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.
Bloom pioneers the discovery of several gut hormones and neurotransmitters.

Dr. Robert Winston, in a 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 the person is full.

The team also demonstrates that the hormone PYY, and more active brain regions during eating, affects brain responses to food stimuli by decreasing reward sensitivity and increasing the sense of being full after giving the hormone ghrelin.

Researchers at the MRC Human Nutrition Research, in collaboration with researchers from the Avon Longitudinal Study of Parents and Children (ALSPAC), identify a family pattern in people with thin body mass index (BMI) who are prone to develop diabetes.

The 2013 annual Health Survey for England shows that 61 per cent of adults and 30 per cent of children aged between two and four 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 Frognel at Imperial College London. In 2007, MRC scientists at the MRC Functional Genomics 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. The scientists bred mice with extra copies of the FTO gene. These mice were healthy, but ate more and became fatter than normal mice. Blood samples were taken to test levels of ghrelin. Man 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 Terminal 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 expression. When 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.

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. 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.
Endnotes
1. Statistics on Obesity, Physical Activity and Diet: England 2013, Health and Social Care Information Centre
7. Batterham R et al. (2012). Link between FTO, ghrelin and impaired brain food-cue responsivity (Clinical Sciences Centre) J Clin Invest (July 2013) doi:10.1172/JCI44403
14. Sandig et al. (2007). Human TH2 cells selectively express the orexigenic peptide, pro-melanin-concentrating hormone. PNAS, 104, 12440

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