.3)	0.94 (0.64-1.5)	0.99 (0.67-1.5)	1.2 (0.81-1.76)	0.86

BMI cut-off points<21.3, 21.3-22.8, 22.9-23.9, 24-24.9, 25-25.9, 26-27, 27.1-28.3, 28.4-30.4, 30.4; Adjusted for age, sex and social class
*P<0.05. **P<0.01, ***P<0.001; Follow up form time of screening 1972-6 till December 1999 excluding the first five years of follow up

Table 4: Relative hazard ratios (95% confidence interval) for mortality for all cause and specific cause of death by equal groups of BMI (after excluding the first five years of follow-up) by social class

	Cause of death	No	Group1	Group2	Group3	Group4	Group5	Group6	Group7	Group8	Group9	P-value
All causes	Non-manual	2270	1.07 (0.9-1.3)	0.996 (0.84-1.2)	0.87 (0.73-1.03)	0.85 (0.72-1.01)	1	1.01 (0.85-1.2)	1.1 (0.91-1.3)	1.1 (0.92-1.3)	1.3 (1.11-1.6)	**0.0008**
	Manual	4750	1.3 (1.15-1.4)***	1.1 (1.01-1.3)*	1.04 (0.9-1.2)	0.99 (0.87-1.2)	1	0.99 (0.88-1.10	1.1 (0.97-1.2)	1.1 (0.99-1.3)	1.3 (1.14-1.5)***	0.85
All cancer	Non-manual	701	0.8 (0.59-1.1)	0.72 (0.53-.99)*	0.84 (0.63-1.1)	0.82 (0.61-1.1)	1	0.91 (0.62-1.2)	0.85 (0.62-1.20	0.87 (0.63-1.2)	1.1 (0.8-1.5)	**0.041**
	Manual	1369	1.3 (1.01-1.6)*	1.3 (1.04-1.6)*	1.1 (0.9-1.4)	1 (0.79-1.3)	1	1.1 (0.84-1.3)	1.3 (1.01-1.6)*	0.96 (0.75-1.2)	1.02 (0.8-1.3)	0.25
Lung cancer	Non-manual	180	0.64 (0.4-1.1)	0.61 (0.35-1.1)	0.62 (0.35-1.1)	0.7 (0.4-1.2)	1	0.87 (0.5-1.5)	0.82 (0.47-1.4)	0.53 (0.28-1.05)	0.6 (0.29-1.2)	0.4
	Manual	494	1.2 (0.9-1.6)	0.89 (0.65-1.24)	0.81 (0.57-1.14)	0.74 (0.52-1.07)	1	0.64 (0.44-0.94)*	0.99 (0.7-1.4)	0.62 (0.42-0.93)*	0.41 (0.26-0.66)***	**<0.0001**
Colorectal cancer	Non-manual	71	2.6 (0.52-12.8)	3.7 (0.79-16.9)	4.1 (0.9-18.6)	6.4 (1.5-27.9)*	1	1.7 (0.3-9.1)	3.4)0.72-16.3)	3.5 (0.7-16)	4.9 (1.03-23.2)*	0.18
	Manual	147	1.5 (0.7-3.1)	0.97 (0.4-2.1)	1.05 (0.48-2.3)	1.02 (0.46-2.2)	1	1.01 (0.47-2.2)	1.4 (0.67-2.9)	1.2 (0.56-2.5)	1.4 (0.69-2.9)	0.49
IHD	Non-manual	720	0.98 (0.71.4)	1.1 (0.8-1.5)	0.84 (0.61-1.2)	0.97 (0.7-1.3)	1	1.05 (0.77-1.4)	1.2 (0.91-1.6)	1.2 (0.85-1.6)	1.5 (1.1-2.02)**	**0.003**
	Manual	1509	1.1 (0.88-1.4)	1.1 (0.86-1.3)	0.91 (0.73-1.2)	0.92 (0.72-1.2)	1	1.1 (0.87-1.4)	1.1 (0.86-1.3)	1.2 (0.96-1.5)	1.5 (1.2-1.8)***	**<0.0001**
Stroke	Non-manual	286	1.3 (0.8-2.2)	1.3 (0.77-2.1)	1.2 (0.73-1.9)	0.75 (0.44-1.30	1	1.3 (0.8-2.1)	1.3 (0.77-2.1)	1.2 (0.74-2.1)	1.3 (0.79-2.3)	0.69
	Manual	621	1.2 (0.84-1.7)	1.1 (0.76-1.6)	1.3 (0.89-1.8)	1.1 (0.74-1.5)	1	0.88 (0.61-1.3)	0.94 (0.66-1.3)	1.3 (0.92-1.8)	1.4 (0.98-1.9)	0.53
Respiratory	Non-manual	180	2.9 (1.6-5.3)***	1.87 (0.99-3.5)	1.13 (0.57-2.2)	1.34 (69-2.6)	1	0.9 (0.43-1.9)	1.4 (0.72-2.8)	0.88 (0.39-1.9)	1.9 (0.93-3.7)	**0.004**
	Manual	474	2.2 (1.6-3.2)***	1.3 (0.89-1.96)	1.2 (0.79-1.80	1.04 (0.69-1.6)	1	0.68 (0.43-1.1)	1.04 (0.69-1.58)	1.19 (0.79-1.77)	0.96 (0.63-1.5)	**<0.0001**
Digestive	Non-manual	71	0.6 (0.2-1.8)	0.44 (0.1-1.4)	0.65 (0.2-1.8)	0.4 (0.1-1.3)	1	0.95 (0.37-2.5)	1.5 (0.64-3.6)	1.8 (0.75-4.2)	1.99 (0.8-4.8)	**0.0001**
	Manual	129	1.04 (0.47-2.3)	0.73 (0.3-1.8)	1.2 (0.55-5.5)	1.2 (0.54-2.50	1	0.93 (4.2-2.1)	1.3 (0.6-2.7)	1.7 (0.81-3.3)	1.3 (0.63-2.8)	0.11
Other causes	Non-manual	30.6	1.12 (0.7-1.78)	1.1 (0.71-1.7)	0.96 (0.42-1.13)	0.66 (0.4-1.1)	1	0.93 (0.59-1.5)	0.93 (0.57-1.5)	1.4 (0.88-2.1)	1.2 (0.75-1.9)	0.19
	Manual	644	1.4 (0.99-1.9)	0.98 (0.69-1.4)	0.94 (0.66-1.3)	0.97 (0.68-1.4)	1	0.95 (0.68-1.4)	0.92 (0.66-1.4)	1.02 (0.73-1.40	1.4 (1.03-1.9)*	0.69

BMI cut-off points<21.3, 21.3-22.8, 22.9-23.9, 24-24.9, 25-25.9, 26-27, 27.1-28.3, 28.4-30.4, 30.4; Adjusted for age, sex and smoking status
*P<0.05, **P<0.01, ***P<0.001; Follow up form time of screening 1972-6 till December 1999 excluding the first five years of follow up

Table 5: Relative hazards ratio for all cause mortality.

			BMI groups								
		No	1	2	3	4	5	6	7	8	9	P-value
Total												
	45-54	3137	1	0.94	0.86	0.75	0.82	0.87	0.89	1.03	1.12	0.019
				(0.78-0.98)	(0.74-0.99)	(0.65-0.87)	(0.71-0.94)	(0.75-1.0)	(0.76-1.03)	(0.89-1.2)	(0.79-1.3)	
	55-64	4802	1	0.82	0.71	0.72	0.78	0.72	0.82	0.82	0.94	0.823
				(0.72-0.9)**	(0.63-0.8)***	(0.64-0.81)***	(0.69-0.88)***	(0.64-0.81)***	(0.73-0.92)**	(0.84-1.1)	(0.88-1.11)	
Men												
	45-54	1830	1	0.99	0.89	0.83	0.89	0.94	0.92	1.1	1.2	0.054
				(0.82-1.2)	(0.73-1.1)	(0.68-1.02)	(0.74-1.1)	(0.78-1.15)	(0.76-1.12)	(0.86-1.28)	(0.98-1.4)	
	55-64	2488	1	0.89	0.77	0.82	0.84	0.72	0.86	0.87	0.88	0.129
				(0.76-1.04)	(0.65-0.9)**	(0.69-0.96)*	(0.84-0.99)	(0.61-0.85)**	(0.74-1.02)	(0.74-1.03)	(0.75-1.04)	
Women												
	45-54	1307	1	0.79	0.82	0.67	0.72	0.78	0.85	1.03	1.06	0.331
				(0.64-0.97)*	(0.66-1.01)	(0.53-0.83)**	(0.58-0.9)**	(0.62-0.98)*	(0.68-1.1)	(0.83-1.3)	(0.84-1.3)	
	55-64	2314	1	0.74	0.65	0.61	0.72	0.73	0.78	0.77	0.99	0.093
				(0.62-0.88)***	(0.54-0.78)***	(0.51-0.74)***	(0.61-0.86)**	(0.61-0.87)**	(0.66-0.92)**	(0.65-0.92)**	(0.84-1.2)	

Table 0-1:Relative hazards ratios for all cancer and specific cancer sites by equal groups of BMI controlling for age, sex, smoking status and social class

Cancer	no of subject	1	2	95% CI	3	95% CI	4	95% CI	5	95% CI	trend test
All cancer											
Total	2972	1	0.93	(0.81-1.05)	0.98	(0.86-1.11)	0.9	(0.79-1.02)	0.89	(0.78-1.01)	0.071
Men	1583	1	0.91	(0.78-1.1)	0.91	(0.78-1.1)	0.94	(0.8-1.1)	0.8	(0.68-0.95)**	**0.039**
Men (excluding lung cancer)	*1035*	*1*	*0.9*	*(0.69-1.05)*	*1*	*(0.78-1.16)*	*1*	*(0.81-1.2)*	*0.9*	*(0.77-1.17)*	*0.85*
Women	1389	1	1.01	(0.91-1.3)	1.1	(0.91-1.3)	0.94	(0.77-1.14)	1.1	(0.87-1.26)	0.86
Breast cancer	251	1	1.2	(0.81-1.86)	1.45	(0.95-2.2)	1.4	(0.94-2.2)	1.7	(1.14-2.54)**	**0.008**
Lung cancer											
Total	764	1	0.88	(0.71-1.07)	0.84	(0.68-1.04)	0.79	(0.63-0.98)*	0.54	(0.42-0.69)***	**<0.0001**
Men	548	1	0.87	(0.68-1.11)	0.82	(0.64-1.06)	0.88	(0.68-1.12)	0.53	(0.39-0.73)***	**0.0008**
Women	216	1	0.88	(0.62-1.26)	0.92	(0.63-1.36)	0.54	(0.34-0.86)**	0.56	(0.35-0.87)**	0.0018
Pancreas cancer	104	1	0.94	(0.51-1.73)	1.1	(0.65-2.11)	1.14	(0.63-2.1)	0.76	(0.39-1.47)	0.69
Prostate cancer	152	1	0.94	(0.54-1.63)	1.1	(0.63-1.8)	1.05	(0.62-1.8)	0.9	(0.51-1.6)	0.87
Colorectal cancer											
Total	330	1	1.1	(.78-1.6)	1.22	(0.87-1.7)	1.1	(0.78-1.7)	0.99	(0.68-1.4)	0.94
Men	155	1	0.97	(0.57-4.6)	1.1	(0.65-1.79)	0.93	(0.55-1.6)	0.94	(0.94-1.6)	0.77
Women	175	1	1.22	(0.76-1.9)	1.39	(0.85-2.2)	1.3	(0.8-2.1)	1.04	(0.64-1.69)	0.812
Ovary and uterus cancer	133	1	0.85	(0.49-1.5)	1	(0.61-1.8)	0.61	(0.32-1.2)	1.3	(0.79-2.2)	0.43
Kidney and bladder cancer	224	1	1.18	(0.75-1.8)	1.4	(0.88-2.1)	1.2	(0.78-1.9)	1.4	(0.87-2.1)	0.22

RIIR adjusted for age, sex, smoking status and social class
BMI cut-off points: <22.5, 22.5-24.5, 24.6-26.3, 26.4-28.7, >28.7
* p>0.05, ** p>0.01, *** p>0.001

Appendix B: Chapter Seven Tables

Table 1: Definition of food groups

Food group name	Foods included in each food group
Bread	All types of bread plus crisp breads and crackers
Cereals	All breakfast cereals
Rice/pasta	All rice and pasta excluding pudding rice
Red meat	Beef, pork, lamb
Poultry	Chicken
Offal	Liver, kidney
Fish	White and oily fish including tinned
Potatoes	All forms of potatoes
Green vegetables	Green vegetables and salad plus onion
Root vegetables	Carrots, swede, turnip, beetroot
Sugar	Table sugar
Pudding	Desserts including tinned fruit, biscuits, cakes, chocolate and sweets
Fruits	Apple, banana, orange, pears
Egg	
Milk	All types
Cheese	All types
Butter	All types
Margarine	
Oil	All types of vegetable oil
Soft drinks	Juices and squashes
Alcohol	All alcohol drinks

Table 2: Macronutrient sources from different food groups

Food group name	Fat	Protein	Carbohydrate
Bread	4.22	9.22	52.26
Cereals	3.26	10.28	64.62
Rice/pasta	0.30	3.20	27.80
Red meat	21.30	24.20	0.33
Poultry	5.40	24.80	0.0
Offal	7.90	24.60	1.50
Fish	4.63	18.13	0.07
Potatoes	3.67	3.00	31.43
Green vegetables	0.13	1.80	4.10
Root vegetables	0.0	0.90	6.55
Sugar	0.0	.00	105.00
Pudding	8.58	3.70	44.94
Fruits	0.08	0.60	10.68
Egg	10.90	12.30	.000
Milk	3.73	4.68	6.48
Cheese	23.70	24.60	0.35
Butter	82.00	0.40	0.0
Margarine	74.86	0.36	0.57
Oil	99.90	0.0	0.0
Soft drinks	0.03	0.17	4.57
Alcohol	0.0	0.13	4.55

LIST OF REFERENCES

Aarnio, M., Winter, T., Kujala, U., & Kaprio, J. 1997, "Familial aggregation of leisure-time physical activity- A three generation study", *International Journal of Obesity*, vol. 18, no. 7, pp. 549-556.

Alberg, A. J., Singh S, May, J. W., & Helzlsouer, K. J. 2000, "Epidemiology, prevention and early detection of breast cancer", *Current Opinion in Oncology*, vol. 12, pp. 515-520.

Alfieri, M., Pomerteau, J., & Grace, D. D. 1997, "A comparison of fat intake of normal weight, moderately obese and severely obese subjects", *Obesity Surgery*, vol. 7, pp. 9-15.

Allison, D. B., Feinleib, M., Heo, M., & Kotler, D. 1997a, "Hypothesis concerning the U-shaped relation between body mass index", *American Journal of Epidemiology*, vol. 146, no. 4, pp. 339-349.

Allison, D. B., Fontaine, K., Manson, J., Stevens, J., & VanItallie, T. 1999, "Annual deaths attributable to obesity in the United States", *JAMA*, vol. 282, no. 16, pp. 1530-1538.

Allison, D. B., Heo, M., Flanders, D., Faith, M., & Williamson, D. 1997b, "Examination of "early morality exclusion" as an approach to control for confounding by occult disease in epidemiologic studies of mortality risk factors", *American Journal of Epidemiology*, vol. 146, no. 8, pp. 672-679.

Allison, D. B., Faith, M. S., & Nathan, J. 1996, "Risch's lambda values for human obesity.", *International Journal of Obesity*, vol. 20, no. 11, pp. 990-999.

Anderson, G. H. 1995, "Sugars, sweetness, and food intake", *American Journal of Clinical Nutrition*, vol. 62, no. 1, pp. 195S-201.

Andersson, S. O., Wolk, A., Bergstrom, R., Adami, H. O., Engholm, G., Englund, A., & Nyren, O. 1997, "Body size and prostate cancer: a 20-year follow-up study among 135006 Swedish construction workers", *Journal of The National Cancer Institute*, vol. 89, no. 5, pp. 385-389.

Andersson, S., Baron, J., Wolk, A., Lindgren, C., Bergstrom, R., & Adami, H. 1995, "Early life risk factors for prostate cancer- a population based case-control study in Sweden", *Cancer Epidemiology Biomarkers & Prevention*, vol. 4, no. 3, pp. 187-192.

Austin, H., Austin, H., Partridge, E., Hatch, K., & Shingleton, H. 1991, "Endometrial cancer, obesity and body fat distribution", *Cancer Research*, vol. 51, no. 2, pp. 568-572.

Auwerx, J. & Staels, B. 1998, "Leptin", *The Lancet*, vol. 351, pp. 737-741.

Baik, I., Ascherio, A., Rimm, E., Giovannucci, E., Spiegelman, D., Stampfer, M., & Willett, W. 2000, "Adiposity and mortality in men", *American Journal of Epidemiology*, vol. 152, no. 3, pp. 264-271.

Banegas, J., Lopez-Garcia, E., Gutierrez-Fisac, J., Guallar-Castillon, P., & Rodriguez-Artalejo, F. 2003, "A simple estimate of mortality attributable to excess weight in the European Union", *European Journal of Clinical Nutrition*, vol. 57, no. 2, pp. 201-208.

Barker, D. J. 1995, "The welcome foundation lecture, 1994: the fetal origins of adult disease", *Proceedings of the Royal Society of London.Series B, Biological Sciences*, vol. 262, pp. 37-43.

Barrett-Connor, E. 1991, "Nutrition epidemiology: how do we know what they ate?", *American Journal of Clinical Nutrition*, vol. 54, no. 1, pp. 182S-187.

Bellisle, F. & Rolland-Cachera, M. F. 2001, "How sugar-containing drinks might increase adiposity in children", *The Lancet*, vol. 357, no. 9255, pp. 490-491.

Berger, A. 2001, "Resistin: a new hormone that links obesity with type 2 diabetes", *British Medical Journal*, vol. 322, p. 193.

Bergström, A., Pisani, P., Tenet, V., Wolk, A., & Adami, H. 2001, "Overweight as an avoidable cause of cancer in Europe", *International Journal of Cancer*, vol. 91, pp. 421-430.

Björntorp, P. 1992, "Abdominal fat distribution and disease: An overview of epidemiological data", *Ann Med* no. 24, pp. 15-18.

Black, A., Goldberg, A., Jebb, S. A., Livingstone, M., Cole, T., & Prentice, A. M. 1991, "Critical evaluation of energy intake data using fundamental principles of energy physiology: 2. Evaluating the results of published surveys", *European Journal of Clinical Nutrition*, vol. 45, pp. 583-599.

Bolton-Smith, C., Brown, C. A., & Tunstall-Pedoe, H. 1991, "Nutrient sources in non-manual and manual occupational groups: Results from the Scottish heart Health Study (SHHS)", *Journal of Human Nutrition and Dietetics*, vol. 4, pp. 291-306.

Bolton-Smith, C., Smith, WCS., Woodward, M., & Tunstall-Pedoe, H. 1991, "Nutrient intake of different social-class groups: Results from the Scottish Heart Health Survey (SHHS)", *British Journal of Nutrition*, vol. 65, pp. 321-335.

Booth, M. 1996, "International Consensus Group on Physical Activity Measurement", *International Jouranl of Epidemiology*, vol. 25, no. 6, pp. 1312-1313.

Bosy-Westphal, A., Eichhorn, C., Kutzner, D., Illner, K., Heller, M., & Muller, M. J. 2003, "The age-related decline in resting energy expenditure in humans is due to the loss of fat-free mass and to alterations in its metabolically active components", *Journal of Nutrition*, vol. 133, no. 7, p. 2356.

Botto, L. D. & Khoury, M. J. 2001, "Commentary: facing the challenge of gene-environment interaction: the two-by-four table and beyond", *American Journal of Epidemiology*, vol. 153, no. 10, pp. 1016-1020.

Bouchard, C. 1994b, "Genetics of obesity: Overview and research directions," in *Genetics of Obesity*, Bouchard C, ed., CRC Press, Boca Rota, FL, pp. 223-233.

Bouchard, C. 1997, "Genetics of human obesity: Recent results form linkage studies", *Journal of Nutrition*, vol. 127, pp. 1887S-1890S.

Bouchard, C. 1998, "The role of Genetics in human obesity", *Canadian Journal of Diabetes Care*, vol. 22, no. 1, p. S3-S4.

Boyle, P. & Langman, J. S. 2000, "ABC of colorectal cancer: Epidemiology", *British Medical Journal*, vol. 321, no. 7264, pp. 805-808.

Bray, G. 1992, "Approach to the classification and evaluation of obesity," in *Obesity*, P. Björntorp & B. Brodoff, eds., J.B. Lippincott Com, London, pp. 294-308.

Buchowski, M. & Sun, M. 1996, "Energy expenditure, television viewing of obesity", *International Journal of Obesity*, vol. 20, pp. 236-244.

Bulik, C. & Allison, D. B. 2001, "The genetic epidemiology of thinness", *Obesity Research*, vol. 2, no. 2, pp. 107-115.

Bundred, P., Kitchiner, D., & Buchan, I. 2001, "Prevalence of overweight and obese children between 1989 and 1998: population based series of cross sectional studies", *British Medical Journal*, vol. 322, pp. 326-328.

Calle, E. E., Miracle-McMahill, H. L., Thun, M. J., & Heath, C. W., Jr. 1995, "Estrogen replacement therapy and risk of fatal colon cancer in a prospective cohort of postmenopausal women", *Journal of the National Cancer Institute.*, vol. 87, no. 7, pp. 517-523.

Calle, E., Thun, M., Reterlli, J., Rodriguez, C., & Heath, C. 1999, "Body mass index and mortality in a prospectice cohort of US adults", *The New England Journal Of Medicine*, vol. 341, no. 15, pp. 1097-1104.

Campfield, L. & Smith, F. 1999, "The pathogenesis of obesity", *Baillière's Clinical Endocrinology and Metabolism*, vol. 13, no. 1, pp. 13-30.

Caro, J. F., Kolaczynski, J. W., Nyce, M. R., Ohannesian, J. P., Opentanova, I., Goldman, W. H., Lynn, R. B., Zhang, P.-L., Sinha, M. K., & Considine, R. V. 1996, "Decreased cerebrospinal-fluid/serum leptin ratio in obesity: a possible mechanism for leptin resistance", *The Lancet*, vol. 348, no. 9021, pp. 159-61.

Chagnon, Y., Pérusse, L., Weisnagel, J., Rankinen, T., & Bouchard, C. 2000, "The Human obesity gene map: the 1999 update", *Obesity Research*, vol. 8, no. 1, pp. 89-117.

Chinn, S. & Rona, R. 2001, "Prevalence and trends in overweight and obesity in three cross sectional studies of British children, 1972-94", *British Medical Journal*, vol. 322, pp. 24-26.

Chlebowski, R. T., Aiello, E., & McTiernan, A. 2002, "Weight loss in breast cancer patient management", *Journal of Clinical Oncology*, vol. 20, no. 4, pp. 1128-1146.

Chow, W. H., Blot, W. J., Vaughan, T. L., Risch, H. A., Gammon, M. D., Stanford, J. L., Dubrow, R., Schoenberg, J. B., Mayne, S. T., Farrow, D. C., Ahsan, H., West, A. B., Rotterdam, H., Niwa, S., & Fraumeni, J. F., Jr. 1998, "Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia", *Journal of The National Cancer Institute*, vol. 90, no. 2, pp. 150-155.

Chow, W. H., Finkle WD, McLaughlin JK, Frankl H, Ziel HK, & Fraumeni JF 1995, "The relation of gastroesophagaeal reflux disease and its treatment to adenocarcinomas of the esophagus and gastric cardia", *JAMA*, vol. 274, no. 6, pp. 474-477.

Chow, W.-H., Gridley, g., Fraumeni, Joseph F, & Jarvholm, B. 2000, "Obesity, hypertension and the risk of kidney cancer in men", *The New England Journal Of Medicine*, vol. 343(18), no. 2, pp. 1305-1311.

Chute, C., Willett, W. C., Colditz, G. A., Stampfer, M. J., Baron, J. A., Rosner, B., & Speizer, F. E. 1991, "A prospective study of body mass, height, and smoking on the risk of colorectal cancer in women.", *Cancer Causes and Control*, vol. 2, no. 2, pp. 117-124.

Chyou, P., Nomur, A., & Stemmermann, G. 1994, "A prospective study of weight, BMI and other anthropometric measurements in relation to site-specific cancers", *International Journal of Cancer*, vol. 57, pp. 313-317.

Clement, K., Boutin, P., & Froguel, P. 2002, "Genetics of obesity", *American Journal of Pharmacogenomics*, vol. 2, no. 3, pp. 177-187.

Cleveland, W. 1993, *Visualizing Data* Hobart Press, Summit, NJ.

Cold, S., Hansen, S., Overvad, K., & Rose, C. 1998, "A woman's build and the risk of breast cancer", *European Journal of Cancer*, vol. 34, no. 8, pp. 1163-1174.

Colditz, G. A., Giovannucci, E., Rimm, E. B., Stampfer, M. J., Rosner, B., Speizer, F. E., Gordis, E., & Willett, W. C. 1991, "Alcohol intake in relation to diet and obesity in women and men", *American Journal of Clinical Nutrition*, vol. 54, no. 1, pp. 49-55.

Cole, T. J., Bellizzi, M. C., Flegal, K. M., & Dietz, W. H. 2000, "Establishing a standard definition for child overweight and obesity worldwide: international survey", *British Medical Journal*, vol. 320, pp. 1240-1243.

Cui, J., Hopper, J. L., & Harrap, S. B. 2002, "Gene and family environment explain correlations between blood pressure and body mass index", *Hypertension*, vol. 40, pp. 7-12.

Dallongeville, J., Marecaux, N., Fruchart, J. C., & Amouyel, P. 1998, "Cigarette smoking is associated with unhealthy patterns of nutrient intake: a meta-analysis", *Journal of Nutrition*, vol. 128, no. 9, pp. 1450-1457.

Davey Smith, G., , H. C., Hole, D., MacKinnon, P., Gillis, C. R., Watt, G. C., Blane, D., & Hawthorne, V. 1998, "Education and occupational social class: which is the more important indicator of mortality risk?", *Journal of Epidemiology and Community Health*, vol. 52, pp. 153-160.

Davey Smith, G., Hart, C., Blane, D., Gillis, C., & Hawthorne, V. 1997, "Lifetime socioeconomic position and mortality: prospective observational study", *British Medical Journal*, vol. 314, p. 547.

Davis, A. M., Giles, A., & Rona, R. 1999, *Tackling obesity: a toolbox for local partnership action*, Faculty of Public Health Medicine in association with the National Heart Forum.

Department of Health 1991, *Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy*, HMSO, London, 41.

Department of Health and Social Security Medical Research Council 1976, "Social factors in obesity in the United Kingdom," in *Research on Obesity*, W. James, ed., Her Majesty's Stationery Office, London, pp. 13-19.

Deuscher, S., Frederick, E. H., & Kjelsberg, M. O. 1966, "Familial aggregation of factors associated with coronary heart disease", *Circulation*, vol. 3, pp. 911-924.

Dietz, W. H. 1994, "Critical periods in adulthood for the development of obesity", *American Journal of Clinical Nutrition*, vol. 59, pp. 955-959.

DiPietro, L. 1995, "Physical activity, body weight, and adiposity: an epidemiological perspective", *Exercise and Sport Sciences Reviews*, vol. 23, pp. 275-303.

Drinkard, C., Sellers, T., Potter, J., Zheng, W., Bostick, M., Nelson, C., & Folsom, A. 1995, "Association of body mass index and body fat distribution with risk of lung cancer in older women", *American Journal of Epidemiology*, vol. 142, no. 6, pp. 600-607.

Ecob, R. 1996, "A multilevel modelling approach to examining the effects of area of residence on health and functioning", *Journal of Royal Statistical Society*, vol. 159, no. 1, pp. 61-75.

Farrell, S. W., Braun, L., Barlow, C. E., Cheng, Y. J., & Blair, S. N. 2002, "The Relation of Body Mass Index, Cardiorespiratory Fitness, and All-Cause Mortality in Women", *Obesity Research*, vol. 10, no. 6, pp. 417-423.

Feinleib, M., Garrison, R. J., Stallones, L., Kannel, W. B., Castelli, W., & McNamara, P. M. 1979, "A comparison of blood pressure , total cholesterol and cigarette smoking in parents in 1950 and their children in 1970", *American Journal of Epidemiology*, vol. 110, no. 3, pp. 291-303.

Felber, J.-P., Acheson, K., & Tappy, L. 1992, *From Obesity to Diabetes* John Wiley & Sons, New York.

Fishbein, L. 2001, "Causes of obesity", *The Lancet*, vol. 357, no. 9272, pp. 1977-1978.

Fitzgerald, S. J., Kriska, A. M., Pereira, M. A., & de Courten, M. P. 1997, "Associations among physical activity, television watching, and obesity in adult Pima Indians", *Medicine and Science in Sports and Exercise*, vol. 29, no. 7, pp. 910-915.

Fitzpatrick, R. 2001, "Social status and mortality", *Annals of Internal Medicine*, vol. 134, no. 10, pp. 1001-1003.

Flegal, K. M., Carroll, M. D., Ogden, C. L., & Johnson, C. L. 2002, "Prevalence and trends in obesity among US adults, 1999-2000", *JAMA*, vol. 288, no. 14, pp. 1723-1727.

Flegal, K. & Troiano, R. 2000, "Changes in the distribution of body mass index of adults and children in the US population", *International Journal of Obesity*, vol. 24, pp. 807-818.

Flegal, K., Troiano, R., Pamuk, E., Kuczmarski, R., & Campbell, S. 1995, "The influence of smoking cessation on the prevalence of overweight in the United States", *The New England Journal Of Medicine*, vol. 333, no. 18, pp. 1165-1170.

Fogelholm, M., Nuutinen, O., Pasanen, M., Myohanen, E., & Saatela, T. 1999, "Parent-child relationship of physical activity patterns and obesity", *International Journal of Obesity*, vol. 23, no. 1, pp. 1262-1268.

Folsom, A., Kushi, L., Anderson, K., Mink, P., Olson, J., Hongn, C.-P., Sellers, T., Lazovich, D., & Prineas, R. 2000, "Association of general and abdominal obesity with multiple health outcomes in older women: The Iowa women health study", *Archives of Internal Medicine*, vol. 160, no. 14, pp. 2117-2128.

Ford, A. 1999, "Body mass index and colon cancer in a national sample of adult US men and women", *American Journal of Epidemiology*, vol. 150, no. 4, pp. 390-398.

Francis, L., Lee, Y., & Birch, L. 2003, "Parental weight status and girls' television viewing, snacking, and body mass indexes", *Obesity Research*, vol. 11, no. 1, pp. 143-151.

Freedman, D. S., Khan, L. K., Serdula, M. K., Galuska, D. A., & Dietz, W. H. 2002, "Trends and correlates of class 3 obesity in the United States from 1990 through 2000", *JAMA*, vol. 288, no. 14, pp. 1758-1761.

Friedlander, Y., Kark, J. D., Kaufmann, N. A., Berry, E. M., & Stein, Y. 1988, "Familial aggregation of body mass index in ethnically diverse families in Jerusalem. The Jerusalem Lipid Research Clinic", *International Journal of Obesity*, vol. 12, pp. 237-247.

Froom, P., Melamed,S., & Benbassat,J. 1998, "Smoking cessation and weight gain", *The Journal of Family Practice*, vol46, no.6, pp.460-464.

The Centers For Disease Control And Prevention 1996, "Prevalence of physical inactivity during leisure time among overweight persons-1994", *JAMA*, vol. 275, no. 12, p. 905.

Garn, S., Hawthorne, V., Pilkington, J., & Pesick, S. 1983, "Fatness and mortality in the West of Scotland", *American Journal of Clinical Nutrition*, vol. 38, pp. 313-319.

Garrison, R. J., Feinleib, M., Castelli, W. P., & McNamara, P. M. 1983, "Cigarette smoking as a confounder of the relationship between relative weight and long-term mortality. The Framingham Heart Study", *JAMA*, vol. 249, no. 16, pp. 2199-2203.

General Register Office Classification of Occupation 1966, HMSO, London.

Gill, T., Antipatis, V., & James, W. 1999, "The global epidemic of obesity", *Asia Pacific J Clin Nutr*, vol. 8, no. 1, pp. 75-81.

Giovannucci, E. 2001, "Insulin, insulin-like growth factors and colon cancer: a review of the evidence", *Journal of Nutrition*, vol. 131 (Suppl), pp. 3109S-3120S.

Goldberg, A., Black, A., Jebb, S. A., Cole, T., Murgatroyd, P., Coward, W., & Prentice, A. M. 1991, "Critical evaluation of energy intake data using fundamental principles of energy physiology: 1. Derivation of cut-off limits to identify under-recording", *European Journal of Clinical Nutrition*, vol. 45, pp. 569-581.

Goldstein, H., Rasbash, J., Plewis, I., Draper, D., Browne, W., Woodhouse, G., & Healy, M. 1998, *A User's Guide to MLwiN* Institute of Education: University of London.

Golstein, H. 1991, "Multilevel modelling of survey data", *Statistician*, vol. 40, no. 2, pp. 235-244.

Goodman, M., Hankin, J., Wilkens, L., Lyu, L., McDuffie, K., Liu, L., & Kolonel, L. 1997, "Diet, body size, physical activity and the risk of endometrial cancer", *Cancer Research*, vol. 57, no. 22, pp. 5077-5085.

Grodstein, F., Martinez, M. E., Platz, E. A., Giovannucci, E., Colditz, G. A., Kautzky, M., Fuchs, C., & Stampfer, M. J. 1998, "Postmenopausal hormone use and risk for colorectal cancer and adenoma.[comment]", *Annals of Internal Medicine.*, vol. 128, no. 9, pp. 705-712.

Grundy, S. 1998, "Multifactorial causation of obesity: implication for prevention", *American Journal of Clinical Nutrition*, vol. 67(Suppl), pp. 563S-572S.

Gurney, M. & Gorstein, J. 1988, "The global prevalence of obesity: an initial overview of available data", *World Health Statistics Quarter*, vol. 41, pp. 251-254.

Gutierrez-Fisac, J., Banegas Banegas, J., Artalejo, F., & Regidor, E. 2000, "Increasing prevalences of overweight and obesity among Spanish adults, 1987-1997", *International Journal of Obesity*, vol. 24, no. 12, pp. 1677-1682.

Gutiérrez-Fisac, J., Regidor, E., Banegas Banegas, J., & Rodríguez Artalejo, F. 2002, "The size of obesity differences associated with educational level in Spain, 1987 and 1995/97", *Journal of Epidemiology and Community Health*, vol. 56, pp. 457-460.

Gutierrez-Fisac, J. L., Regidor, E., & Rodriguez, C. 1996, "Trends in obesity differences by educational level in Spain", *Journal of Clinical Epidemiology*, vol. 49, no. 3, pp. 351-354.

Han, T., Richmond, P., Avenell, A., & Lean, M. 1997, "Waist circumference reduction and cardiovascular benefits during weight loss in women", *International Journal of Obesity*, vol. 21, pp. 127-134.

Han, T., van Leer, E., Seidell, J., & Lean, M. 1996, "Waist circumference as a screening tool for cardiovascular risk factors: evaluation of receiver operating characteristics (ROC)", *Obesity Research*, vol. 4, no. 6, pp. 533-547.

Han, T., McNeill, G., Seidell, J., & Lean, M. 1997, "Predicting intra-abdominal fatness from anthropometric measures: the influence of stature", *International Journal of Obesity*, vol. 21, pp. 587-593.

Han, T., van Leer, E., Seidell, J., & Lean, M. 1995, "Waist circumference action levels in the identification of cardiovascular risk factors: prevalence study in a random sample", *British Medical Journal*, vol. 311, pp. 1401-1405.

Hanley, A., Johnson, K., Villeneuve, P., Mao, Y., & Canadian Cancer Registries Epidemiology Research Group 2001, "Physical activity, anthropometric factors and risk of pancreatic cancer: results from the Canadian enhanced cancer surveillance system", *International Journal of Cancer*, vol. 94, no. 1, pp. 140-147.

Hanson, R.L., Ehm, M.G., Pettitt, D.J., Prochazka, M., Thompson, D.B., Timberlake, D., Foroud, T., Kobes, S., Baier, L., Burns, D.K., Almasy, L., Blangero, J., Garvey, W.T., Bennett, P.H., Knowler, W.C. 1998, " An autosomal genomic scan for loci linked to type II diabetes mellitus and body-mass index in Pima Indians", *American Journal of Human Genetics*, vol.63, pp 1130-1138.

Harrap, S., Stebbing, M., Hopper, J., Hoang, H., & Giles, G. 2001, "Familial patterns of covariation for cardiovascular risk factors in adults: The Victorian Family Heart Study", *American Journal of Epidemiology*, vol. 152, pp. 704-715.

Hart, C., Hole, D., Gillis, C. R., Davey Smith, G., Watt, G. C., & Hawthorne, V. 2001, "Social class differences in lung cancer mortality: risk factor explanations using two Scottish cohort studies", *International Jouranl of Epidemiology*, vol. 30, no. 2, pp. 268-274.

Hart, C., Hole, D., & Davey Smith, G. 1999, "Risk factors and 20-year stroke mortality in men and women in the Renfrew/Paisley study in Scotland", *Stroke*, vol. 30, pp. 1999-2007.

Hawthorne, V., Watt, G., Hart, C., Smith, G., & Gillis, C. 1995, "Cardiorespiratory disease in men and women in urban Scotland: Baseline characteristics of the Renfrew/ Paisley (MIDSPAN) study population", *Scottish Medical Journal*, vol. 40, pp. 102-107.

Hebebrand, J., Wulftange, H., Goerge, T., Ziegler, A., Hinney, A., Mayer, H., & Remschmidt, H. 2000, "Epidemic obesity: are genetic factors involved via increased rates of assortative mating?", *International Journal of Obesity*, vol. 24, pp. 345-353.

Heini, A. & Weinsier, R. 1997, "Divergent trends in obesity and fat intake patterns: The American paradox", *American Journal of Medicine*, vol. 102, no. 3, pp. 259-264.

Heitmann, B. L. & Lissner, L. 1995, "Dietary underreporting by obese individuals- is it specific or non-specific?", *British Medical Journal*, vol. 311, pp. 986-989.

Heitmann, B., Erikson, H., Ellsinger, B.-M., Mikkelsen, K., & Larsson, B. 2000, "Mortality associated with body fat, fat-free mass and body mass index among 60 year old Swedish men- a 22 year follow up. The study of men born in 1913", *International Journal of Obesity*, vol. 24, pp. 33-37.

Heller, R., Garrison, R. J., Havlik, R. J., Feineib, M., & Padgett, S. 1984, "Family resemblances in height and relative weight in the Framingham Heart Study", *International Journal of Obesity*, vol. 8, pp. 399-405.

Henry, J. & Warren, J. 2001, "Causes of obesity", *The Lancet*, vol. 357, no. 9272, p. 1978.

Hill, J. O. & Prentice, A. M. 1995, "Sugar and body weight regulation", *American Journal of Clinical Nutrition*, vol. 62, no. 1, pp. 264S-273.

Hill, J. O. & Peters, J. C. 1998, "Environmental contributions to the obesity epidemic", *Science*, vol. 280, no. 5368, pp. 1371-1374.

Hill, J. & Melanson, E. 1999, "Overview of the determinants of overweight and obesity: current evidence and research issues", *Medicine and Science in Sports and Exercise*, vol. 31(suppl1), no. 11, p. S515.

Hinney, A., Schmidt, A., Nottebom, K., Heibult, O., Becker, I., Ziegler, A., Gerber, G., Sina, M., Gorg, T., Mayer, H., Siegfried, W., Fichter, M., Remschmidt, H., & Hebebrand, J. 1999, "Several mutations in the melanocortin-4 receptor gene including a nonsense and a frameshift mutation associated with dominantly inherited obesity in humans", *Journal of Clinical Endocrinology & Metabolism.*, vol. 84, no. 4, pp. 1483-1486.

Hise, M. E., Sullivan, D., Jacobsen, D. J., Johnson, S. K., & Donnelly, J. E. 2002, "Validation of energy intake measurements determined from observer-recorded food records and recall methos compared with the doubly labeled water method in overweight and obese individuals", *American Journal of Clinical Nutrition*, vol. 75, pp. 263-267.

Hole, D. J. Renfrew and Paisley Mortality. 2003. (Personal Communication).

Hopkins, P. 1992, "Effects of dietary cholesterol on serum cholesterol: a meta-analysis and review", *American Journal of Clinical Nutrition*, vol. 55, pp. 1060-1070.

Hsing, A., Deng, J., Sesterhenn, I., Mostofi, F., Stanczyk, F., Benichou, J., Xie, T., & Gao, Y. 2000, "Body size and prostate cancer: a population-based case-control study in China", *Cancer Epidemiology Biomarkers and Prevention*, vol. 9, no. 12, pp. 1335-1341.

International Collaborative Group 1982, "Circulating cholesterol level and risk of death from cancer in men aged 40 to 69 years: Experience of an International collaborative Group", *JAMA*, vol. 248, no. 21, pp. 2853-2859.

Isles, C. G., Hole, D. J., Gillis, C. R., Hawthorne, V. M., & Lever, A. F. 1989, "Plasma cholesterol, coronary heart disease, and cancer in the Renfrew and Paisley survey", *British Medical Journal*, vol. 298, pp. 920-924.

Janghorbani, M., Hedley, A., Jones, R., Gilmour, W., & Zhianpourn, M. 1992, "Is the association between blood glucose level and all causes and cardiovascular mortality risk dependent on body mass index?", *Medical Journal of the Islamic Republic of Iran*, vol. 6, no. 3, pp. 205-212.

Jebb, S. A. & Moore, M. S. 1999, "Contribution of a sedentary lifestyle and inactivity to the etiology of overweight and obesity: current evidence and research issues", *Medicine and Science in Sports and Exercise*, vol. 31(Suppl1), no. 11, p. S534-S541.

Jequier, E. 1999, "Alcohol intake and body weight: a paradox", *American Journal of Clinical Nutrition*, vol. 69, no. 2, pp. 173-174.

Ji, B., Hatch, M., Chow, W., McLaughlin, J., Dai, Q., Howe, G., Gao, Y., & Fraumeni, J. J. 1996, "Anthropometric and reproductive factors and the risk of pancreatic cancer: a case-control study in Shanghai, China", *International Journal of Cancer*, vol. 66, no. 4, pp. 432-437.

Jousilahti, P., Tuomilehto, J., Vartiainen, E., Pekkanen, J., & Puska, P. 1996, "Body Weight, Cardiovascular Risk Factors, and Coronary Mortality : 15-Year Follow-up of Middle-aged Men and Women in Eastern Finland", *Circulation*, vol. 93, no. 7, pp. 1372-1379.

Kaaks, R., Van Noord, P., Tokelaar, I., Reeters, P., Riboli, E., & Grobbee, D. 1998, "Breast cancer incidence in relation to height, weight and body fat distribution in the Dutch "Dom" cohort", *International Journal of Cancer*, vol. 76, pp. 647-651.

Kabat, G. & Wynder, E. 1992, "Body mass index and lung cancer risk", *American Journal of Epidemiology*, vol. 135, no. 7, pp. 769-774.

Kannel, W., Agostino, R., & Cobb, J. 1996, "Effect of weight on cardiovascular disease", *American Journal of Clinical Nutrition*, vol. 63 (suppl), pp. 419S-422S.

Khoury, P., Morrison, J. A., Laskarzewski, P. M., & Glueck, C. J. 1983, "Parent-Offspring and sibling body mass index association during and after sharing of common household environments: The Princeton School District Family Study", *Metabolism*, vol. 32, no. 1, pp. 82-89.

Kirschmann, G. & Kirschmann, J. 1996, *Nutrition Almance*, 4th ed, McGraw Hill, New York.

Klesges, R. & Klesges, L. 1993, "The relationship between body mass and cigarette smoking using a biochemical index of smoking exposure", *International Journal of Obesity*, vol. 17, pp. 585-591.

Knekt, P., Heliovaara, M., Rissanen, A., Aromaa, A., Seppanen, R., Teppo, L., & Pukkala, E. 1991, "Leanness and lung cancer risk", *International Journal of Cancer*, vol. 49, no. 2, pp. 208-213.

Knowler, W. C., Pettitt, D. J., Saad, M. F., Charles, M. A., Nelson, R. G., Howard, B. V., Bogardus, C., & Bennett, P. H. 1991, "Obesity in the Pima Indians: its magnitude and relationship with diabetes", *American Journal of Clinical Nutrition*, vol. 53, no. 6, pp. 1543S-1551.

Kopelman, P. 2000, "Obesity as a medical problem", *Nature*, vol. 404, no. 6778, pp. 635-643.

Kroke, A., Klipstein-Grobusch, K., Voss, S., Moseneder, J., Thielecke, F., Noack, R., & Boeing, H. 1999, "Validation of a self-administered food-frequency questionnaire administered in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study: comparison of energy, protein, and macronutrient intakes estimated with the doubly labeled water, urinary nitrogen, and repeated 24-h dietary recall methods", *American Journal of Clinical Nutrition*, vol. 70, no. 4, pp. 439-447.

Kubik, A., Zatloukal, P., Boyle, P., Robertson, C., Gandini, S., Tomasek, L., Gray, N., & Harvel, L. 2001, "A case-control study of lung cancer among Czech women", *Lung Cancer*, vol. 31, pp. 111-122.

LaVecchia, C., Franceschi, S., Gallus, G., Decarli, A., Colombo, E., Mangioni, C., & Tognoni, G. 1982, "Oestrogens and obesity as a risk factors for endometrial cancer in Italy", *International Journal of Epidemiology*, vol. 11, pp. 120-126.

Lean, M., Han, T., & Morrison, C. 1995, "Waist circumference as a measure for indicating need for weight management", *British Medical Journal*, vol. 311, pp. 158-161.

Lean, M. E. 2000, "Obesity: Burdens of illness and strategies for prevention or management", *Drugs of Today*, vol. 36, no. 11, pp. 773-784.

Lee, I., Paffenbarger, R., & Hsieh, C. 1991, "Physical activity and risk of developing colorectal cancer among college alumni", *Journal of The National Cancer Institute*, vol. 83, pp. 1324-1329.

Lee, J., Reed, D., & Price, R. 1997, "Familial risk ratios for extreme obesity: implication for mapping human obesity genes", *International Journal of Obesity*, vol. 21, pp. 935-940.

Lindsay, R. S., Kobes, S., Knowler, W. C., Bennett, P. H., & Hanson, R. L. 2001, "Genome-Wide Linkage Analysis Assessing Parent-of-Origin Effects in the Inheritance of Type 2 Diabetes and BMI in Pima Indians", *Diabetes*, vol. 50, no. 12, pp. 2850-2857.

Lissner, L. & Heitmann, L. 1995, "Dietary fat and obesity: evidence form epidemiology", *European Journal of Clinical Nutrition*, vol. 49, pp. 79-90.

Lissner, L., Heitmann, B. L., & Bengtsson, C. 2000, "Population studies of diet and obesity", *British Journal of Nutrition*, vol. 83(Suppl1), p. S21-S24.

Ludwig, D. S. 2000, "Dietary Glycemic Index and Obesity", *Journal of Nutrition*, vol. 130, no. 2, p. 280.

Ludwig, D. S., Peterson, K. E., & Gortmaker, S. L. 2001, "Causes of obesity", *The Lancet*, vol. 357, no. 9272, pp. 1978-1979.

Macdiarmid, J. & Blundell, J. 1998, "Assessing dietary intake: Who, what and why of under-reporting", *Nutrition Research Reviews*, vol. 11, pp. 231-253.

Maes, H. H. M., Neals, M. C., & Eaves, L. J. 1997, "Genetic and environmental factors in relative body weight and human adiposity", *Behavior Genetics*, vol. 27, no. 4, pp. 325-351.

Magnusson, C., Baron, J., Persson, I., Wplk, A., Bergtrom, R., Trichopoulos, D., & Adami, H. 1998, "Body size in different periods of life and breast cancer risk in post-menopausal women", *International Journal of Cancer*, vol. 76, pp. 29-34.

Maillard, G., Charles, M., Thibult, N., Forhan, A., Sermet, C., Basdevant, A., & Aschwège, E. 1999, "Trends in the prevalence of obesity in the French adult population between 1980 and 1991", *International Journal of Obesity*, vol. 23, pp. 389-394.

Manson, J., Willett, W., Stampfer, M., Colditz, G., Hunter, D., Hankinson, S., Hennekens, C., & Speizer, F. 1995, "Body weight and mortality among women", *The New England Journal Of Medicine*, vol. 333, no. 11, pp. 677-685.

Marques-Vidal, P., Puidavets, J., Cambou, J., & Ferrieres, J. 2002, "Trends in overweight and obesity in middle-aged subjects from Southern France 1985-1997", *International Journal of Obesity*, vol. 26, no. 5, pp. 732-734.

McMinn, J., Baskin, D., & Schwartz, M. 2000, "Neuroendocrine mechanisms regulating food intake and body weight", *Obesity Reviews*, vol. 1, pp. 37-46.

McTernan, C. L., Mcternan, P. G., Harte, A. L., Levick, P. L., Barnett, A. H., & Kumar, S. 2002, "Resisten, central obesity, and type 2 diabetes", *The Lancet*, vol. 359, pp. 46-47.

Megnien, J., Denaric, N., Simon, A., & Levenson, J. 1999, "Predictive value of waist to hip ratio on cardiovascular risk events", *International Journal of Obesity*, vol. 23, pp. 90-97.

Metges, C. C. & Barth, C. A. 2000. "Metabolic consequences of a high dietary-protein intake in adulthood: Assessment of the available evidence". Journal of Nutrition, Vol130, pp. 886-889.

Mokdad, A., Bowman, B., Ford, E., Vinicor, F., Marks, J., & Koplan, J. 2001, "The continuing epidemic of obesity and diabetes in the United States", *JAMA*, vol. 286, no. 10, pp. 1195-11200.

Moller, H., Mellemgaard, A., Lindvig, K., & Olsen, J. 1994, "Obesity and cancer risk: a Danish record-linkage study", *European Journal of Cancer*, vol. 30A, no. 3, pp. 344-350.

Monteiro, C., Mondini, L., Desouza, A., & Popkin, B. 1995, "The nutrition transition in Brazil", *Eur J Clin Nutr*, vol. 49, pp. 105-113.

Moore, L., Lombardi, D., White, M., Campbell, J., Oliveria, S., & Ellison, R. 1991, "Influence of parents' physical activity levels on activity levels of young children", *Journal of Pediatrics*, vol. 118, no. 2, pp. 215-219.

Murphy, T., Calle, E., Rodriguez, C., Kahn, H., & Thun, M. 2000, "Body mass index and colon cancer mortality in a large prospective study", *American Journal of Epidemiology*, vol. 152, no. 9, pp. 847-854.

National Institutes of Health: National Heart, L. a. B. I. 1998, *Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults* June 1998.

Nothen, M. M., Cichon, S., Hemmer, S., Hebebrand, J., Remschmidt, H., Lehmkuhl, G., Poustka, F., Schmidt, M., Catalano, M., & Fimmers, R. 1994, "Human dopamine D4 receptor gene: frequent occurrence of a null allele and observation of homozygosity", *Human Molecular Genetics.*, vol. 3, no. 12, pp. 2207-2212.

Ogden, C., Flegal, K. M., Carroll, M. D., & Johnson, C. L. 2002, "Prevalence and trends in overweight among US children and Adolescents, 1999-2000", *JAMA*, vol. 288, no. 14, pp. 1728-1732.

Olson, J. E., Yang, P., Schmitz, K., Vierkant, R. A., Cerhan, J. R., & Sellers, T. A. 2002, "Differential Association of Body Mass Index and Fat Distribution with Three Major Histologic Types of Lung Cancer: Evidence from a Cohort of Older Women", *American Journal of Epidemiology*, vol. 156, no. 7, pp. 606-615.

Ottman, R. 1990, "An epidemiologic approach to gene-environment interaction", *Genetic Epidemiology*, vol. 7, pp. 177-185.

Pérusse, L. & Bouchard, C. 2000, "Gene-diet interactions in obesity", *American Journal of Clinical Nutrition*, vol. 72 (Suppl), pp. 1285S-1290S.

Pérusse, L., Chagnon, Y. C., Weisnagel, J., Rankinen, T., Snyder, E., & Sands, J. 2001, "The human obesity gene map: the 2000 update", *Obesity Research*, vol. 9, no. 2, pp. 135-168.

Pérusse, L., Rice T, Province M, Gagnon J, Leon AS, Shinner JS, Wilmore JH, Rao DC, & Bouchard C 2000, "Familial aggregation of amount and distribution of subcutaneous fat and their responses to exercise training in the Heritage family study", *Obesity Research*, vol. 8, no. 2, pp. 140-150.

Pescatello, L. S. & VanHeest, J. L. 2000, "Physical activity mediates a healthier body weight in the presence of obesity", *British Journal of Sports Medicine*, vol. 34, pp. 86-93.

Pi-Sunyer, F. X. 2000, "Comorbidities of overweight and obesity: current evidence and research issues", *Medicine and Science in Sports and Exercise*, vol. 31 (Suppl1), no. 11, p. S602-S608.

Piers, L. S., Soares, M. J., McCormack, L. M., & O'Dea, K. 1998, "Is there evidence for an age-related reduction in metabolic rate?", *Journal of Applied Physiology*, vol. 85, no. 6, p. 2196.

Piper, B. 1996, "Dietary energy," in *Diet and nutrition: A guide for student and practitioners*, Chapman &Hall, London, pp. 146-196.

Potter, J., Bostick, M., & Garndits, G. 1996, "Hormone replacement therapy is associated with lower risk of adenomatous polyps of the large bowel: the Minnesota Cancer Prevention Research Unit Case-Control Study", *Cancer Epidemiology Biomarkers & Prevention*, vol. 5, pp. 779-784.

Pounder, D., Carson, D., Davidson, M., & Orihara, Y. 1998, "Evaluation of indices of obesity in men: descriptive study", *British Medical Journal*, vol. 316, pp. 1428-1429.

Prentice, A. M. & Jebb, S. A. 1995, "Obesity in Britain: gluttony or sloth?", *British Medical Journal*, vol. 311, no. 7002, pp. 437-439.

Putnam, S., Cerhan, J., Parker, A., Bianchi, G., Wallace, R., Cantor, K., & Lynch, C. 2000, "Lifestyle and anthropometric risk factors for prostate cancer in a cohort of Iowa men", *Annals of Epidemiology*, vol. 10, pp. 361-369.

Rasbash, J., Browne, W., Goldstein, H., Yang, M., Plewis, I., Healy, M., Woodhouse, G., Draper, D., Langford, I., & Lewis, T. 2000, *A user's guide to MLwiN* Institute of Education, University of London, London.

Rauscher, G. H., Mayne, S. T., & Janerich, D. T. 2000, "Relation between body mass index and lung cancer risk in men and women never and former smokers", *American Journal of Epidemiology*, vol. 152, no. 6, pp. 506-513.

Ravelli, A. C., van der Meulen, J. H., Osmond, C., Barker, D. J., & Bleker, O. P. 1999, "Obesity at the age of 50 y in men and women exposed to famine prenatally", *American Journal of Clinical Nutrition*, vol. 70, pp. 811-816.

Rice, T., Daw, W., Gagnon, J., Bouchard, C., Leon, A. S., Skinner, J. S., Wilmore, J. H., & Rao, D. C. 1997, "Familial resemblance for body composition measures: The HERITAGE Family Study", *Obesity Research*, vol. 5, no. 6, pp. 557-562.

Rice, T. & Province, M. 1994, "Cross-trait resemblance for body fat and blood pressure: familial correlation in the Quebec Family Study", *American Journal of Human Genetics*, vol. 55, pp. 1019-1029.

Rimm, E. B., Stampfer, M. J., Giovannucci, E., Ascherio, A., Spiegelman, D., Colditz, G. A., & Willett, W. C. 1995, "Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men", *American Journal of Epidemiology*, vol. 141, no. 12, pp. 1117-1127.

Risch, N. 1990a, "Linkage strategies for genetically complex traits. I. Multilocus Models", *American Journal of Human Genetics*, vol. 46, pp. 222-228.

Risch, N. 1990b, "Linkage strategies for genetically complex traits. II. The power of affected relative pairs", *American Journal of Human Genetics*, vol. 46, pp. 229-241.

Risch, N. 1990c, "Linkage strategies for genetically complex traits.III. The effect of marker polymorphism on analysis of affected relative pairs", *American Journal of Human Genetics*, vol. 46, pp. 242-253.

Rissanen, A. & Fogelholm, M. 1999, "Physical activity in the prevention and treatment of other morbid conditions and impairments associated with obesity: current evidence and research issues", *Medicine and Science in Sports and Exercise*, vol. 319(Suppl1), no. 11, p. S635-S645.

Rodriguez, C., Patel, A., Calle, E., Jacobs, E., Chao, A., & Thun, M. 2001, "Body mass index, height and prostate cancer mortality in tow large cohorts of adult men in the United States", *Cancer Epidemiology Biomarkers & Prevention*, vol. 10, pp. 345-353.

Rose, G., Holland, W., & Crowley, E. 1964, "A sphygmomoanometer for epidemiologists", *The Lancet*, vol. i, pp. 296-300.

Rose, G. & Day, S. 1990, "The population mean predicts the number of deviant individuals", *British Medical Journal*, vol. 301, pp. 1031-1034.

Ross, R. & Janssen, I. 2001, "Physical activity, total and regional obesity: dose-response considerations", *Medicine and Science in Sports and Exercise*, vol. 33(Suppl), no. 6, p. S521-S527.

Russo, A., Franseschi, S., La Vecchia, C., Maso, L., Montella, M., Giacosa, A., Falcini, F., & Negri, E. 1998, "Body size and colorectal cancer", *International Journal of Cancer*, vol. 78, pp. 161-165.

Samaras, K., Kelly, P., & Campbell, L. 1999, "Dietary underreporting is prevalent in middleaged British women and is not related to adiposity (percentage body fat)", *International Journal of Obesity*, vol. 23, pp. 881-888.

Samaras, K., Kelly, P. J., Chiano, M. N., Arden, N., Spector, T., & Campbell, L. V. 1998, "Genes versus environment: the relationship between dietary fat and total and central abdominal fat", *Diabetes Care*, vol. 21, no. 12, pp. 2069-2076.

Sawaya, A. L., Tucker, K., Tsay, R., Willett, W., Saltzman, E., Dallal, G. E., & Roberts, S. B. 1996, "Evaluation of four methods for determining energy intake in young and older women: comparison with doubly labeled water measurements of total energy expenditure", *American Journal of Clinical Nutrition*, vol. 63, no. 4, pp. 491-499.

Scheen, A. J. 2003, "Current Management Strategies for Coexisting Diabetes Mellitus and Obesity. *Drugs*, vol. 63, no. 12, pp. 1165-1184.

Schoen, R., Tangen, C., Kuller, L., Burke, G., Cushman, M., Tracy, R., Dobs, A., & Savage, P. 1999, "Increased blood glucose and insulin, body size, and incident colorectal cancer", *Journal of The National Cancer Institute*, vol. 91, pp. 1147-1154.

Sclafani, A. 1996, "Dietary Obesity," in *Obesity: Theory and Therapy*, 2nd edn, A. J. Stunkard & T. A. Wadden, eds., Lippincott-Raven, New York, pp. 125-136.

Scottish Intercollegiate Guideline Network 1996, *Obesity in Scotland: A National Clinical Guideline Recommended for use in Scotland* EC 55.

Seidell, J. C., Kahn, H. S., Williamson, D. F., Lissner, L., & Valdez, R. 2001, "Report from a Centers for Disease Control and Prevention Workshop on Use of Adult Anthropometry for Public Health and Primary Health Care", *American Journal of Clinical Nutrition*, vol. 73, no. 1, pp. 123-126.

Seidell, J. C., Verschuren, M. W., van Lee, E. M., & Kromhout, D. 1996, "Overweight, Underweight, and Mortality: A Prospective Study of 48287 Men and Women", *Archives of Intenal Medicine*, vol. 156, no. 9, pp. 958-963.

Sempos, C. T., Durazo-Arvizu, R., McGee, D. L., Cooper, R. S., & Prewitt, E. 1998, "The influence of cigarette smoking on the association between body weight and morality. the Framingham Heart Study revisited", *Annals of Epidemiology*, vol. 8, pp. 289-300.

Senior, K. 2001a, "Looking at the molecular explanation for obesity", *The Lancet*, vol. 357, p. 1344.

Senior, K. 2001b, "Resistin Links obesity to type 2 diabetes", *The Lancet*, vol. 357, p. 202.

Shaper, A. G., Wannamethee, S. G., & Walker, M. 1997, "Body weight: implications for the prevention of coronary heart disease, stroke, and diabetes mellitus in a cohort study of middle aged men", *British Medical Journal*, vol. 314, no. 7090, p. 1311.

Shaper, G. A., Pocock, S. J., Walker, M., Cohen, N. M., Wale, C. J., & Thomson, A. G. 1981, "British Regional Heart Study: cardiovascular risk factors in middle-aged men in 24 towns", *British Medical Journal*, vol. 283, pp. 179-186.

Shu, X., Jin, F., Dai, Q., Shi, J., Potter, J., Brinton, L., Hebert, J., Ruan, Z., Gao, Y., & Zheng, W. 2001, "Association of body size and fat distribution with risk of breast cancer among Chinese women", *International Journal of Cancer*, vol. 94, pp. 449-455.

Silverman, D. T., Swanson, C. A., Gridley, G., Wacholder, S., Greenberg, R. S., Brown, L. M., Hayes, R. B., Swanson, G. M., Schoenberg, J. B., Pottern, L. M., Schwartz, A. G., Fraumeni, J. F., Jr., & Hoover, R. N. 1998, "Dietary and nutritional factors and pancreatic cancer: a case-control study based on direct interviews", *Journal of The National Cancer Institute*, vol. 90, no. 22, pp. 1710-1719.

Silverston, T. J. 1969, "Psychological factors in obesity," in *Obesity: Medical and Scientific Aspects*, I. McLean Baird & A. N. Howard, eds., E & S Livingston Ltd, Edinburgh, pp. 45-55.

Sjostrom, C. D., Peltonen, M., Wedel, H., & Sjostrom, L. 2000, "Differentiated Long-Term Effects of Intentional Weight Loss on Diabetes and Hypertension. [Article]", *Hypertension*, vol. 36, no. 1, pp. 20-25.

Slattery, M. L., Edwards, S., Ma, K., Friedman, G., & Potter, J. 1997a, "Physical activity and colon cancer: a public health perspective", *Annals of Epidemiology*, vol. 7, no. 2, pp. 137-154.

Slattery, M., Potter, J., Caan, B., Edwards, S., Coates, A., Ma, K., & Berry, T. 1997b, "Energy balance and colon cancer-beyond physical activity", *Cancer Research*, vol. 57, no. 1, pp. 75-80.

Sonnenschein, E., Toniolo, P., Terry, M., Bruning, P., Dato, I., Koenig, K., & Shore, R. 1999, "Body fat distribution and obesity in pre-and postmenopausal breast cancer", *International Journal of Epidemiology*, vol. 28, pp. 1026-1031.

Sørensen, T. I. A. 2000, "The changing lifestyle in the world: Body weight and what else?", *Diabetes Care*, vol. 23(Suppl2), p. B1-B4.

Sørensen, T. I. A. & Echwald, S. 1996, "Leptin in obesity", *British Medical Journal*, vol. 313, pp. 953-954.

Stam-Moraga, M., Kolanwski, J., Dramaix, M., De Henenw, S., De Bacquer, D., De Backer, G., & Kornitzer, M. 1998, "Trends in the prevalence of obesity among Belgian men at work, 1977-1992", *International Journal of Obesity*, vol. 22, no. 10, pp. 988-992.

StataCorp 1999, *Stata Statistical Software: Release 6.0* Stata Corporation, College Station, TX.

Steering Committee 2000, *The Aisa-Pacific Perspective: Redefining obesity and its treatment*, Health Communication Australia Pty Limited pn behal of the steering committee, Australia.

Steppan, C., Bailey, S., Bhat, S., Brown, E., Banerjee, R., Wright, C., Patel, H., Ahima, R., & Lazar, M. 2001, "The hormone resistin links obesity to diabetes", *Nature*, vol. 409, no. 18, pp. 307-312.

Stevens, J., Juhaeri, & Cai, J. 2001, "Changes in body mass index prior to baseline among participants who are ill or who die during the early years of follow-up", *American Journal of Epidemiology*, vol. 153, no. 10, pp. 946-953.

Stoll, B. 2000, "Adiposity as a risk determinant for postmenopausal breast cancer", *International Journal of Obesity*, vol. 24, pp. 527-533.

Strobel, A., Issad, T., Camoin, L., Ozata, M., & Strosberg, A. 1998, "A leptin missense mutation associated with hypogonadism and morbid obesity", *Nature Genetics*, vol. 18, pp. 213-215.

Stubbs, R. J., Mazlan, N., & Whybrow, S. 2001, "Carbohydrates, Appetite and Feeding Behavior in Humans", *Journal of Nutrition*, vol. 131, no. 10, pp. 2775S-2781.

Stunkard, A. J. & Sorensen, T. I. A. 1993, "Obesity and socioeconomic status: a complex relation", *The New England Journal Of Medicine*, vol. 329, no. 14, pp. 1036-137.

Suter, P., Hasler, E., & Vetter, W. 1997, "Effect of Alcohol on energy metabolism and body weight regulation: is alcohol a risk factor for obesity?", *Nutrition Reviews*, vol. 55, pp. 157-171.

Swanson, C., Brown, C., Sinha, R., Kulldroff, M., Brownson, R., & Alavanja, M. 1997, "Dietary fats and lung cancer risk among women: the Missouri Women's Health Study (United States)", *Cancer Causes and Control*, vol. 8, no. 6, pp. 883-893.

Tambs, k., Moum, T., Eaves, L., Neale, M., Midthjell, K., Lund-Larsen, P., Naess, S., & Holmen, J. 1991, "Genetic and environmental contributions to the variance of the body mass index in Norwegian sample of first and second degree relatives", *American Journal of Human Biology*, vol. 3, pp. 257-267.

Tarasuk, V. S. & Brooker, A. S. 1997, "Interpreting Epidemiologic Studies of Diet-Disease Relationships", *Journal of Nutrition*, vol. 127, no. 9, pp. 1847-1852.

Teasdale, T., Sørensen, T., & Stunkard, A. 1990, "Genetic and early environmental components in sociodemographic influences on adult body fatness", *British Medical Journal*, vol. 300, pp. 1615-1618.

The National Audit Office 2001, *Tackling obesity in England*, The Stationery Office, London, HC 220 session 2000-2001.

The Scottish Office: Scotland's Health 1995, *Scottish Health Survey 1995*, The Stationery Office, Edinburgh, 1.

The Trials of Hypertension Prevention Collaborative Research Group 1997, "Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure: The Trials of Hypertension Prevention, Phase II", *Archives of Intenal Medicine*, vol. 157, no. 6, pp. 657-667.

Thorogood, M., Appleby, P. N., Key, T. J., & Mann, J. 2003, "Relation between body mass index and mortality in an unusually slim cohort", *Journal of Epidemiology and Community Health*, vol. 57, no. 2, pp. 130-133.

Tucker LA & Bagwell M. 1991, "Television viewing and obesity in adult females", *American Journal of Public Health*, vol. 81, no. 7, pp. 908-911.

Tucker LA & Friedman GM 1989, "Television viewing and obesity in adult males", *American Journal of Public Health*, vol. 79, no. 4, pp. 516-518.

Upton, M., McConnachie, A., McSharry, C., Hart, A., Davey Smith, G., Gillis, C., & Watt, G. 2000, "Intergenerational 20 year trends in the prevalence of asthma and hay fever in adults: the Midspan family study survey of parents and offspring", *British Medical Journal*, vol. 321, pp. 88-92.

van den Brandt, P., Spiegelman, D., Yaun, S., Adami, H., Beeson, L., Folsom, A., Fraser, G., Golbohm, A., Graham, S., Kushi, L., Marshall, J., Miller, A., Rohan, T., Smith-Warner, S., Speizer, F., Willett, W., Wolk, A., & Hunter, D. 2000, "Pooled analysis of prospective cohort studies on height, weight and breast cancer risk", *American Journal of Epidemiology*, vol. 152, no. 6, pp. 514-527.

Visscher, T. & Seidell, J. 2001, "The public health impact of obesity", *Annual Review of Public Health*, vol. 22, pp. 355-375.

Visscher, T., Seidell, J., Menotti , A., Blackburn, H., Nissinen, A., Feskens, E., & Krombout, D. 2000, "Underweight and overweight in relation to mortality among men aged 40-59 and 50-69 years: the seven countries study", *American Journal of Epidemiology*, vol. 151, no. 7, pp. 660-666.

Visscher, T. L., Kromhout, D., & Seidell, J. C. 2002, "Long term and recent time trends in the prevalence of obesity among Dutch men and women", *International Journal of Obesity*, vol. 29, no. 9, pp. 1218-1224.

Visser, M., Deurenberg, P., van Staveren, W. A., & Hautvast, J. G. 1995, "Resting metabolic rate and diet-induced thermogenesis in young and elderly subjects: relationship with body composition, fat distribution, and physical activity level", *American Journal of Clinical Nutrition*, vol. 61, no. 4, p. 772.

Voss, S., Kroke, A., Klipstein-Grobsch, K., & Boeing, H. 1998, "Is macronutrient composition of dietary intake data affected by underreporting? Results from the EPIC-Potsdam study", *European Journal of Clinical Nutrition*, vol. 52, pp. 119-126.

Wannamethee, S. G. & Shaper, A. G. 2003, "Alcohol, body weight, and weight gain in middle-aged men", *American Journal of Clinical Nutrition*, vol. 77, no. 5, pp. 1312-1317.

Wardle, J. & Griffith, J. 2001, "Socioeconomic status and weight control practices in British adults", *Journal of Epidemiology and Community Health*, vol. 55, pp. 185-190.

Wareham, N. & Rennie, K. 1998, "The assessment of physical activity in individuals and populations: why try to be more precise about how physical activity is assessed?", *International Journal of Obesity*, vol. 22, no. Suppl 2, p. S30-S38.

Waterland, R. A. & Garza, C. 1999, "Potential mechanisms of metabolic imprinting that lead to chronic disease", *American Journal of Clinical Nutrition*, vol. 69, pp. 179-197.

Watt, G., Hart, C., Hole, D., Smith, G., Gillis, C., & Hawthorne, V. 1995, "Risk factors for cardiorespiratory and all cause mortality in men and women in urban Scotland:15 year follow up.", *Scottish Medical Journal*, vol. 40, pp. 108-112.

Wee, C. C., McCarthy, E. P., Davis, R. B., & Phillips, R. S. 2000, "Screening for cervical and breast cancer: Is obesity an unrecognized barrier to preventive care?", *Annals of Internal Medicine*, vol. 132, no. 9, pp. 696-704.

Weinstoch, R., Dai, H., & Wadden, T. 1998, "Diet and exercise in the treatment of obesity", *Archives of Internal Medicine*, vol. 158, pp. 2477-2483.

West, P., Ford, G., Hunt, K., MacIntyre, S., & Ecob, R. 1994, "How sick the west of Scotland? Age specific comparisons with national datasets on a range of health measures", *Scottish Medical Journal*, vol. 39, pp. 101-109.

Westerterp-Plantenga, M. S. & Verwegen, C. R. 1999, "The appetizing effect of an aperitif in overweight and normal-weight humans", *American Journal of Clinical Nutrition*, vol. 69, no. 2, pp. 205-212.

Willett, W. C. 1998a, "Is dietary fat a major determinant of body fat?", *American Journal of Clinical Nutrition*, vol. 67(suppl), pp. 556S-562S.

Williamson, D., Madabs, J., Anda, R., Kleinman, J., Giovino, G., & Byers, T. 1991, "Smoking Cessation and severity of weight gain in a national cohort", *The New England Journal Of Medicine*, vol. 324, no. 11, pp. 739-745.

Wolk, A., Gridley, G., Svensson, M., Nyren, O., McLaughlin, J., Fraumeni, J. F., & Adam, H. 2001, "A Prospective study of obesity and cancer risk", *Cancer Causes &Control*, vol. 12, no. 1, pp. 13-21.

World Health Organisation 1998, *Obesity: Preventing and Managing the Global Epidemic*, Report of a WHO consultation on obesity, Geneva.

Wu, A., Paganini-Hill, A., Ross, R., & Hemderson, B. 1987, "Alcohol, physical activity and other risk factors for colorectal cancer: a prospective study", *British Journal of Cancer*, vol. 55, pp. 687-694.

Yarnell, J. W. G., Milbank, J. E., Swectnam, P. M., & Walker, C. L. 1983, "A short dietary Questionnaire for use in an epidemiological survey: comparison with weighed dietary", *Human Nutrition: Applied Nutrition*, vol. 37A, pp. 103-112.

Zhang, Y., Felson, D., Ellison, R., Kreger, B., Scjatzhin, A., Dorgan, J., Cupples, L., Levy, D., & Kiel, D. 2001, "Bone mass and the risk of colon cancer among postmenopausal women: the Framingham study", *American Journal of Epidemiology*, vol. 153, no. 1, pp. 31-37.

Zimmet, P., Hodge, A., Nicolson, M., Staten, M., de Courten, M., Moore, J., Morawiecki, A., Lubina, J., Collier, G., Alberti, G., & Dowse, G. 1996, "Serum leptin concentration, obesity and insulin resistance in Western Samoans: cross sectional study", *British Medical Journal*, vol. 313, pp. 965-969.