Obesity is one of the greatest threats to health. Research has shown that obesity severely increases the risk of type 2 diabetes, heart and liver disease, some forms of cancer, and also increases the likelihood of developing other long-standing illnesses. In 2008 high blood pressure was recorded in 48 per cent of men and 46 per cent of women classified as obese (a body mass index — BMI — of over 30), compared with just 17 per cent of men and women in the normal weight group. The 2013 annual Health Survey for England showed that 61 per cent of adults, and 30 per cent of children aged between two and 15 in England are now either overweight or obese. The number of adults classed as obese has increased by 60 per cent in the last two decades (from 15 per cent in 1993 to 25 per cent in 2011). In 2004 research by a House of Commons Select Committee estimated that 34,100 deaths were attributable to obesity — 6.8 per cent of all deaths in England. Health problems associated with being overweight or obese cost the NHS £5 billion every year.

Although obesity cannot be attributed to a single factor, the overarching cause is the simple imbalance between energy in (from the food and drink choices we make) and the energy out (from physical activity). The increased availability of large portions of energy dense food in combination with an increasingly sedentary lifestyle, caused by an increase in numbers of desk-based workers and increased leisure time spent watching television and using the internet, has played a major part in the rising levels of obesity. Although researchers have now identified genes that make some people more susceptible to obesity, it is also clear that the underlying susceptibility to obesity is more likely to be manifest in an environment where food is plentiful and activity levels are low. Research has also shown that this risk can be partly offset by regular physical activity. See ‘Obesity and your genes’.

The MRC has played a leading role in obesity research for more than three decades, from the initial investigation into metabolism and why obese people put on weight, to research into genetics and strategic reviews to influence Government policy.
1980s: MRC-funded researcher Professor Sir Stephen Bloom discovered gut hormones and established their endocrine physiology, exploring their influence on appetite regulation and their simultaneous role as neurotransmitters.

1986: Professor Andrew Prentice at the MRC Dunn Nutrition Unit in Cambridge, working with Dr. Andy Cavanagh, further develops the ‘doubly-labelled water method’ for estimating how much energy a person expends as a by-product of energy expenditure.

1986: Researchers at the MRC Epidemiology Unit show that being overweight or obese is associated with a mutation in the gene coding for Leptin, a hormone that reduces energy intake and expenditure. This provides the first genetic evidence that leptin is an important regulator of energy balance in humans.

1999: Professors Andrew Prentice and Susan Jebb highlight reports of low energy intake among children from different areas in the UK, and finds that the amount of physical activity undertaken is related to a long-term obesity-related effect on health.

2003: Dr. Robert Barteltner, an MRC researcher at University College London, discovers that a high protein diet can help weight loss by increasing levels of the gut hormone peptide YY (PYY), which helps to regulate appetite by sending signals to the brain that suppress appetite.

2006: Researchers at the MRC Epidemiology Unit track 3,000 children from different areas to age 25 and finds that the amount of physical activity undertaken is related to a long-term obesity-related effect on health.

2008: A study led by the MRC Epidemiology Unit, using data from 218,000 adults, shows that physical activity mitigates the effect of possessing the FTO obesity-risk variant.

2011: Researchers at the MRC CSG Social and Public Health Sciences Unit find that men with the highest BMIs are 20.2 per cent more likely to die from cancer than those with lower BMIs.

2012: MRC-funded researchers at the University of Oxford show that women who breastfed their children have a lower body mass index (BMI) than those who did not, even decades after going into menopause.

2013: The MRC/US National Institute on Aging (MRC/NIH) builds on the work of the earlier MRC Centre for Obesity and Related Metabolic Diseases (MRC COORD), aiming to improve understanding of the basic mechanisms responsible for obesity-related and related metabolic diseases.

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Obesity and the FTO gene

A consortium of researchers, predominantly supported by the MRC and Wellcome Trust, identified the obesity-risk FTO variant gene in 2007 after undertaking a genome-wide search for type 2 diabetes-susceptibility genes. The researchers found that this gene variant does in fact predispose the carrier to diabetes through its effect on body mass index. The researchers discovered single ‘letter’ variations in the genetic code of the FTO gene and showed that those with one copy of the obesity-risk variant were on average 1.6kg heavier than those without the variant, and those with two copies, 16 per cent of the population, were 3kg heavier. The FTO gene’s association with obesity was confirmed by MRC researcher Philippe Froguel at Imperial College London23. Later in 2007, MRC scientists at the MRC Functional Genetics Unit in Oxford and the University of Cambridge discovered that the FTO gene codes for an enzyme that can act directly on DNA to modify it — suggesting that it might have a role in controlling the turning on and off of other genes. They also found that FTO is highly expressed in a region of the brain called the hypothalamus, which has important roles in the control of hunger and satiety and that, in certain parts of the hypothalamus, the levels of FTO are influenced by feeding and fasting.

In a further study in 2010, researchers at MRC Harwell set out to determine whether it was differences in the activity of the FTO gene itself that was directly causing the increase in body weight24. The scientists bred mice with extra copies of the FTO gene. These mice were healthy, but ate more and became fatter than normal mice. Female mice with two extra copies of the FTO gene, when fed a standard diet, became 22 per cent heavier than normal female mice after 20 weeks. The difference in weight for male mice was 10 per cent. The researchers also showed that this difference was because mice with FTO over-activity consumed more food.

Despite the identification of genetic factors predisposing people to obesity, MRC researchers found in 2011 that daily physical activity can actually offset this risk by 30 per cent25. The researchers analysed data on 218,000 adults from 45 previous studies that had looked at body weight, physical activity and the FTO gene. They found that the effect of the FTO gene was reduced by 27 per cent in people classed as physically active compared with their physically inactive counterparts.

Until 2013 it was unknown how variations in the FTO gene were associated with obesity. Research from the MRC Clinical Sciences Centre’s Metabolic Signalling Group, in collaboration with scientists at UCL and King’s College London, has now shown for the first time how these variations are linked26. This study demonstrated that FTO gene variations affect circulating levels of ‘hunger hormone’ ghrelin in the blood. Ghrelin stimulates appetite and so levels are normally high before a meal and then decrease afterwards. However, for the one in six people who carry two copies of the high obesity-risk FTO variant gene, ghrelin levels do not drop off after eating, and so they soon start to feel hungry again. A group of 20 participants were asked to rate their hunger before and after a standard meal, while blood samples were taken to test levels of ghrelin. Men with the high-risk variation had much higher circulating ghrelin levels and felt hungrier after the meal than those without. The scientists then used functional magnetic resonance imaging (fMRI) in a different group of 24 participants and found that individuals with the obesity-risk FTO variant rated pictures of high-calorie foods as more appealing after a meal than the low-risk group. In addition, the Ventral Tegmental Area (VTA) responsible for appetite control responded differently in participants with two copies of the FTO mutation.

The researchers also investigated the situation at the molecular level. Boosting the expression of FTO in mouse cells effectively increased the production of ghrelin. When they compared this to human cells from the high-risk group, they found levels of FTO expression were significantly higher, and correspondingly more ghrelin mRNA was found than in cells from the low-risk group. The study uncovers a novel mechanism for manipulating ghrelin levels whether by drug or behavioural means. There are some drugs in the pipeline that suppress ghrelin, which might be particularly effective if they are targeted to patients with the obesity-risk variant of the FTO gene.

The MRC has long played a key role in advising the UK Government on the increasingly important issue of obesity and helping to shape public policy. The MRC in conjunction with the Department of Health wrote the first report on obesity research in 1976, which showed that an increase in BMI led to increased risk of death. This led to Professor Philip James establishing the MRC Dunn Clinical Nutrition Centre in Cambridge.

Professor Susan Jebb, an MRC scientist for 27 years, previously at MRC Human Nutrition Research and now at the University of Oxford was the science advisor on obesity to the Department of Health and chair of the cross-government Expert Advisory Group on Obesity in England from 2007-2012. Between 2005 and 2007, she was also the science advisor for the Foresight Project "Tackling Obesities: Future Choices", a long-term plan on how the Government could deliver a sustainable response to obesity in the UK over the next 40 years. The report set out a broad, ambitious strategy which includes the promotion of healthy diets, redesigning the built environment to promote walking, and wider cultural shifts to societal values around food and activity. Foresight likewise linked the obesity crisis to climate change — both issues needed individual and societal action. The report, which includes major contributions from MRC scientists, acknowledged that individuals do have a personal responsibility for their diet and lifestyle. However, it concluded that in our ‘obesogenic’ environment, with its abundance of energy-dense food, motorised transport and sedentary lifestyles, obesity is the default condition.

This report led to the development of the cross-Government strategy "Healthy weight, healthy lives", published in 2008.

Effect on health

The major concern with obesity is that it leads to other illnesses. Around three-fifths of type 2 diabetes and one-fifth of heart disease cases are attributable to excess body fat. Six cancers are also linked to obesity27. Obese people are more likely to suffer from social and psychological problems, such as depression, prejudice, discrimination, stigmatisation and low self-esteem. Being overweight also increases the risk of dementia — Alzheimer’s disease for example — and could lead to infertility.

In 2011 researchers at the MRC/CSO Social and Public Health Sciences Unit found that men with the highest BMIs at age 18 are 35 per cent more likely to die from cancer than those with lower BMIs28. The MRC scientists, in collaboration with researchers at University College London (UCL) and the Harvard School of Public Health, analysed the medical records of around 20,000 male graduates who attended Harvard between 1916 and 1950. They found that the link between men being overweight or obese at age 18 and death from cancer in later life was apparent even if they reduced their weight during middle age. The associations between weight and cancer were particularly strong for lung, skin, oesophageal and urogential (kidney, bladder, prostate and testicular) cancers. For example, men whose BMI had been greater than the average (21.7) at age 18 had more than a 50 per cent greater risk of dying from lung cancer than those with the lowest BMIs, even after accounting for whether or not they smoked.

Diabetes is a huge and growing problem. Since 1996 the number of people in the UK diagnosed with diabetes has increased from 1.4 million to 2.9 million. By 2025 it is estimated that more than five million people will have diabetes. Most of these cases will be type 2 diabetes, because of the rapidly rising numbers of overweight and obese people29. Diabetes is the fifth most common cause of death in the world30. An estimated 15 to 16 per cent of all deaths occurring in England can be attributed to diabetes31. Scientists are investigating the molecular mechanisms of why obesity leads to diabetes. Professor Antonio Vidal-Puig, an MRC researcher at the University of Cambridge, is genetically manipulating mice and has found a mechanism in fat cells that delays the onset of obesity-associated diabetes32.

Researchers have also shown that women who are obese are twice as likely to be diagnosed with asthma as women who aren’t. A team at the MRC and Asthma UK Centre for Allergic Mechanisms at King’s College London extracted a type of immune cell from the blood of obese asthmatics and found that, as well as causing asthma, the cells secreted high levels of a hormone, proemelin. This is usually found in the brain and affects appetite. If obese people lose weight, their asthma usually improves33.
Endnotes

1. Statistics on Obesity, Physical Activity and Diet: England 2013, Health and Social Care Information Centre
10. http://www.mrc-uk.ac.uk

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