



## Obesity - a growing concern

*Policy on the prevention and management of obesity focuses on environmental causes. As understanding of the genetic basis for obesity improves, is it time for a rethink?*

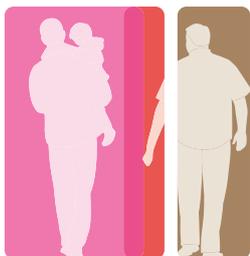
Obesity is a significant and increasing problem worldwide. It is causally linked to a number of the leading causes of mortality and morbidity in the UK, including type 2 diabetes, cardiovascular disease and some cancers. It also has a significant economic impact, with high costs to the health service and to the wider economy.

Overweight and obesity are defined as “*abnormal or excessive fat accumulation that may impair health*”. This is measured using body mass index (BMI), a simple index of weight for height which is calculated as weight in kilograms divided by height in metres squared. In England today, more than two-thirds of men and more than half of women are overweight or obese. Prevalence has risen rapidly over recent years, a trend which is predicted to continue. Obesity is also occurring earlier in life, and more than one-third of children in England are overweight or obese by the time they start secondary school.

### What makes us obese?

At the most basic level, an individual becomes obese when they consume more energy than they expend. We live in an ‘*obesogenic*’ environment in which energy-dense foods are plentiful and there is little need for physical activity as a part of daily life. In this context it is perhaps not surprising that prevalence of obesity in the population is rising, although many individuals do manage to maintain a healthy body weight in this environment.

Behind the simple energy balance equation lies a complex web of interacting biological, societal and behavioural determinants, and BMI is a highly heritable trait. We - scientists, health professionals and increasingly, the public - have a fairly good understanding of the environmental and even the behavioural factors that lead to weight gain, yet the genetic determinants, in the main, remain elusive.



*This is a summary of a new report from the PHG Foundation, “The genomics of obesity”, which is available to download for free at:*

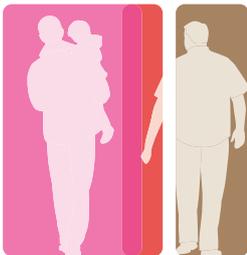
[www.phgfoundation.org](http://www.phgfoundation.org)

## The genetic basis of obesity

We know that genetic differences between individuals are responsible for a large proportion (40% to 70%) of the differences in BMI between individuals within populations.

*In 'common' obesity, genome-wide association studies have identified 32 loci robustly associated with BMI. However, these 32 loci combined explain less than 1.5% of the total variation in BMI within the population.*

Extreme obesity early in life can be caused by a defect in a single gene. Patients with these 'monogenic' (single gene) forms of obesity display a greatly increased drive to eat and consume far more energy than individuals without these mutations. To date, eight genes and one large deletion have been implicated in monogenic disorders in which obesity is the primary feature. These gene discoveries have contributed to our understanding of the biological mechanisms involved in the development of obesity, as all play a role in the central regulation of energy intake. Mutations in the identified genes disrupt appetite and satiety mechanisms, but have little or no known effect on energy expenditure, the other side of the energy balance equation. Monogenic obesity is very severe, but while each type is rare individually, as a group, the monogenic disorders may account for up to one in ten of the cases of severe childhood obesity.



Genes also play an important contributing role in 'common' obesity in the population, although this role is complex and less well understood. Multiple genes are involved, and these interact both with each other and with environmental factors. This 'polygenic' (many gene) obesity has been investigated in large genome-wide association studies, which have to date robustly associated 32 genetic loci with BMI. Several of these loci indicate genes which are highly expressed or known to act in the central nervous system, further emphasising the role of central regulation in obesity susceptibility. In addition, several of the loci include, or are near, genes in which rare variants cause the severe monogenic forms of obesity. However, most of the 32 loci are for markers that are not in known genes, and much remains unknown about the identity and biological mechanisms of the contributing genes. As there is developing evidence for the genetic influence in the drive to eat, this will need to be considered in population approaches to obesity prevention and management in a calorie dense environment.

## Genetic testing for obesity?

Research into the genetic basis of obesity can inform decisions about the utility of genetic testing for identifying the risk and/or causes of obesity in an individual. These decisions should balance what the test can tell us with what can be done with that knowledge, and the ethical, social and legal implications of testing.

In the case of common polygenic obesity, the 32 genetic loci combined explain less than 1.5% of the total variation in BMI within the population, and their ability to predict obesity risk in an individual is extremely limited. For common obesity, genetic testing is therefore not useful. It could even be harmful if knowledge of some genetically influenced risk, however small, acts as a de-motivator for behaviour changes which could improve health.

# The genomics of obesity

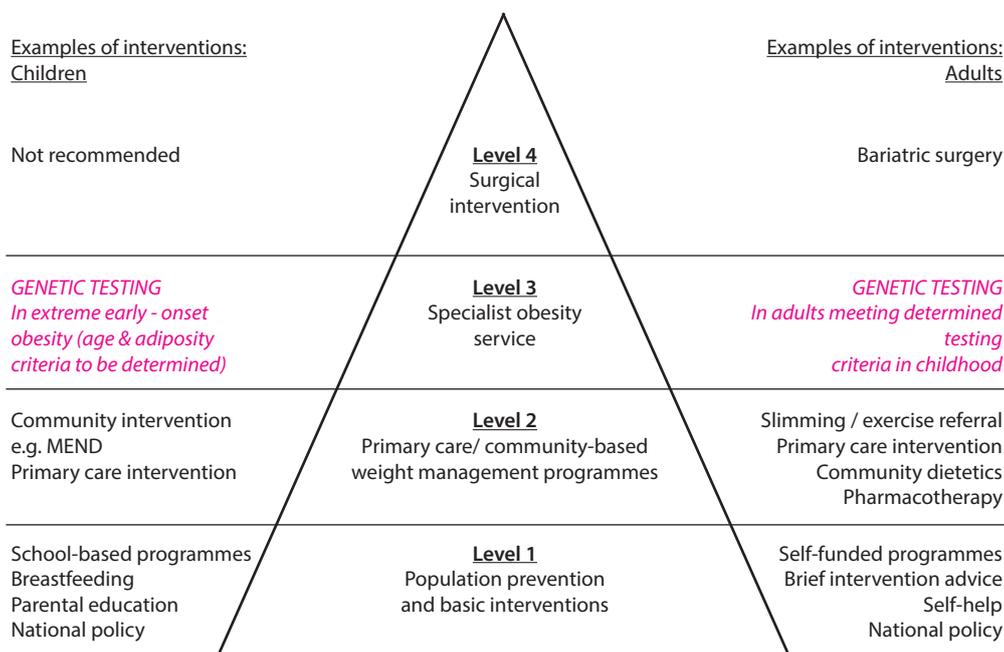
In contrast, there is utility to genetic testing in clinically suspected monogenic cases of obesity. The health consequences of these very severe forms of obesity are significant, with both physiological and psychological morbidity experienced by many affected individuals. In the case of one monogenic disorder, congenital leptin deficiency, a rapidly effective treatment is available. For other genetic causes, whilst no pharmacological treatment is available, identification of a single gene cause of obesity can enable tailored and appropriate management.

## Current approaches to the treatment of obesity?

UK guidelines and policies for the prevention and management of obesity focus on the environmental causes, and current care guidelines make little mention of the role of genetics, other than in particularly severe or complicated cases.

The full PHG Foundation report, *“The genomics of obesity”*, identifies a typical four-tier system of obesity services and care pathways in the NHS. Although services differ between areas, they are typically based on increasing intervention intensity for increasing severity and complexity of the condition, as shown in the figure.

In individuals with extreme, early-onset obesity with hyperphagia, a monogenic cause of obesity should be considered and the known implicated genes tested. This genetic testing should take place within the context of a specialist obesity service, and must include provision of genetic counselling both before and after testing.



*Figure 1 on the left suggests a possible intervention point for consideration of genetic testing.*

## Recommendations

Based on the current state of evidence, the report sets out five recommendations in relation to genetic testing in obesity services.

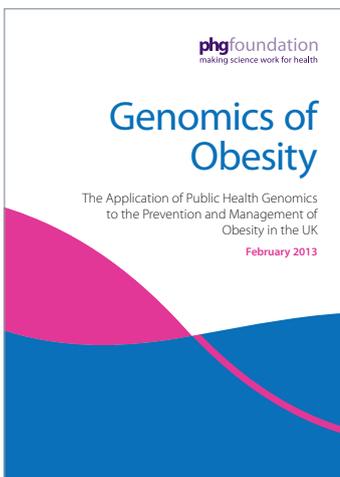
*The full report includes a review of the literature, a synthesis of current understanding of the genetics of obesity and a discussion about the utility of genetic testing for monogenic and polygenic obesity.*

### Polygenic obesity

1. There is currently no utility in testing for common obesity genes.
2. Direct-to-consumer genetic testing for obesity risk should not be recommended.

### Monogenic obesity

3. Children with extreme early onset obesity with hyperphagia should be investigated using a genetic panel test for genes already identified as single gene causes of this condition. Failure to find a defect in such a panel does not exclude a single gene cause as it is unlikely that all causative genes have yet been identified. Relating this to the obesity care pathway (see Figure 1), this testing should take place in the context of a specialist obesity service (level 3 intervention) and an established clinical pathway of care. Criteria for testing should be determined by clinical experts and informed by a health needs assessment. This should also apply to adults who meet the criteria if their obesity was present before the age specified.
4. Patients identified as having a single gene cause of their obesity where there is no pharmacological treatment should receive on-going lifetime support to lose weight and then manage their weight.
5. In future, there may be some utility for testing for monogenic causes of obesity in patients being assessed for bariatric surgery, however this is dependent on strengthened evidence in this area, which should be kept under review.



You can download the report for free at  
[www.phgfoundation.org](http://www.phgfoundation.org)

## About the PHG Foundation

We enjoy an international reputation as leaders in the field of public health genomics. With expertise in public health medicine, biomedical science, epidemiology, law and the social sciences and strong connections in the health, research and policy communities worldwide, we work in strategic partnerships to make science work for health.

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