Obesity

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[1]. 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.

MRC Medical Research Council

1980s

1980s: MRC-funded researcher Professor Sir Stephen Bloom pioneers the discovery of several gut hormones and establishes their endocrine physiology, including 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 Coward, develops the 'doubly labelled water method' for use in humans. This uses a tracer to track the amount of carbon dioxide produced by the body as a by-product of energy generation to estimate how much energy a person expends. He finds that obese people have a higher metabolic rate than their lean counterparts, reflecting their larger body size – dispelling the myth that their obesity is caused by a metabolic defect resulting in reduced energy expenditure[2]. The team also demonstrate that reports of low energy intake were inaccurate and obese people were eating more calories than previously thought.

1995

1995: Professors Andrew Prentice and Susan Jebb highlight the link between an increasingly sedentary lifestyle and the risk of calorie overconsumption[3].

1995: Professors Andrew Prentice and James Stubbs at the MRC Dunn Nutrition Unit show that a high-energy, high-fat diet can produce a surplus energy balance without any apparent knowledge of those consuming it[4].

1997

1997: MRC researchers led by Professors Sadaf Farooqi and Stephen O'Rahilly at the University of Cambridge identify a mutation in the gene coding for leptin, a hormone that has profound effects on appetite and energy expenditure. This provides the first genetic evidence that leptin is an important regulator of energy balance in humans[5].

1999

1999: Professors Sadaf Farooqi and Stephen O'Rahilly show that treating a severely obese child caused by the leptin gene mutation with leptin leads to a sustained reduction in weight, predominantly as a result of fat loss[6].

2006

2006: Researchers at the MRC Epidemiology Unit track 2,000 children from different areas in Europe and finds that the amount of physical activity undertaken is linked to long-term obesity-related effects on health[7].

2006: Dr Rachel Batterham, 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 indicating that the person is full[8].

2006: The Mind, Exercise, Nutrition, Do it (MEND)[9] programme becomes widespread in schools across England. MEND was set up by MRC researchers at the UCL Institute of Child Health in conjunction with Great Ormond Street Hospital and provides healthy living programmes for children and families in local communities, including ways to make life changes in physical activity, food, self-confidence and personal development. It is now the most extensive child obesity treatment programme in the UK. It is currently running more than 200 programmes per school term across the UK and is also being delivered in Denmark, the US, Canada, Australia and New Zealand.

2006: Professor Sir Stephen Bloom at Imperial College shows how gut hormones restore energy balance. Oxyntomodulin acts as a satiety signal, reducing energy intake when adminstered to humans, resulting in significant weight loss[10]. Thiakis Ltd, the spin out company co-founded by Professor Bloom to commercialise these findings, raises £10 million in funding.

2007

2007: Professors Andrew Prentice and Susan Jebb show that humans have a weak innate ability to recognise foods with a high energy density and to reduce the bulk of food eaten to maintain energy balance[11]. For example, fast food generally has a high energy density, and people tend to consume similar volumes of this with little reference to calorie content.

2007: Professor Nick Wareham, Director of the MRC Epidemiology Unit, produces detailed measures of physical activity in individuals, looking at both activity and sedentary behaviour such as watching television[12].

2007: MRC-funded researchers identify for the first time a gene variant that predisposes the carrier to obesity. Researchers discover single letter variations in the genetic code of the *FTO* gene; those with two copies of the variant gene are on average 3kg heavier than those without.

2007: Professor Sir Stephen Bloom uses Magnetic Resonance Imaging (MRI) to show areas of the brain that are more active during hunger. These areas became less active after administering the gut hormone PYY, and more active with the hormone ghrelin, known to increase hunger.

2007: Researchers at the MRC Centre for Obesity and Related Metabolic Diseases use MRI scans to show that the hormone leptin, known to play a role in regulating energy intake and expenditure, affects brain responses to food stimuli by decreasing reward associated with food and by increasing the sense of being full during eating[13].

2007: The influential Foresight report from the Government Office for Science is published, with contributions from numerous MRC scientists, and paves the way for the development of the first obesity strategy in the UK[14].

2008

2008: An MRC-funded study of almost 90,000 people identifies a second genetic variant that influences body fat, weight and risk of obesity[15]. The new variant is closely related to a gene called *MC4R*, mutations in which are the most common genetic cause of severe obesity within families.

2008: Scientists at MRC Human Nutrition Research, in collaboration with researchers from the Avon Longitudinal Study of Parents and Children (ALSPAC), identify a dietary pattern characterised by high energy density, high fat and low fibre which is prospectively associated with overweightness in children[16].

2008: Thiakis Ltd is sold to Wyeth (later becoming part of Pfizer) for a reported £100 million.

2011

2011: Professor Susan Jebb and her team show that commercial weight loss programmes are an effective intervention for weight management in primary care and are more cost effective than standard NHS weight management programmes[17].

2011: 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 gene.

2011: Researchers at the MRC/CSO Social and Public Health Sciences Unit find that men with the highest BMIs at age 18 are 35 per cent more likely to die from cancer than those with lower BMIs.

2012

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 giving birth[18].

2013

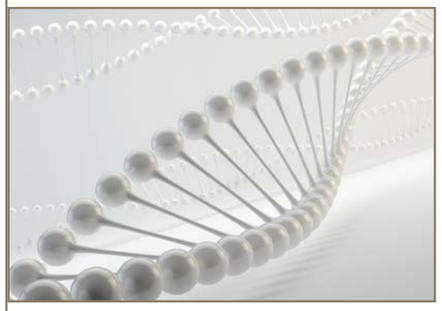
2013: The MRC Metabolic Diseases Unit, the first MRC university unit to be developed from scratch, opens at the University of Cambridge. Led by Professor Stephen O'Rahilly, it builds on the work of the earlier MRC Centre for Obesity and Related Metabolic Diseases (MRC CORD), aiming to improve understanding of the basic mechanisms responsible for obesity and related metabolic diseases.

2013: An MRC-funded study demonstrates that people with the high-risk variant of the *FTO* gene have higher levels of the 'hunger hormone' ghrelin.

2013: Researchers at Imperial College London led by Professor Chris Toumazou and Professor Sir Stephen Bloom develop a microchip to suppress appetite. They believe the device will be able to read signals from the vagus nerve, which among other roles, plays a part in regulating appetite. Human trials may begin in as little as three years and it is hoped that the technique could be an alternative to surgery for the very obese.

2013: The 2013 annual Health Survey for England shows that 61 per cent of adults and 30 per cent of children aged between two and 15 in England are overweight or obese. Health problems associated with being overweight or obese cost the NHS £5 billion every year.

Obesity and the FTO gene



A consortium of researchers led by the MRC 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 London[19]. 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 weight[20]. 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 the 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 cent[21]. 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 linked[22]. 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 study 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.

Obesity and policy

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 changes to shift societal values around food and activity. Foresight likened 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[23].

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 obesity[24]. 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 BMIs[25]. 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 urogenital (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 people[26]. Diabetes is the fifth most common cause of death in the world[27]. An estimated 15 to 16 per cent of all deaths occurring in England can be attributed to diabetes[28]. 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 diabetes[29].

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 of Asthma 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, promelanin. This is usually found in the brain and affects appetite. If obese people lose weight, their asthma usually improves[30].

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Endnotes

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