



The big issue

Another day, another headline about the obesity epidemic and, it seems, it's only getting worse. Dr Eleanor Kennedy invites two leading researchers to put their case for the causes of our current crisis – genes or environment? Let the debate begin

Obesity is now universally recognised as a major risk factor in a number of chronic conditions, including diabetes and, indeed, is defined by the World Health Organisation (WHO) as 'abnormal or excessive fat accumulation that presents a risk to health'. The WHO's global projection is that the number of people classified as obese will increase from the 2005 figure of 400 million to more than 700 million by 2015.

We are bombarded on an almost daily basis with media stories about obesity and its causes. Programmes on the subject abound. Morgan Spurlock's 2004 film *Supersize Me* documented the damaging effects of eating three meals a day from the McDonald's chain of fast-food restaurants over a period of 30 days. Worldwide, the film grossed (if you'll pardon the pun) over \$28m. But, far from generating a mood of moral

panic, obesity seems to have become something of a permanent media fixture, with programmes such as *Celebrity Fit Club*, *Fat Camp* and *Fat Nation* clogging up our television screens.

Meanwhile, the headlines, in a seemingly unceasing stream, proclaim that scientists are investigating yet more 'miracle pills' promising a quick fix for the problem. Xenical and Acomplia launched to great acclaim, but the side effects have led to perhaps less than spectacular successes. Hot on their heels though comes news of a phase II trial of tesofensine, which, its Danish manufacturers hope, will help people to lose twice as much weight as they presently can with currently approved obesity drugs.

So, is it easier just to sit on our couches watching these programmes and waiting for the next blockbuster obesity drug to be delivered along with tonight's pizza or is it worth taking a closer

About the protagonists



Genes: Professor Steve O'Rahilly

Steve is the Professor of Clinical Biochemistry and Medicine in the Department of Clinical Biochemistry in IMS Metabolic Research Laboratories based at the

University of Cambridge. His research focus is on the two major components of Type 2 diabetes, namely obesity and insulin resistance, and how these two phenomena interlink to predispose people to metabolic disease.



Environment: Professor John Wilding

John is based at University Hospital Aintree in Liverpool. His group has developed a considerable reputation for research into the role

of various hypothalamic neuropeptides in weight control and appetite, the clinical study of new diabetes treatments and anti-obesity compounds. He is also Chair of the UK Association for the Study of Obesity.

look at the underlying basis of the condition and debating its fundamental causes?

It is generally, though not universally, agreed that the principal cause of obesity can be distilled down to this: changed dietary habits around the world, with people consuming increasing amounts of high-sugar, high-fat, energy-dense foods, coupled to a corresponding decrease in physical activity. This is all exacerbated by a comfortable quality of life in most developed and many developing countries – where people have easy access to more and more convenience and fast foods. Where our ancestors burned off energy as hunter-gatherers, we sit for hours on end at deskbound jobs, drive or take public transport, zip up and down in lifts and on escalators, rarely walking any significant distance, and idle away evenings in front of TVs, computers and Playstations.

Another school of thought suggests that our calorie-rich and very sedentary existence may not, though, be the only cause of the rising tide of obesity, and that this is, perhaps, nothing new. Obesity is, for example, symptomatic for both Prader-Willi Syndrome and Bardet-Biedl Syndrome, both of which are caused by well-mapped genetic mutations. These conditions, though, are relatively rare.

In 2007, however, research teams at the Peninsula Medical School and the University of Oxford attracted a lot of media attention when they suggested that carrying a particular variant of the FTO gene predisposes someone to having

a 70 per cent higher risk of being obese and to weighing, on average, 3kg more than those who do not have this gene variation.

So is the typical message that you are overweight because of sloth and gluttony, and that it is all your own fault, wrong after all? Is it now the case that you are obese because of your genes and that this is yet something else that we can blame on our parents?

Here, Professor Steve O'Rahilly goes up to bat for genetics, while Professor John Wilding takes on the mantle of environment and lifestyle.

Professor Steve O'Rahilly



"At first glance, it is very easy to dismiss the notion that the set of genetic variants a person inherits from their parents can be 'responsible' for their becoming obese. The prevalence of obesity has increased over the past few decades at a rate far faster than could be accounted for by any systematic changes in the genetic make-up of those populations where the obesity epidemic is rampant.

It is logical, therefore, to conclude that changes in our environment must be, by far, the most important factor. It is also obvious that, if deprived of adequate calories for long enough, then there is no one who could not lose weight. However, on deeper inspection of the scientific data, we find a surprising and much more complex truth.

The existence of genes that lead to obesity is no longer a matter of speculation. Several have been identified and more are on the way. It's true that some people just inherit a bad 'hand of cards', genetically speaking. This is usually caused by a major, damaging mutation in a single, critically important gene, such as leptin. For the most part, these disorders are rare, but others, for example mutations in the melanocortin-4 receptor, affect up to 50,000 people in the UK alone.

Many more people carry a set of genetic variants that makes them much more susceptible than others to becoming obese. And as our modern environment has changed to provide easy access to cheap calories and discouraged physical activity, the people who have inherited the susceptibility genes are much more likely to fall prey to obesity.

More importantly, the genes that have been identified largely influence our drive to eat. For a long time it was assumed that, if so-called obesity genes existed, they were most likely to affect people's metabolic rate. Surprisingly, such genetic effects seem to be in the minority. The vast majority of the major damaging mutations strongly linked to obesity act on the hypothalamus, the part of the brain that senses when we are hungry and when we should stop eating. Now that we are discovering the much more common and, some may say, 'milder' genetic variants that have effects across whole populations, we are finding that these also affect the same processes."

Professor John Wilding



"There is no question that genetics and other biological factors play an important role in determining whether an individual is likely to become overweight or obese, but I will present the case that it is the rapid changes in our environment and lifestyles over the past 30 years that are largely responsible for the current obesity epidemic.

Where populations with a high burden of 'obesity genes' have become rapidly urbanised, the prevalence of obesity can rise rapidly to extremely high levels: this has been seen, for example, on the Pacific Island of Nauru, and in

the Pima Indians of North America. In the latter group, those of the same tribe who maintain a traditional lifestyle remain lean. Some countries in the Middle East have very high rates of obesity in women, but much less so in men – this is again likely to be due to cultural and environmental differences, rather than differences in genetic susceptibility in those populations. The strong social class gradient of obesity also argues against genes being the predominant driving force behind these changes.

Of course, some obese people will probably be found in all societies, but the recent shift in the distribution curve of adiposity in virtually every country worldwide is likely to be the result of a complex interplay between the easy availability of tasty, energy-dense foods (fuelled by relentless, aggressive marketing) and the reduced physical activity at work and in leisure time that seems to be an inevitable consequence of our modern lifestyle. In 1950, the average person in the UK walked nearly 30 miles per week; today, many people walk less than 3 miles each week, and more than two-thirds of the adult population do not reach minimum recommended levels of physical activity.

Individuals are not to blame for these social changes, any more than they can be blamed for the biological traits that they inherit from their parents. However, it is everyone's responsibility to work towards a future in which the environment is less obesogenic. Those people who already have weight problems must acknowledge that they have a problem and seek appropriate advice. Healthcare professionals, meanwhile, need to offer that advice in a supportive and non-judgemental way.

For the majority of people who are at risk of developing obesity in the future, the solution lies in policy makers re-engineering their environment, rather than scientists re-engineering their genes."

Professor Steve O'Rahilly



"While this lifestyle argument is doubtless true to some degree, the evidence is there that the most important influence on whether an individual becomes obese or stays lean remains the set of inherited genetic variants.

Studies of the body weight of identical twins versus non-identical twins, and of adopted children versus members of their natural and adopted families, consistently highlight the dominant influence of genes. Easily the most compelling data comes from studies of identical twins separated at birth and brought up in different families. In adult life, these twins have similar degrees of adiposity to each other and not at all to the family that brought them up. This remarkable data has never been seriously challenged and the implications are profound.

Additionally, studies of several thousand identical and non-identical twins aged 9–11 living in the London area in 2005 have recently been reported. The 'heritability' of adiposity is still high, with approximately 70–80 per cent of the differences between these children in their degree of obesity firmly attributed to genetic differences.

Such discoveries are, to some, 'an inconvenient truth'. They can be interpreted, at worst, as an excuse for inaction, a counsel of despair or even as a challenge to the concept of human 'free will' and moral choice. To counter those views, I would suggest that we really must gain a deeper understanding of the underlying biological predispositions to obesity if we are to develop effective approaches to combating the crisis that faces us.

A deeper appreciation of the underlying biology of obesity should also help to ensure that, instead of being treated as moral pariahs, people with obesity receive the same sympathy and compassion that those with other common, complex and life-shortening diseases have come to expect as standard care."

Professor John Wilding



"Professor O'Rahilly is correct in highlighting the importance of genetics in determining body weight and fat distribution in individuals. However, it is clear that the environmental pressures in modern society make it more likely that everybody could become obese, though maybe the likelihood is slightly higher in those with a greater genetic predisposition to fatness.

Perhaps what is not recognised as easily is that subtle environmental influences are every bit as

pervasive as small differences between the genetic make-up of individuals. Like our genes, there are very many such pressures. While no single such pressure may account for the obesity epidemic, their effect is likely to be synergistic and, in combination, they can create a very large effect. For example, simply switching to high-fat foods – as in *Supersize Me* – may have an effect as least as great as the FTO gene. Combine that with reduced physical activity as a result of our modern lifestyle and its multiple labour-saving devices, and the effect is much greater. We are all affected by these changes to some extent, so the population as a whole is getting fatter.

Perhaps the key point here is that, although genetic and environmental influences play their respective roles in the determination of fatness, we both agree that these influences are largely beyond individual control. If we are to find solutions to the worldwide obesity problem, we must acknowledge this key fact, and consider how best to make our environment less likely to create more obesity – if we are to avoid storing up greater risk for serious conditions, such as diabetes, for generations to come."

No simple solution

So, where does this leave us? Can obesity really be explained away either solely by genetics or solely by environment? Clearly, it cannot.

Like Type 2 diabetes, obesity appears to be caused by a complex interplay between genes and environmental triggers and the widespread lifestyle habits of developed societies. The latter will have a greater impact if they collide with the gene sequences that predispose someone to obesity. Once again, behaviour and physiology are intertwined in a relationship that is difficult to tease apart.

Meanwhile, drug-based solutions to the obesity problem may not be the answer, so we must persist with multidisciplinary approaches to science and medicine if we are to find the answer.

Ironically, as we continue to grapple with the dual problems of energy surplus and obesity, consider this: the WHO also estimates that while one-third of the world is well fed, one-third is underfed, and the remaining third starving. Food enough for thought, everyone?