



**REPORT ON OBESITY AND DISEASE**

**DECEMBER 2005**

**Introduction**

Human genes have gradually evolved over thousands of years, adapting so as to ensure human survival as conditions changed. As a result, man entered the twentieth century as a robust species. However, the pace of change in the broader environment within which we live has really accelerated over the last 50 years.

As a result, the environment in which we live now is maladapted to the genes we possess. These evolutionary pressures are affecting all of us. It is not just the fat who are getting fatter. The whole population is getting fatter. Thirty years ago, the median Body Mass Index (BMI) for a British male adult was 23 kg/m<sup>2</sup>. Today, the median BMI is 26.3 kg/m<sup>2</sup>.

Approximately one in four people in the UK are now obese, costing the NHS and the wider economy between £3.3 billion and £3.7 billion each year. For the individual, being obese means that they are far more likely to suffer from certain diseases as a result of their increased weight. Obese patients are twice as likely to suffer from hypertension and cardiovascular disease, and four times as likely to develop diabetes, compared to patients of normal weight.

The medical consequences of overweight and obesity are many and various. They include metabolic, endocrine, physical, psychological and social problems.

The benefits of achieving just a 10% weight loss are also well-established, and have been shown to include the following:

- A 20% fall in total mortality from obesity-related disease
- A 30% fall in diabetes related deaths
- A 40% fall in obesity related deaths

During 2005, the All Party Parliamentary Group on Obesity held a series of meetings to discuss the impact of co-morbid conditions or diseases caused by overweight and obesity: high cholesterol, stroke, heart disease and the metabolic syndrome, cancer and diabetes.

This paper summarises the main points and key recommendations from the meeting series.

## **Obesity and Stroke**

Each year, approximately 130,000 people in England and Wales suffer a stroke, of which 85,000 have a stroke for the first time. Stroke is the third biggest killer behind cancer and coronary heart disease and greatest cause of disability in the UK.

According to the Stroke Association, there appears to be a clear, albeit indirect, link between obesity and stroke. Overweight people are more likely to have high blood cholesterol levels and high blood pressure than people of a normal healthy weight. Both high blood pressure and high cholesterol are risk factors for stroke, as is diabetes. The distribution of the fat is also important, with abdominal fat carrying greater risk of stroke and cardiovascular disease than fat on the hips and thighs.

Unfortunately, the risk factors for stroke don't just add up – they multiply! For example:

- Smoking doubles the risk of having a stroke
- High blood pressure increases the risk of stroke seven-fold
- Binge drinking (defined as more than 6 units in 6 hours) increases the risk of stroke five-fold
- However, all three increases the risk by  $2 \times 5 \times 7 = 70$  times!

## **Diet, Cholesterol and Cardiovascular Risk Reduction**

Raised blood cholesterol is the greatest single risk factor for heart health, contributing to almost half of all deaths in the UK from coronary heart disease (CHD). Overweight and obesity are directly linked to raised triglycerides, reduced levels of protective HDL-cholesterol, and an increase in small dense atherogenic LDL-cholesterol particles. However, cholesterol is one factor that can be modified and managed, often through diet and lifestyle changes.

Cholesterol, therefore, plays an integral role in related diseases/conditions and should be a specific area of focus for public health initiatives, if the government is to successfully improve the health of the nation.

According to the Health Development Agency (HDA) in 2004, reducing cholesterol levels by even a small amount would prevent 25,000 deaths. The HDA attributes much of the 51% decline in CHD deaths in recent years in Scotland to a reduction in risk factors – such as smoking, cholesterol levels, blood pressure and improvements in social and economic deprivation.

It is well established that primary prevention of CHD works, as is illustrated by the example of North Karelia in Finland. In the 1960s, Finland was recognised as having one of the highest CHD rates in world. Research identified raised cholesterol, specifically related to diet, as a major risk factor.

The North Karelia CHD prevention project started in 1972 and was rolled out nationally five years later. The project focused on changing dietary habits through health education and cholesterol awareness campaigns, community participation programmes, national guidance by government and heart associations, as well as food and agriculture industry collaborations.

Whilst government policies have now been put in place to tackle obesity in a number of ways, reducing cholesterol is the one factor that has fallen through the net. Any government action on CHD and stroke is welcome, but the current approach is too

focused on treatment (of people who have already had a stroke or developed CHD), NOT primary prevention of CHD.

Cholesterol UK has called for further government action to:

- Fund a public awareness campaign on fat, which would include cholesterol advice
- Propose an integrated services approach to provide accessible heart health check-ups, including cholesterol tests, thereby leading to greater understanding of personal risk
- Draw up practical guidelines for a healthy heart diet to enable healthcare professionals to offer diet and lifestyle advice
- Introduce a coherent public health strategy that includes diet and lifestyle for heart health.

## Obesity and Cancer

Until recently, the data on the relationship between obesity with cancer was somewhat fragmentary and, in some instances, conflicting. The relationship between obesity and the incidence of cancer is not clear-cut. There is, however, a body of evidence to suggest that obesity and severe overweight *can* have an impact on cancer mortality. Some studies have found an association between various measures of obesity and the incidence of, or death rates from, a variety of different cancers. Clearly, with the rapid rise in the BMI of the UK population, there is potential for that rise in obesity to translate over time into increased incidence and/or deaths from several common cancers.

So, what is established scientifically? What do we know for certain? First, scientists *do* know that:

- Alcohol consumption increases the risk of developing certain types of cancer
  - Alcohol has a large effect on mouth, throat, oesophageal cancers
  - Alcohol has a small effect on breast cancer
- Smoking and alcohol cause cancers of the mouth, throat and oesophagus
- Stomach cancer can be caused by infection with *Helicobacter pylori*, as well as salt-preserved foods, and low consumption of fruit and vegetables
- Obesity increases risk for some cancers – e.g. adenocarcinoma of the oesophagus, post-menopausal breast and endometrial cancers - but not all
- The consumption of fruit, vegetables and meat may also play a role in certain types of cancer, but more research is needed to be certain of that.

Recently, the Cancer Prevention Study has examined the relationship between obesity and mortality from individual cancers in large numbers of people in North America (Calle, EE et al. *N Engl J Med* 2003;348:1625-1638). To calculate relative risk of cancer death, Calle and her colleagues made a comparison between subjects in the highest BMI category and those in the reference category (BMI of 18.5 to 24.9 – i.e. normal, healthy weight).

The study concluded that the relative risk of death from uterine cancer, for example, was 6.25 times higher in obese women than in women of healthy weight. In the case of cervical and breast cancers, the relative risk of death was 3.2 times and 2.12 times greater, respectively. Also, and somewhat unexpectedly, deaths from several less common cancers, including bone marrow disorders such as leukaemia and myeloma, were apparently more common in overweight and obese people, than in those of a healthy weight.

The reasons why some (but not all) cancers are more common in obese people are open to considerable debate, and worthy of further research. It is now largely accepted that the prolonged oestrogenic state in post-menopausal women is the primary cause of breast cancer. Some cancers are simply more common in obese people, owing to hormonal changes in the obese state. So far as cancer mortality is concerned, some cancers may simply present later in obese people, resulting in a lower chance of survival. Another possibility is that obese people are less able to withstand cancer treatments, including surgical or onerous medical treatments such as chemotherapy. This can also have an impact on cancer mortality.

What is also apparent is that weight loss has the reverse effect on the risk of dying from cancer. A study that looked at the impact of intentional weight loss on obesity-related health problems in women, found that women losing between 1-8kg in weight reduced their risk of dying from cancer by nearly 30%. Women losing more than 9kg in weight reduced their cancer mortality risk by over 35%.

Consequently, it is possible to conclude that the control of weight gain, through the adoption of healthier diet and lifestyles, could make an important contribution to cancer prevention in the UK.

Breast cancer and endometrial cancer in women are particularly affected by obesity in that increased body mass increases the production of oestrogen, a known factor in raising the risk of these diseases. As regards colorectal cancer, obesity seems to be a known risk factor for men, but only a small risk factor for women. This suggests that there are other risk factors at work, causing the different effects on each sex.

Whilst a certain amount is known about the relationship between obesity and cancer, therefore, there are a large number of research questions that are still outstanding. These include:

- Does the distribution of the fat matter? Does visceral fat carry more risk than adipose fat?
- Can physical activity cancel out the risk associated with obesity or do both matter?
- What are the mechanism for how certain cancers – such as colorectal and kidney cancers - are related to obesity?
- How can we reduce obesity and the risks of developing cancer?

In conclusion:

- Currently, obesity accounts for approximately 5% of all cancer cases in Europe (3% in men, 6% in women)
- In breast, endometrial, prostate and colorectal cancers, the effect of obesity on cancer mortality is greater than the effect of cancer incidence.
- Obesity is clearly a risk factor for these tumour types, but the magnitude of the risk is quite modest compared to the relative risk increase in lung cancer if you smoke, for example.
- The mechanism between obesity and endometrial and breast cancers is well understood; it is oestrogen-driven.
- For other tumour types, like prostate cancer, although there is a small increase in risk for people who are obese, scientists have yet to determine why, or even whether, the link is causative.
- In terms of cancer mortality, obesity accounts for about 14% of cancer deaths in men and 20% of cancer deaths in women in the US.

## Obesity and Heart Disease

Obesity leads to cardiovascular disease (CVD) through the action of the “Metabolic Syndrome”. In fact, Metabolic Syndrome is at the heart of CVD. It consists of a cluster of conditions including central obesity, insulin resistance and hyperinsulinaemia, which can result in a series of related conditions including dyslipidaemia and hypertension. These conditions, in turn, result in CVD.

These conditions are, to some extent, synergistic. What is clear is that everyone who is diagnosed as having Metabolic Syndrome will also have some or all of these other conditions, which are themselves root causes of CVD. The Metabolic Syndrome is the greatest public health threat facing the UK over the next decade.

Whilst there are a number of definitions of Metabolic Syndrome, the definition developed by Professor Tony Barnett is probably the most practical in terms of clinical practice: *Metabolic Syndrome can be defined as the presence of central obesity plus two other cardiovascular risk factors.*

What do we know about Metabolic Syndrome?

- Prevalence rises with age
- Prevalence is highest in the obese population
- Approximately 1 in 5 of the UK population have Metabolic Syndrome
- A significant proportion of other diseases are attributable to Metabolic Syndrome.

Insulin resistance is a complex, multifactorial problem, which is influenced (both favourably and unfavourably) by a variety of factors. Weight loss and physical activity have a positive or favourable impact, reducing insulin resistance. Therapeutic agents such as metformin and glitazones have a similar effect. Weight gain and physical inactivity, however, have the opposite effect, increasing insulin resistance.

A person's weight is not, in itself, an adequate indicator of his or her risk of developing a co-morbid condition; what is important is the amount of body fat (as opposed to lean muscle tissue) and the location of that fat. It is important to differentiate between gluteo-femoral fat (as typified in a woman who is said to be “pear-shaped”) and android or abdominal fat (“apple-shaped”). It is the *distribution* of fat that is of greatest importance in determining health outcomes.

In summary, therefore:

- Visceral, abdominal fat has been identified as a key driver of CVD
- The substances produced in the body by excess visceral fat influence metabolism in a variety of ways:
  - Increased secretion of bioactive substrates that impair metabolism and increase cardiovascular risk (e.g. free fatty acids, adipokines, inflammatory mediators)
  - Decreased secretion of beneficial hormones (e.g. adiponectin)
- Excess visceral fat is associated with a marked net increase in cardiovascular risk, resulting in hypertension, thrombosis, coronary inflammation, insulin resistance and type 2 diabetes.

BMI is a standard measure of obesity currently, but BMI values are variable and do not provide the best correlation with excess visceral fat. Waist circumference and

triglyceride levels could be used instead to diagnose excess visceral or abdominal fat and, therefore, elevated CVD risk.

Waist circumference is straightforward to measure and provides a superior diagnosis of excess visceral fat compared to BMI or waist-hip ratio measurements. Generally speaking, a man with a waist circumference of more than 94cm is at increased risk and at greatest risk with a waist circumference of 102cm or more. Women are at increased risk if their waist circumference exceeds 80cm and at greatest risk when it exceeds 88cm. For certain ethnic populations, the risk increases at lower waist circumference measurements than those given above.

Biochemical markers (e.g. fasting triglycerides) can be added to increase predictive power for diagnosing excess visceral fat and elevated CV risk. Research has indicated that a high waist circumference and elevated triglyceride levels often coincide, thereby suggesting that a simultaneous measurement may aid diagnosis.

To conclude:

- Abdominal obesity is a root cause of CVD and metabolic disorders (through the genesis of the Metabolic Syndrome)
- Waist circumference and fasting triglyceride measurements should become part of everyday clinical practice to identify patients at risk of CVD
- Metabolic Syndrome is common and deadly, but also poorly-recognised
- Healthcare professionals now have a practical working definition of Metabolic Syndrome that they can apply in everyday clinical practice, as well as a simple means to measure risk, which they should be using.

## **Obesity and Diabetes**

### **Children's Predisposition to Diabetes**

The connection between obesity and diabetes can be summed up in two words: insulin resistance. Insulin is produced in the pancreas and circulates around the body, acting in the muscles, adipose tissue (fat) and liver to regulate the amount of glucose (or energy). When the body becomes overweight, it becomes less responsive to the action of the insulin (i.e. it becomes insulin-resistant).

So, for every stepwise increase in weight, we see a stepwise reduction in insulin efficiency. As a result, the pancreas produces more and more insulin and the body finds it more and more difficult to cope. Once a body has lost the ability to control the amount of glucose in the blood, that person is, by definition, diabetic.

The Early Bird Study is a non-intervention prospective cohort study of healthy schoolchildren designed to identify the earliest changes that lead to type 2 diabetes. If the day that diabetes strikes is the explosion, Early Bird aims to understand what ignited the fuse, what keeps it alight and, most importantly, how best to extinguish it before detonation occurs. The fuse is a state of insulin resistance which is known to precede diabetes, and the study asks the question: Which children develop insulin resistance, and why?

At the outset, the study took a cohort of 300 healthy five-year olds with the aim of studying them over a period of 11 years when they reach 16. Every six months, the study investigators take a snapshot of all of the kids. The 'snapshots' are detailed studies of body composition, dietary composition, metabolic rate, physical activity

and anthropometry. Uniquely, blood samples are taken on each occasion to measure insulin resistance and the metabolic changes with which it is associated.

The Early Bird study started in January 2000 and is programmed to continue for 12 years. Although the study is still ongoing, the interim findings have led to some fascinating early conclusions:

- Girls as young as five years old already show signs of being predisposed to developing diabetes in later life. The same is not true for boys. Girls have a 35% greater insulin resistance than boys, even when all other factors were controlled for i.e. this is an intrinsic difference between little boys and little girls.
- The level of adiposity (or percentage of the body that is fat) rises year on year and it is increasing at a much faster rate - in both boys and girls - than was seen in the 1990s.
- Bizarrely, however, there is a correlating year on year decrease in levels of insulin resistance. Essentially then, these children appear to be getting healthier, metabolically speaking, as their fat percentage increases!
- Looking at levels of physical activity, the study found that the activity cost of being driven to school was 16%, compared to children who walked to school. However, the loss of activity is recouped during the week so that, by the end of the week, there was no difference in activity between children who were driven to school and those who weren't. Girls overall are less active than boys.
- Children who were very active at school were less active out of school, and vice versa. Overall, therefore, there was no difference in activity in the group of children over the course of the whole week.
- Fathers are very bad at estimating their own weight and that of their children. Of the very overweight kids, 60% of their fathers thought that they were of a normal weight and 35% of their mothers thought so too.

### **Obesity and Genetic Susceptibility**

One meeting considered the extent to which genetic susceptibility is a factor in obesity, insulin resistance and type 2 diabetes.

Obesity has both mechanical and metabolic effects. When it comes to obesity, everyone is well aware that it is the energy imbalance that does the damage; too many calories in, too few out, causes individuals to put on weight over time. In truth, however, no one knows which side of the equation causes the most difficulties. When one considers the link between obesity and developing type 2 diabetes, this simple fact of an energy imbalance does not explain why plenty of people of normal weight develop diabetes and yet plenty of fat people do not get diabetes.

The obvious - and scientific - explanation is that there is a huge variation in people's susceptibility to developing certain conditions and diseases. In the case of obesity, individuals vary hugely in their ability to store any additional energy (calories) consumed in our adipose tissue. This variability usually has a genetic or congenital

cause. We are not entirely powerless in the face of the current obesogenic environment – there are biological controls in place.

For example, leptin is a biologically active human hormone. Without it, the appetite goes haywire and the brain tells the individual that they are starving hungry. A group of children were developmentally normal but extremely obese. They had intense hunger and appetite. In all cases the children were found to have inadequate natural levels of leptin. Once the children were treated with leptin, their weight came down and their insulin resistance and other metabolic variables began to improve as well.

In short then, there are three potential causes of obesity. “Gluttony and sloth” are two of them, but genetic factors can also play a key role in the development of obesity. As much as 70% of the variation in individual BMI measurements could be attributable to genetic factors. Unfortunately, many commentators have chosen to overlook or ignore that obesity can have a genetic cause. It is vital that we start to communicate this information out to parents, schoolteachers, healthcare professionals and the media.

Ten years ago, researchers knew of no obesity-related genes. Four are now known to exist and all of them have the effect of stimulating the appetite. The newspapers were full recently of the story of a three-year old girl, who had allegedly died “from obesity”. Technically, there was some truth in that; the child was grossly overweight at the time she died. However, what the media chose to disregard or overlook was that this particular child had a genetic abnormality, which meant that she had two mutant leptin receptors. Therefore, she would have been obese in any society, not just in the UK.

Unfortunately, ignorance of the role that genetic factors can play in causing obesity and associated conditions resulted in a miscarriage of justice and a gross misrepresentation of the true facts of this particular case.

## **Speakers**

The All Party Parliamentary Group on Obesity would like to thank the following speakers and contributors to its 2005 programme on “Obesity and Disease”:

- Sandra Field - South London Regional Manager for The Stroke Association
- Eve Knight - representative, British Cardiac Patients Association (BCPA)
- Louise McCombie - weight management adviser, Counterweight Project on behalf of HEART UK
- Cholesterol UK - a coalition between two independent advocacy organisations: HEART UK and the British Cardiac Patients Association
- Dr Jonathan Pinkney - Senior Lecturer, University of Liverpool and Consultant Physician at University Hospital Aintree
- Professor Tim Key - Cancer Research UK Epidemiology Unit, University of Oxford Professor Colin Waine OBE, FRCGP, FRCPath – University of Sunderland
- Professor Terrence Wilkin - the New Peninsula Medical School, Plymouth
- Professor Stephen O’Rahilly - the University of Cambridge
- The All Party Parliamentary Group on Diabetes
- Cancer Research UK
- Diabetes UK
- National Obesity Forum
- Stroke Association