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Genomics of Obesity

The Application of Public Health Genomics to the Prevention and Management of Obesity in the UK

February 2013

Authors: Louise M. Aston and Mark Kroese

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Executive Summary

Overweight and obesity are "abnormal or excessive fat accumulation that may impair health", as measured using body mass index (BMI), a simple index of weight-for-height.

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

Currently, more than two-thirds of men and more than half of women aged 16 years and over in England are either overweight or obese. Prevalence has risen rapidly over recent years, and this trend is predicted to continue. Excess weight is also occurring earlier in life, with more than one-fifth of children aged 4-5 years and more than one-third of those aged 10-11 years in England being overweight or obese.

Obesity is causally linked to a number of the leading causes of mortality and morbidity in the UK, including type 2 diabetes, cardiovascular disease, some cancers, mental health problems and musculoskeletal disorders. Obesity also has a significant economic impact, with high costs to the health service and to the wider economy through lost working days.

The current policy approach to obesity in the UK is based on the belief that maintenance of a healthy weight is the ultimate responsibility of the individual, whilst the role of government and wider society is to ensure people have access to healthy options and to the information and guidance they need to adopt healthier lifestyles. NICE provide guidance on weight management for adults, children and pregnant women, and commissioning of services in line with these takes place at the local level of the NHS. Whilst specific obesity services and care pathways differ between areas, they are typically based on a four-tier system of increasing intervention intensity for increasing severity and complexity of the condition.

Determinants of obesity

Obesity is a complex, multifactorial condition. It is ultimately caused by an energy imbalance, where intake exceeds expenditure. However, this imbalance is underpinned by multiple complex and interacting biological, societal and behavioural determinants. The leading determinants of obesity in an individual are not necessarily those that are driving the increase in prevalence in the population. The extremely rapid rise in prevalence implicates environmental rather than genetic causes at the population level, and our environment favours weight gain through provision of plentiful, energy-dense foods and little need for obligatory energy expenditure as part of normal daily life. However, some individuals manage to maintain a healthy body weight in the face of this, and whether or not an individual becomes obese in an 'obesogenic' environment is likely to be determined in part by their genetic susceptibility.

The genetic basis of obesity

Genetic differences between individuals are responsible for a large proportion (40% to 70%) of the differences in BMI between individuals within populations. However despite this, UK guidelines and policy for the prevention and management of obesity focus on environmental causes with little mention of the role of genetics, other than in particularly severe or complicated cases. This perhaps reflects the relative understanding of these determinants, with far less known about the genetic basis of obesity than the environmental contributors.

Technological advances are currently facilitating improved understanding of the genetic basis of obesity. Over the past two decades, examination of patients with severe early-onset obesity has identified a number of highly penetrant monogenic disorders in which obesity is the primary feature. Eight genes and one large deletion have been implicated to date, and these discoveries have contributed greatly to understanding of the biological mechanisms involved in the development of obesity. All of these genes have a role in the central regulation of energy intake, with defects in them disrupting appetite and satiety mechanisms. Patients with these monogenic conditions are severely hyperphagic, displaying a greatly increased drive to eat and consuming far more energy than individuals without these mutations. At present, there is little evidence that mutations in the identified genes have an effect on energy expenditure (the other side of the energy balance equation) in humans, although this could be a result of difficulty in measurement.

In contrast, far less is known about the genetic basis of 'common' obesity in the general population. Large genome-wide association studies have identified 32 loci robustly associated 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 to genes in which rare variants cause severe monogenic forms of obesity. Most of the 32 loci, however, are for markers that are not in known genes. Further work is therefore required to elucidate the responsible genes and thereby the functions and pathways involved.

The application of public health genomics to obesity management

Whilst research into the genetics of obesity has increased the understanding of obesity biology, a primary aim and key application of the discovery of disease-associated genes and variants is to enable genetic testing of individuals. In the case of common polygenic obesity, the 32 loci combined explain less than 1.5% of the total variation in BMI within the population. Their ability to predict obesity risk in an individual is therefore extremely limited. This means that there is currently no utility in testing for these susceptibility genes, and direct-to-consumer genetic testing for obesity risk should not be recommended.

In contrast, there is utility to genetic testing in clinically suspected monogenic cases of obesity. In individuals with extreme, early-onset obesity with hyperphagia, a monogenic cause of obesity should be considered and the known implicated genes tested. Whilst these monogenic causes of obesity are individually rare in the population, their combined consequence in the population is not insignificant, with up to 10% of severe childhood obesity possibly having a monogenic cause. These conditions represent very extreme forms of obesity that can result in significant physiological and psychological morbidity in affected individuals. In the case of congenital leptin deficiency, a rapidly effective treatment is available. For other causes,

Whilst the rapid rise of obesity in the population has environmental causes, whether an individual becomes obese in this obesogenic environment is likely to be determined in part by their genes.

whilst no pharmacological treatment is available currently, identification of a single gene cause of obesity can enable provision of tailored and appropriate management, including on-going support for weight loss and/or maintenance. Genetic testing should take place in the context of a specialist obesity service, an established clinical pathway of care. This should also include provision of genetic counselling both before and after testing.

There are still many more genetic causes and contributors to obesity to be identified, both rare single gene defects and common variants. Further research may bring a stratified approach to treatment. This is not yet the case in monogenic obesity except in leptin deficiency, and it is a very long way off in common obesity, although it is important that public health and health care professionals are aware that for some individuals, weight loss and maintenance will be far more of a challenge due to increased genetic susceptibility. The prospect of a stratified approach remains however, and there is much research and commercial interest. Further knowledge of the genetic basis of obesity will continue to increase understanding of the biological mechanisms involved in the development of obesity, and may point to potential pharmacological targets for future drug development.

1 Obesity: what is the problem?

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

Overweight and obesity are defined as "abnormal or excessive fat accumulation that may impair health"[1]. Overweight and obesity in adults are commonly classified using body mass index (BMI), a simple measure of weight-for-height. BMI is calculated as weight in kilograms divided by the square of height in metres (kg/m^2). The World Health Organisation defines weight status for adults according to the following BMI categories:

Overweight is now the most common BMI category for adults in England.

BMI (kg/m2)	Classification
< 18.5	Underweight
18.5 – 24.9	Normal weight
25.0 – 29.9	Overweight
30.0 – 39.9	Obese
≥ 40.0	Morbidly obese

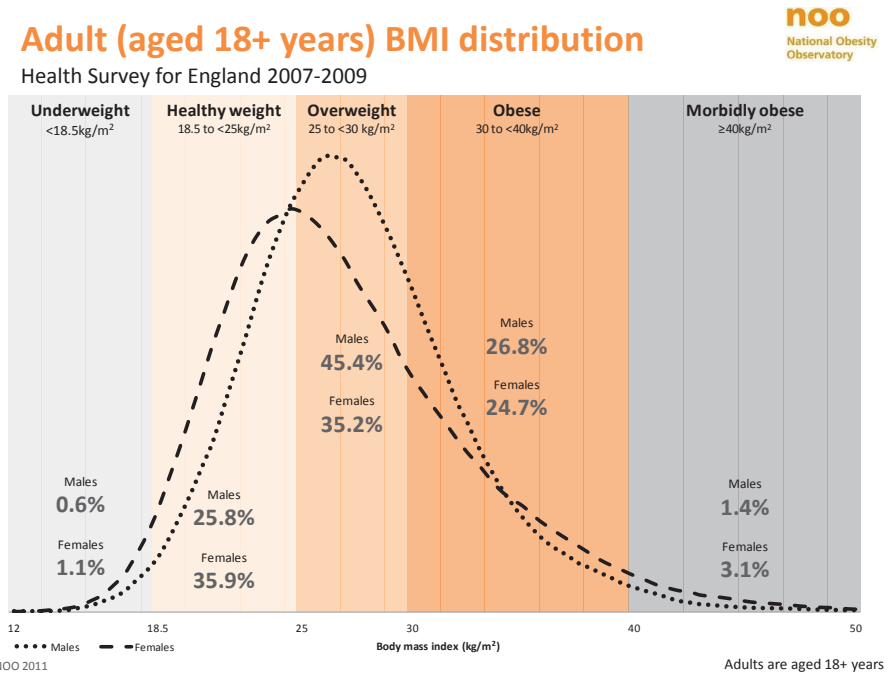
In children, BMI varies with age and sex, making it more complicated to define weight status. For this reason, BMI measurements are related to centiles on sex-specific BMI-for-age reference curves. The World Health Organisation provides BMI-for-age growth reference curves compiled in 2007, for children aged 5-19 years[2]. In England, the National Child Measurement Programme uses the British 1990 growth reference curves to classify the weight status of children according to their age and sex, as follows:

BMI Centile	Classification
≤ 2nd	Underweight
85th – < 95th	Overweight
≥ 95th	Obese

1.1 Prevalence of obesity: who is affected?

The 2010 Health Survey for England (HSE) reveals that more than two-thirds of all men and more than half of all women aged 16 years and over in England are either overweight or obese (as classified by BMI; 42% of men and 32% of women overweight, and an additional 26% of both men and women obese)[3]. Among those aged 45-65 years, more than 70% are above a healthy weight, with over 30% being obese. The distribution of BMI in the English population aged 18 years and over (2007-2009) is illustrated in Figure 1, which highlights that overweight is now the most common BMI category in this population.

Figure 1. BMI distribution in adults in England (figure from the National Obesity Observatory[4])



The prevalence of overweight and obesity has risen rapidly over recent years. Over the past two decades since 1993, the proportion of adults in England who are obese has doubled in men from 13%, and increased by over 50% in women from 16%[3]. Extrapolation of these trends in obesity prevalence has been modelled by the government's Foresight Programme[5]. Their projections indicate that, by 2025, around half of adult males and over a third of adult females will be obese; by 2050, this could rise to 60% of males and 50% of females. The proportion of the population who are a healthy weight may be just 10-15% by this time. These projections are illustrated in Figure 2 for adults aged 21-60 years.

These trajectories are of course only predictions. As with any extrapolation of past trends to predict a future situation, they rely on assumptions and are limited by a lack of knowledge of the future. Whilst the ten years of data the projections are based on show a remarkably consistent trend, we do not know what will happen in the future. This is particularly relevant to complex multifactorial conditions such as obesity where the interplay between and the relative importance of the different determinants are still poorly understood. Here, ten years of data have been used to predict 50 years into the future, and the uncertainty will increase with time as highlighted by the widening of the 95% confidence intervals over time.

Figure 2. Proportions of the population belonging to different BMI categories from each year of the Health Survey for England (marked by dots) and the predicted future proportions to 2050 shown by the curves, with 95% confidence intervals shaded (figures from *The Foresight Report*[5]):

- Underweight (BMI <20) in green
- Appropriate weight (BMI 20-25) in blue
- Overweight (BMI 25-30) in red
- Obese (BMI 30-40) in purple
- Morbidly obese (BMI >40) in pink

Figure 2a. Proportion of males aged 21-60 belonging to different BMI categories in a given year

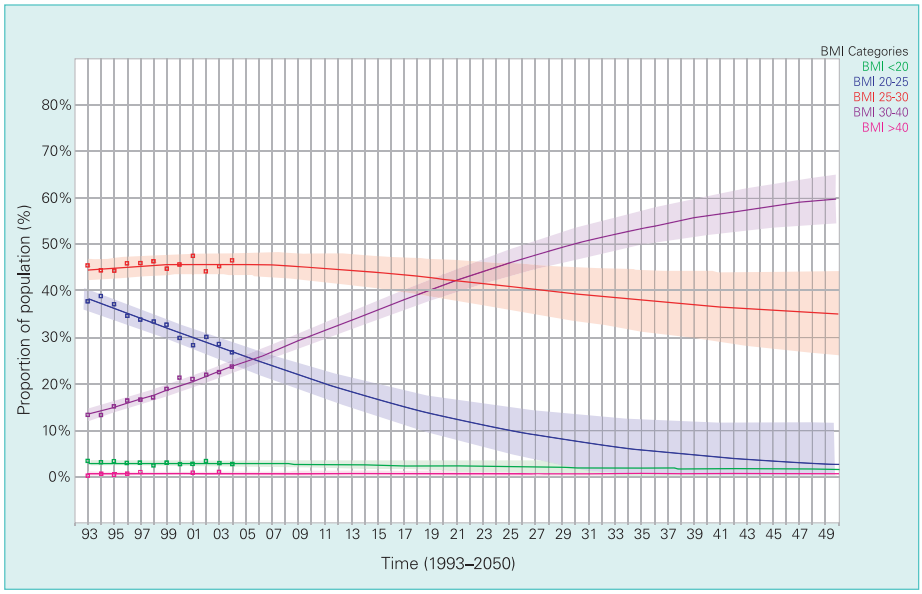
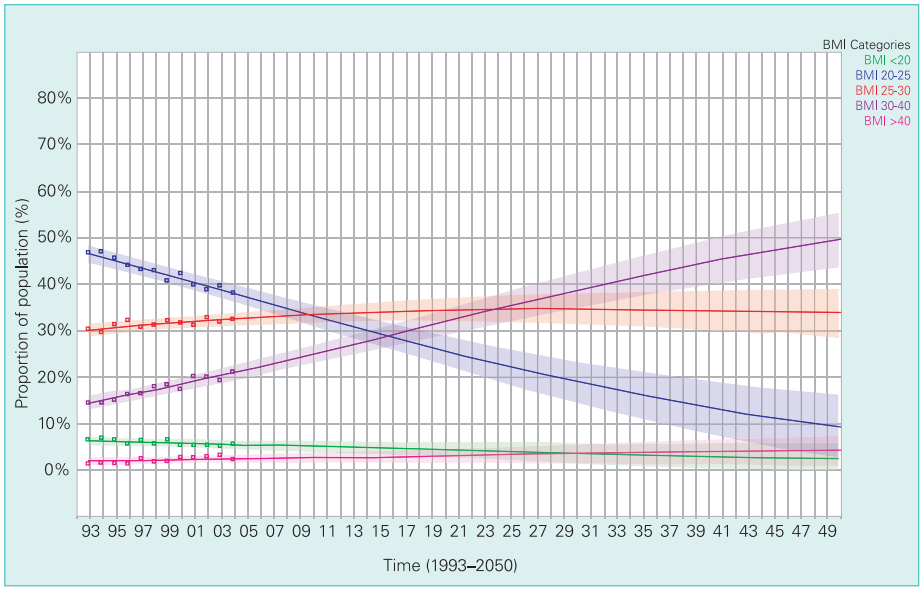


Figure 2b. Proportion of females aged 21-60 belonging to different BMI categories in a given year



Consistent with increasing prevalence of obesity in adulthood, increasing numbers of women are obese prior to and during pregnancy. Over two decades to 2007, first trimester maternal obesity has doubled in the UK to 16%[6]. An additional 26% were overweight, resulting in 42% of women being above a healthy weight in the first trimester of pregnancy.

In addition to becoming more prevalent in the adult population, overweight and obesity are occurring earlier in life. Prevalence of overweight and obesity in schoolchildren in England is measured annually by the National Child Measurement Programme (NCMP). Data for 2010/11 show that more than one in five children in reception year (aged 4-5 years) are either overweight or obese (13.2% overweight plus 9.4% obese)[7]. By year 6 (aged 10-11 years), this has risen to one in three (14.4% overweight plus 19.0% obese). Figure 3 illustrates the BMI distribution of primary school children aged 4-5 years and 10-11 years in England. These figures also show the 1990 reference population, which highlights the shift of the distribution curves to the right as overweight and obesity have increased in prevalence over the past two decades.

1.2 Consequences of obesity: why are we concerned?

Obesity is causally linked to a number of health problems, including some of the leading causes of mortality and morbidity in the UK. These are principally: type 2 diabetes, hypertension, cardiovascular disease (including stroke), some cancers (oesophageal, breast, endometrial, colon and rectal, kidney, pancreatic, thyroid and gallbladder[8]), mental health problems and musculoskeletal disorders. This results in shortening of life expectancy by 2-4 years in obese adults who become obese by middle age. In extremely obese adults (BMI ≥40), life expectancy is reduced by 8-10 years[9]. It is likely that the current pattern of development of obesity earlier in life will result in even greater shortening of life expectancy in future generations. Not reflected in these figures is the high impact of obesity on healthy life expectancy. The comorbidities are long-term chronic conditions, and obesity is associated with increased levels of sick leave[10].

Maternal obesity is associated with increased morbidity and mortality for both the woman and her child[11]. Obese pregnant women are at increased risk of miscarriage, gestational diabetes, pre-eclampsia and thrombo-embolism, and have higher rates of induced labour, caesarean sections and post-partum haemorrhage. In addition, not only are the babies of obese women at increased risk of foetal anomaly, preterm birth, still birth and neonatal death, they are also at greatly increased risk of becoming obese themselves. Childhood obesity is particularly concerning as obesity tracks very strongly throughout the life course, and rapid weight gain in both infancy and early childhood have been consistently associated with being overweight in later childhood, adolescence and adulthood[12]. Comorbidities (including impaired glucose tolerance, hyperinsulinaemia and dyslipidaemia) are now being seen in overweight and obese schoolchildren from an early age[13].

Obesity also has a significant economic impact on society. It has been estimated that obesity cost the NHS over £5 billion in 2006/07[14]. In addition to this, obesity has serious financial consequences to the economy as a whole, including through sick days and lost years of working life due to premature deaths[15]. If the prevalence of obesity continues to rise along the trajectory of recent years, this will have substantial economic implications, and by 2050, a doubling of the direct healthcare costs of overweight and obesity is anticipated, with the wider cost to society and business reaching an estimated £49.9 billion per year (at 2007 prices)[5].

Figure 3. BMI distribution in English primary schoolchildren (figures from the National Obesity Observatory[4].)

Figure 3a. Children aged 4-5 years

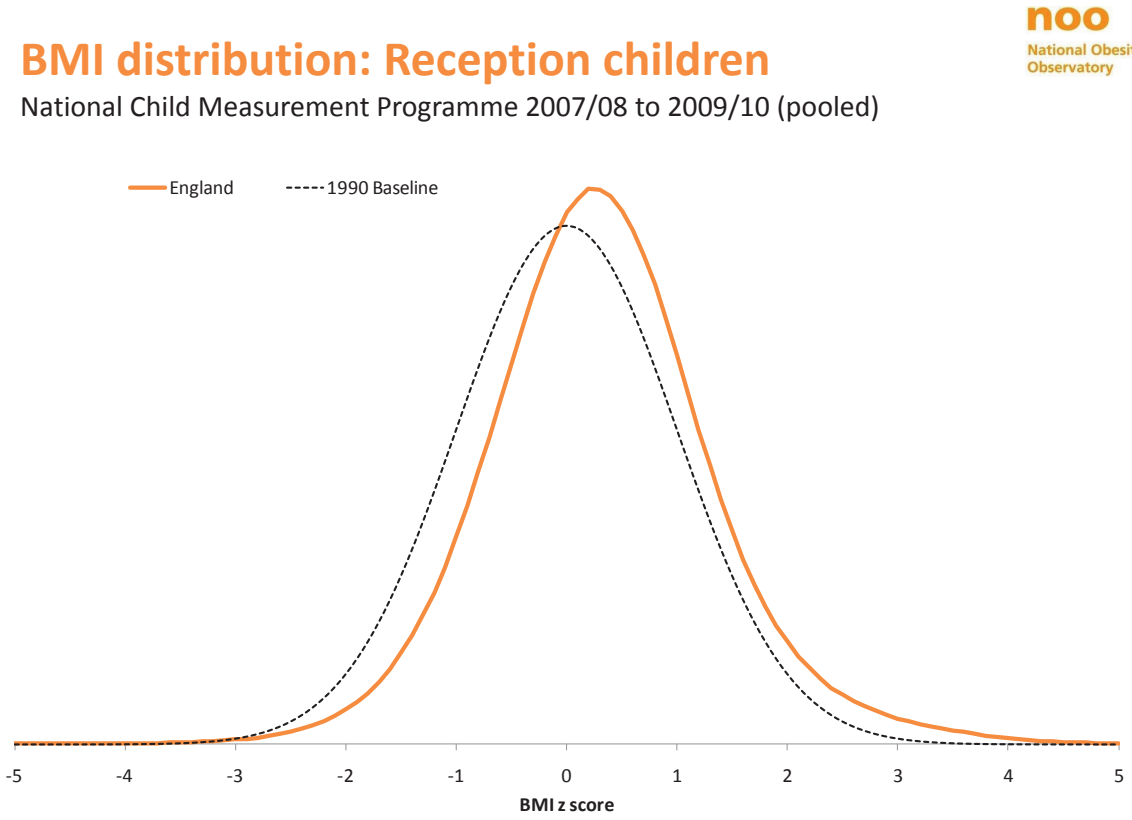
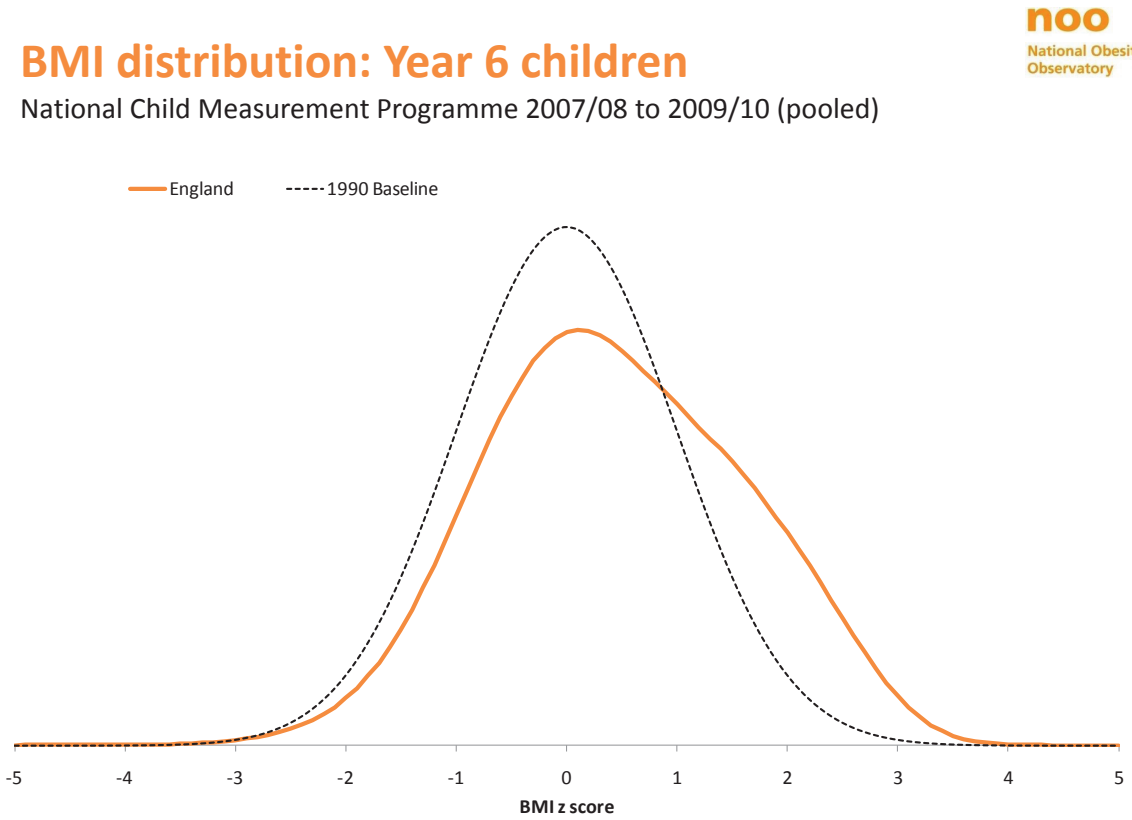


Figure 3b. Children aged 10-11 years



The current government's approach favours interventions that equip people to make the best choices for themselves, and which are minimally intrusive.

1.3 Prevention and treatment of obesity in the UK: what are we doing about it?

1.3.1 National obesity policy

In October 2011, the government announced national ambitions for a sustained downward trend in the level of excess weight in children by 2020, and a downward trend in the level of excess weight averaged across all adults by 2020[16]. The focus of government strategy for tackling obesity in recent years has been to support people in making healthy choices[17]. Whilst maintenance of a healthy weight is seen by government as the ultimate responsibility of the individual, the role of government and wider society is considered as ensuring that people have access to healthy options by transforming the environment, and to the information and guidance they need to adopt healthier lifestyles.

The current government's approach favours interventions that equip people to make the best choices for themselves, and which are minimally intrusive. At the individual level, information is provided through campaigns, including the *Change 4 Life* social marketing campaign[18]. Whilst provision of information carries the risk of increasing health inequalities, *Change 4 Life* has taken a targeted approach with more intense intervention for people in the lowest socio-economic groups. At the population level, the government aims to shape the environment to make it easier for people to adopt and maintain healthy lifestyles. They have engaged with the food industry to encourage voluntary nutrition labelling on front-of-packs, in restaurants and on alcoholic drinks; reformulation of products to reduce energy density; reduction of portion size; and promotion of healthier foods in balance with that of less healthy foods. These are recent strategies for tackling obesity and their effectiveness remains to be demonstrated.

1.3.2 National guidelines for obesity management

Current NICE guidance on weight management in adults dates from 2006[19]. with new guidance on lifestyle weight management services for adults expected in 2013. Recommendations of the 2006 guidance are summarised below. SIGN, the Scottish equivalent of NICE has produced more recent guidelines, although these are largely in line with those of NICE[20].

Summary of NICE recommendations for weight management in adults

- Health professionals should receive training in raising the issue of weight with patients, assessing receptiveness, delivering tailored weight management interventions (including addressing concerns about the benefits of these), and using motivational and counselling techniques.
- Health professionals should discuss a range of available weight management options with people who want to lose weight or who are at risk of gaining weight to help them decide what best suits them and what they will be able to sustain in the long-term.
- Weight management programmes should be multi-component and include behaviour change strategies for diet and activity level. Components should be tailored to preferences, health status and lifestyle.
- Referral to self-help, commercial and community programmes that follow best practice should be considered, however health professionals should continue to monitor patients and provide support and care.

- Diets with a 600 kcal/d deficit are recommended in combination with support and follow-up for maintenance of weight loss. Very low calorie diets of <1000 kcal/d may be used intermittently for short-term periods by people who are obese whose weight loss has reached a plateau. Diets of <600 kcal/d should only be used under clinical supervision.
- Pharmacological intervention should only be considered if BMI ≥30 (or BMI ≥28 with comorbidities) after lifestyle approaches, in patients who have not achieved target weight loss or who have reached a plateau.
- Bariatric surgery can be considered if BMI ≥40 (or BMI ≥35 with significant comorbidities) and if all appropriate non-surgical measures have been tried but failed to achieve/maintain adequate weight loss for 6 months. Patients must have been receiving intensive management in a specialist obesity service and must understand and commit to the need for long-term follow-up, and be fully aware of the risks of surgery. Bariatric surgery should only be a first-line option if BMI ≥50.

Summary of NICE recommendations for weight management in children

- Tailored clinical intervention should be considered where BMI ≥91st centile, depending on the needs of the individual child and the family. Assessment of comorbidity should be considered for children BMI ≥98th centile.
- Interventions for childhood overweight or obesity should address lifestyle within family and social settings, and should actively involve parents and/ or carers.
- Behavioural interventions should include stimulus control, self-monitoring, goal setting and rewards, and problem solving. Parental role modelling should also be encouraged.
- Children who are overweight or obese with comorbidities or complex needs (*e.g.* learning difficulties) should be referred for secondary care assessment, which should include assessment of comorbidities in the context of the degree of overweight/ obesity, possible genetic causes, and family history of metabolic disease.
- Pharmacological treatment is not generally recommended in children <12y, and only in older children in a specialist paediatric setting when severe physical or psychological comorbidities are present.
- Surgical intervention is not generally recommended in children or young people unless they have achieved or nearly achieved physiological maturity. Where surgery is considered, it must be preceded by a full medical evaluation including genetic screening/ assessment to exclude rare treatable causes of obesity.

Summary of NICE recommendations for weight management in pregnant women

NICE has also published specific guidelines for weight management in pregnant women[21].

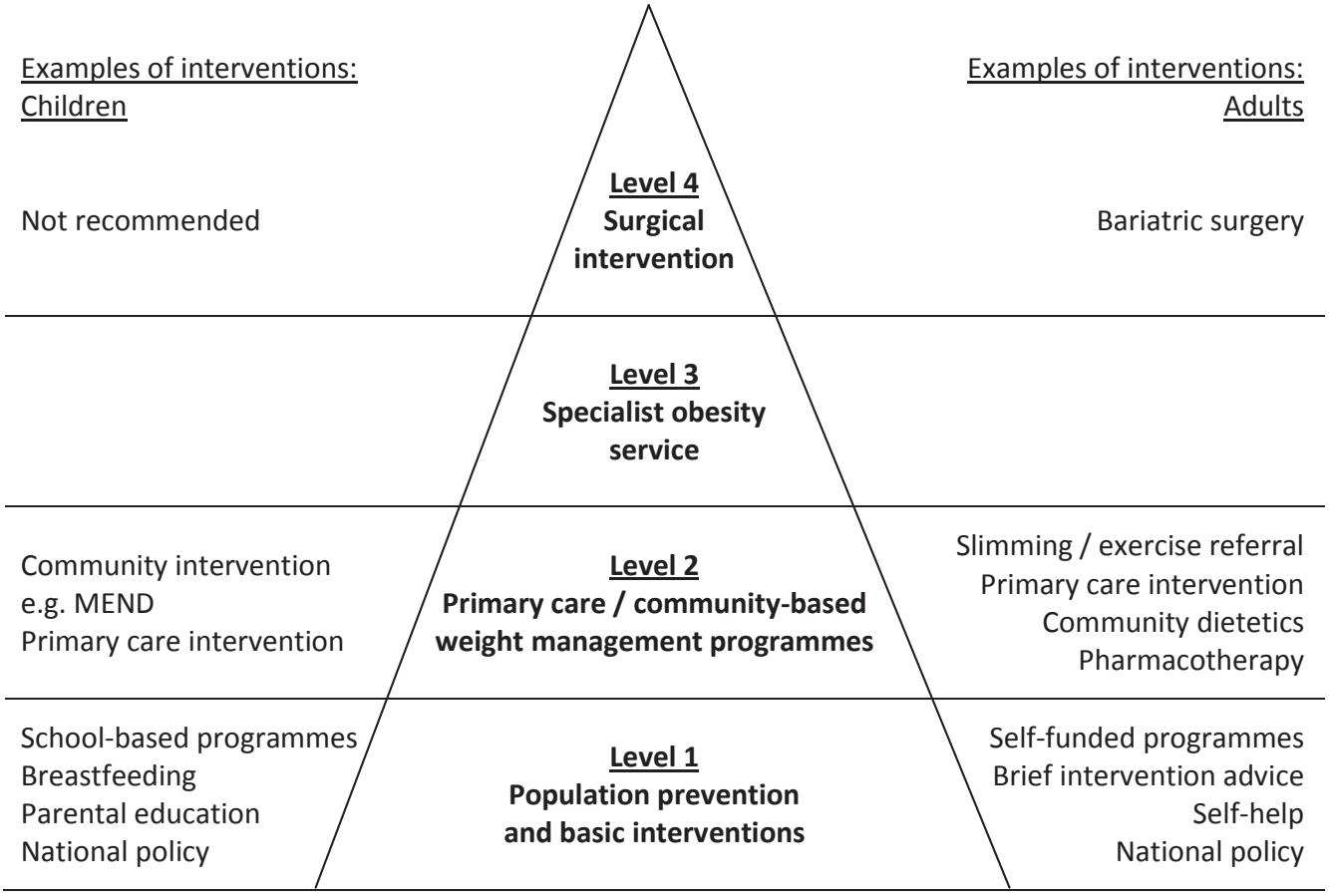
- Health professionals should use any appropriate opportunity to provide obese women with information about benefits of losing weight pre-pregnancy and should advise and support obese women to lose weight before conceiving.
- Weight and height should be measured and recorded at first contact during pregnancy.

- Health professionals should advise pregnant women that eating healthily and being physically active will benefit both the woman and her unborn child. Dieting should not occur during pregnancy, but women should be encouraged and supported to lose weight after pregnancy.
- Weight should be discussed at the 6-8 week postnatal check. Clear tailored advice should be provided and women wanting support should be given details of community-based services. Women should be encouraged to breastfeed and advised that a healthy diet and regular moderate intensity physical activity will not affect the quantity or quality of breast milk.

1.3.3 Obesity service provision in the NHS

Commissioning of services for obesity management takes place at the local level, with local areas deciding upon provision for their population. Specific service provision for obesity and treatment models followed vary between areas of the UK, although these should be in line with the guidelines outlined above. Local obesity care pathways are typically based on a four-tier system, as illustrated in Figure 4 and described beneath.

Figure 4. The obesity care pathway



Level 1: Population prevention / basic intervention

Level 1 includes prevention strategies aimed at the entire population, such as the national *Change 4 Life* social marketing campaign.

This level also includes assessment of weight and brief advice from health professionals in primary care. In people who are overweight but not obese (BMI 25-29[9]), who do not have comorbidities, the healthcare professional should raise the issue of weight and give brief advice on healthy eating, physical activity and behaviour. They can also signpost these patients to self-help community-based interventions, which will be self-funded at this level. In people who have a BMI ≥30 or ≥28 with associated comorbidities, healthcare professionals should assess readiness to change. If the patient is not ready to change, they should be given advice on lifestyle and the benefits of weight loss. This assessment and advice in primary care is described in the NHS care pathway for the management of overweight and obesity, which gives guidance to primary care clinicians for identification and treatment for these conditions in children, young people and adults, illustrated in Figure 5[22].

Level 2: Primary care or community-based weight management programmes

In patients with a BMI ≥30 (or ≥28 with comorbidities) who are ready to make changes, healthcare professionals should discuss options for intervention in order to identify one which suits the patient and which the patient can sustain. Interventions at level 2 include referral to a community-based slimming or exercise club or primary care-based weight management services, which may be individual or group-based. For patients who are considered to be unsuitable for these interventions, or who need more specialist support, referral to community dietetics is an option.

All patients referred to community-based options should still be monitored in primary care. Patients who achieve weight loss should be offered maintenance and support options. For patients who do not achieve or maintain weight loss after 6 months, alternative options at this level can be tried, or pharmacotherapy considered.

Level 3: Specialist obesity service

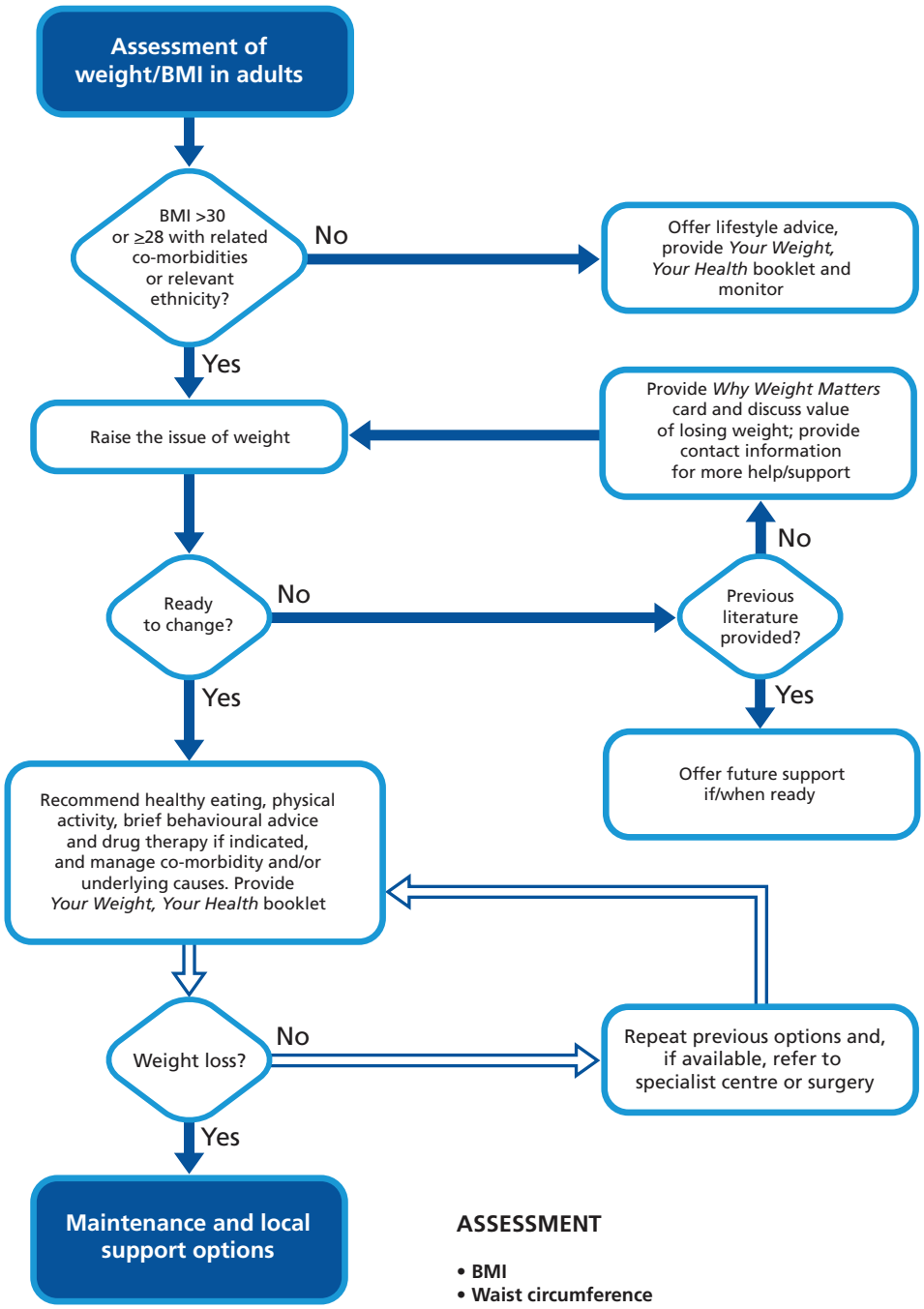
Patients who are not successful in achieving or maintaining weight loss at level 3, and who have BMI ≥40 (or ≥35 with significant comorbidities) should be referred to a specialist obesity service. These services are generally consultant-led clinics, with input from specialist dieticians and clinical psychologists. They are able to assess patients and provide more intense and tailored interventions than at level 2, including low calorie diets, pharmacotherapy and assessment and advice for surgery.

Level 4: Surgical intervention

Bariatric surgery can be considered if BMI ≥40 (or BMI ≥35 with significant comorbidities). All appropriate non-surgical measures must have been tried but failed to achieve or maintain adequate loss for six months, and patients must have been receiving intensive management in a specialist obesity service including assessment of suitability for surgery, and must commit to the need for long-term follow-up.

Figure 5. NHS care pathways for management of overweight and obesity in primary care (figures from NHS leaflet[22].)

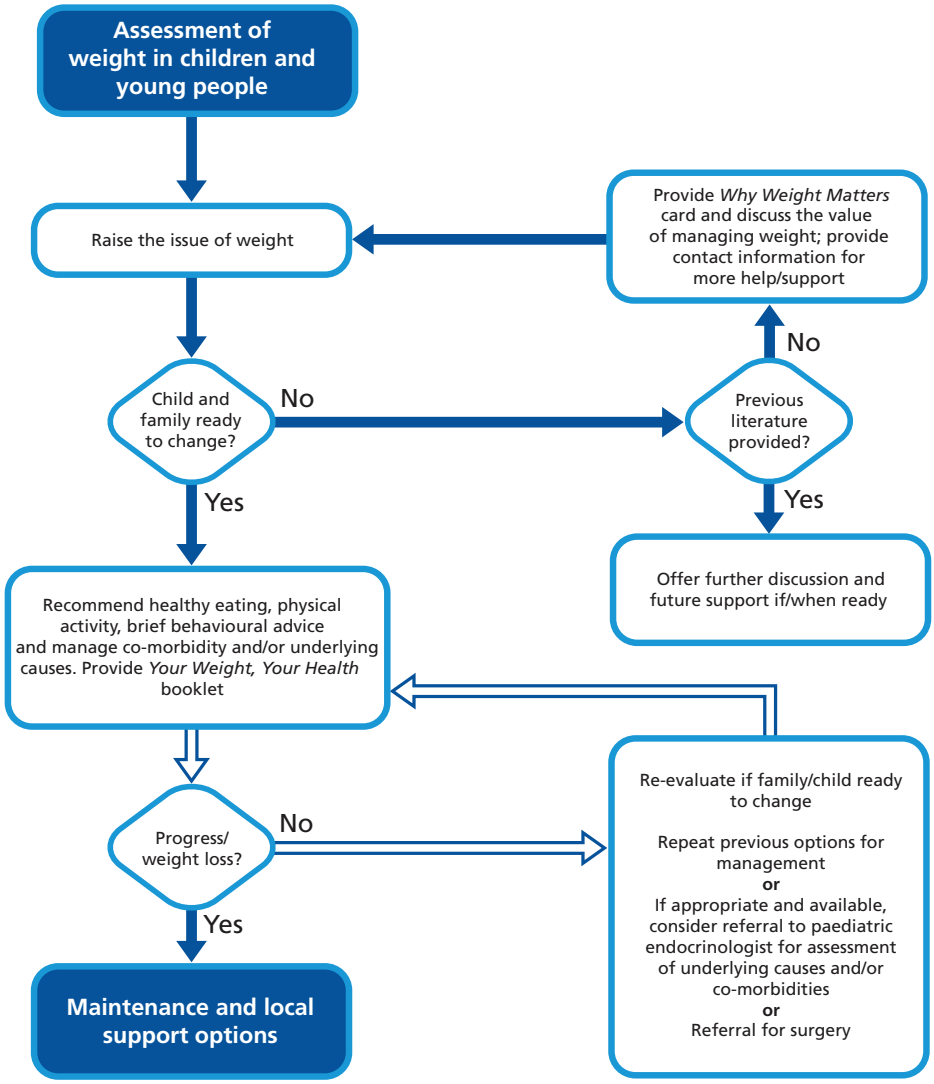
Figure 5a. The NHS adult care pathway for primary care.



ASSESSMENT

- **BMI**
- **Waist circumference**
- **Eating and physical activity**
- **Emotional/psychological issues**
- **Social history** (including alcohol and smoking)
- **Family history**
  eg diabetes, coronary heart disease (CHD)
- **Underlying cause**
  eg hypothyroidism, Cushing's syndrome
- **Associated co-morbidity**
  eg diabetes, CHD, sleep apnoea, osteoarthritis, gallstones, benign intracranial hypertension, polycystic ovary syndrome, non-alcoholic steato-hepatitis

Figure 5b. The NHS children and young people care pathway for primary care.



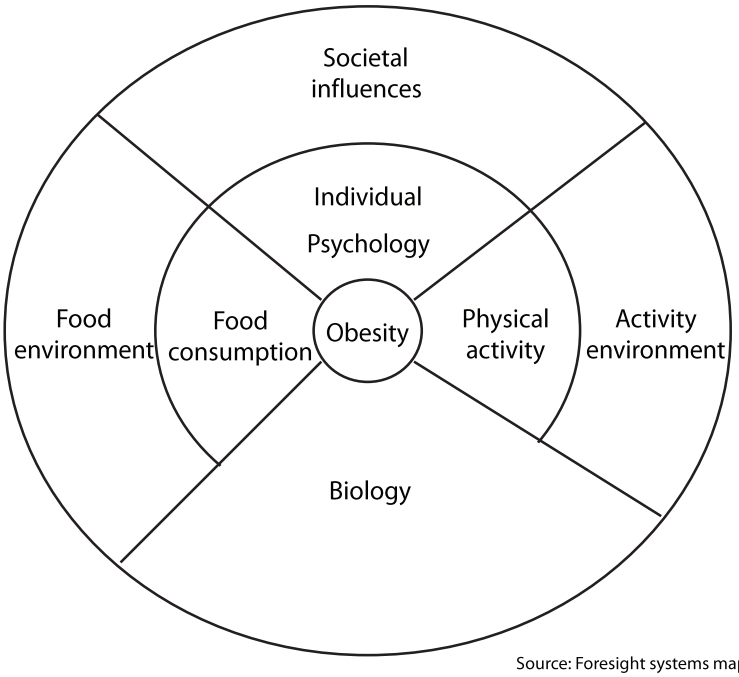
ASSESSMENT

- **Eating habits, physical patterns, TV viewing, dieting history**
- **BMI** – plot on centile chart
- **Emotional/psychological issues**
- **Social and school history**
- **Level of family support**
- **Stature of close family relatives**
  (for genetic and environmental information)
- **Associated co-morbidity**
  eg metabolic syndrome, respiratory problems, hip (slipped capital femoral epiphysis) and knee (Blount's) problems, endocrine problems, diabetes, coronary heart disease (CHD), sleep apnoea, high blood pressure
- **Underlying cause**
  eg hypothyroidism, Cushing's syndrome, growth hormone deficiency, Prader-Willi syndrome, acanthosis nigricans
- **Family history**
- **Non-medical symptoms**
  eg exercise intolerance, discomfort from clothes, sweating
- **Mental health**

1.4 Determinants of obesity: What is the cause?

Obesity is a complex, multifactorial condition. It is ultimately caused by an energy imbalance, where energy intake exceeds expenditure. However, this imbalance is underpinned by multiple complex biological, societal and behavioural determinants, with interactions occurring between these and no single influence dominating[5]. A comprehensive systems map of the direct and indirect determinants of energy balance has been produced by the *Foresight* programme, illustrated in Figure 6. This includes seven predominant themes and illustrates the relationship between individual factors and societal and environmental factors[23].

Figure 6. The determinants of obesity (figure from the National Obesity Observatory[23].)



Source: Foresight systems map, 2007

- Biology: the influence of genetics and ill health
- Societal influence: the impact of society, including the media, education, culture and norms
- Individual psychology: including individual consumption and activity patterns and preferences
- Activity environment: the influence of the environment on an individual's activity behaviour
- Physical activity: the type, frequency and intensity of activities an individual carries out
- Food environment: the influence of the food environment on food choice, including availability
- Food consumption: the type, amount and frequency of foods consumed

The relative contribution of these factors is undetermined and debated. The rate of increase in the prevalence of obesity in the UK over recent years indicates an environmental cause at the population level. Our environment and lifestyle have changed rapidly over the same period of time, resulting in an 'obesogenic' environment. This is one which favours the development

of obesity by providing high energy foods in plentiful supply and removing the need for significant physical activity as a requirement of normal daily life. Humans are adapted for an environment in which food is limited and physical activity necessary, and in which the ability to store energy as fat is an advantage for survival[24].

As our genetic make-up will not have altered over the same short time period, humans are susceptible to weight gain in the modern environment. However, not everyone is obese, and a substantial proportion of the population manages to maintain a healthy weight despite exposure to this environment. This suggests that some people are more predisposed to gain weight than others under the same environmental conditions. Studies of twins have shown heritability of BMI in adults to be in the range of 40% to 70%, indicating that genetic differences between individuals are responsible for a large proportion of the variation in body fatness between individuals within populations[25,26]. Human monogenic obesity syndromes have been identified which tend to result in morbid obesity presenting in childhood, however these are only present in a small proportion of the population[27]. More commonly, the genetic determinants of obesity are likely to be multiple and interacting, and the cumulative effect of genetic loci identified to date only account for a very small proportion of this total genetic variation in BMI.

The leading determinants of obesity in an individual are therefore not necessarily the same as those that are driving the increase in prevalence in the population. Whilst the rapid rise in the population has environmental causes, whether an individual becomes obese in this obesogenic environment is likely to be determined largely by their genes. Genetic variability in weight within a population becomes more observable as the prevalence of obesity in that population increases.[25] This suggests that the expression of genes predisposing to obesity is highly dependent on the environment, and that gene-environment interactions may account for a large part of the genetic variance in obesity.

Figure 6 could therefore be adapted to illustrate the influencing and modifying effect of genes on individual responses to the food and activity environments in terms of food consumption and physical activity respectively, and on how societal influences impact on individual psychology.

1.5 Summary

Obesity is an increasingly important global problem with high societal costs. It is a complex multifactorial condition, with both environmental and genetic determinants, and interactions between these. UK guidelines and policy for the prevention and management of obesity focus on environmental causes with little mention of the role of genetics, other than in particularly severe or complicated cases. This is perhaps not surprising as it reflects the relative knowledge about these determinants. However, technological advances are now facilitating improved understanding of the genetic basis for obesity. This report will synthesise what is known in this area and explore the potential contribution of public health genomics to the prevention and management of obesity.

2 Obesity susceptibility genes

A number of single genes have been identified as highly penetrant causes of severe early-onset obesity, and more are likely to be uncovered. Less is known about polygenic contributors to common obesity.

Genome-wide association studies have robustly identified more than 30 genes which contribute to common human obesity in the general population.

A literature search was performed on 23 February 2012 to identify reviews and meta-analyses describing the genetic basis of obesity. The search was performed using PubMed (MEDLINE)[28] and the online database of genome-wide association studies[29]. Further information on genes was obtained from Orphanet[30] and the OMIM (Online Mendelian Inheritance in Man) database[3,1] The full search strategy is included as an appendix to this report.

Studies investigating the association of genetic variants with overall adiposity, as measured by body mass index (BMI) were included, but those exploring genetic determinants of the distribution of body fat (waist circumference, waist-to-hip ratio) were excluded. For monogenic obesity, genetic defects which cause obesity as a primary phenotype were included, and those causing more generalised syndromes in which obesity is one of a range of symptoms, and not the predominant or most clinically significant, were not covered in great detail.

2.1 Identification of susceptibility genes

BMI is a highly heritable trait, with heritability estimates of 40% to 70%, however much remains unknown about the identity and biological mechanisms of the contributing genes[32]. Whilst common obesity in the general population has a complex multifactorial aetiology, rare mutations in a single gene can alone be sufficient to cause very severe and early-onset obesity. Over the past two decades, candidate gene and family-based linkage approaches have been highly successful in identifying a number of causal genes in these monogenic forms of obesity, and these discoveries have contributed greatly to the understanding of the aetiology of the condition.

However, far less is understood about the polygenic contributors to common obesity and the approaches taken in the discovery of the monogenic causes have not identified genes contributing to common obesity[33]. Common obesity occurs as a result of numerous contributing and interacting genetic and non-genetic factors. Whilst candidate gene and linkage studies are well suited to identification of genes which have a large effect on risk, as is the case in the highly penetrant monogenic forms of obesity, they do not lend themselves to conditions such as common obesity where multiple variants each exert small effects[34].

The common disease-common variant hypothesis proposes that in common diseases with a genetic component, such as obesity, some predisposing variants are relatively common and a combination of these, in association with environmental factors, is required for the disease to occur[35, 36]. Under this hypothesis, disease-associated alleles may be identified by using

commonly found gene variants such as single nucleotide polymorphisms (SNPs) and comparing cases with controls, which is the paradigm employed in genome-wide association studies (GWAS). GWAS are a hypothesis-free method of investigating the association between common genetic variation and a condition or disease, in which the entire genome of a large number of individuals (both cases and controls) are screened at high resolution, providing genomic locations of associated variants.

GWAS are therefore better suited to detecting common disease-associated alleles with modest effects than the aforementioned approaches[37], and over the past five years through very large and increasing sample sizes, GWAS have robustly identified more than 30 genes which contribute to common human obesity in the general population[38]. However, whilst GWAS identify common SNPs associated with a condition or disease, these are not necessarily the causative variants, but are in linkage disequilibrium with these. For identified SNPs, there is a lack of evidence for associations with expression of the closest genes, and further investigation is therefore required to elucidate the causal variant at each locus, and then to determine its function if this is unknown[34,39].

2.2 Monogenic obesity

A number of syndromic conditions exist in which obesity is one of a collection of characteristics, such as Prader-Willi syndrome. These 'pleiotropic' obesity syndromes are complex clinical syndromes in which obesity is one of a range of symptoms, often including developmental delay and intellectual deficit[27]. In these syndromes, described briefly in Table A1 in the appendix, obesity is not the primary or most clinically significant feature. These syndromes will not be discussed further in this report, other than to observe that they often involve hypothalamic dysfunction and hyperphagia is a common feature, with obesity resulting from the consequent increase in energy intake[32]. Whilst it has long been known through these genetic syndromes that a single gene defect is sufficient to cause obesity in the context of accompanying central symptoms, the first human single gene defect to cause obesity in the absence of developmental delay was identified in the mid-1990s with the discovery of congenital human leptin deficiency in a severely obese child caused by a mutation in the gene encoding leptin (*LEP*)[40]. Since that first discovery, a number of additional monogenic causes of obesity have been identified.

Over the past two decades, examination of patients with severe early-onset obesity has identified a number of highly penetrant monogenic disorders in which obesity is the primary feature. These are listed in Table 1 and described in further detail below[40, 41]. Common with the syndromic forms, the identified non-syndromic monogenic forms of obesity also disrupt hypothalamic functions, with most being involved in the control of appetite through action at points along the leptin-melanocortin pathway. These include variants in genes encoding the leptin receptor (*LEPR*), pro-opiomelanocortin (POMC), prohormone convertase 1 (*PC1/3*), the melanocortin 4 receptor (*MC4R*), brain-derived neurotrophic factor (*BDNF*) and neurotrophic tyrosine kinase receptor type 2 (*NTKR2*)[34, 42].

Mutations in *BDNF* and *NTKR2* have also been found to be associated with cognitive impairment and/or behavioural problems, and may therefore be considered syndromic in this respect[42]. The leptin-melanocortin pathway and the relationship between these genes and their products is illustrated and described in Figure A1 in the appendix[34]. A monogenic cause of obesity separate from this pathway has also been identified: *SIM1*, a gene involved in hypothalamic development, has been associated with severe early-onset

obesity, often with accompanying cognitive impairment[42]. In addition, a large deletion at locus 16p11.2 has recently been identified as a highly penetrant form of obesity, with or without cognitive impairment. Whilst the causal gene has not yet been confirmed, the association with cognitive impairment suggests a central role, and one candidate gene is *SH2B1*, which is involved in leptin signalling[43].

It is notable that all of these monogenic disorders affect the central hypothalamic sensing and control of energy balance[40]. The central nervous system plays a primary role in regulating food intake, with the hypothalamus acting as the central regulator. The hypothalamus receives both long and short-term feedback on energy intake, expenditure and storage from the periphery through hormone signals, which it integrates, and then acts through various pathways to maintain energy balance[34]. Patients with these monogenic disorders demonstrate significant increases in appetite and reductions in satiety, resulting in much higher energy intake than control subjects of equal body size. In contrast energy expenditure studies reveal that this is not, or not markedly, reduced in these disorders.

Whilst these monogenic causes of obesity are individually rare in the population, they represent very severe forms of obesity that can result in significant physiological and psychological morbidity in affected individuals. Furthermore, their combined consequence in the population is not insignificant, with up to 10% of cases of severe obesity in childhood possibly having a monogenic cause[42]. The prevalence of morbid obesity (BMI ≥40) in adults in England is around 2%[44]. Statistics for children are not readily available for very severe obesity, but applying the adult prevalence to the entire UK population (62,218,76145) and assuming 10% of this has a monogenic cause, gives a figure of 124,438. It is likely that there are more genes still to be discovered, in addition to further variants in each gene.

Table 1. Single genes in which defects have been found to lead to human obesity

Gene(OMIM No)	Encoded product	Function	Location	Population prevalence	Inheritance
LEP (+164160)	Leptin	Adipocyte-derived hormone	7q31.3	<1/1,000,000	Autosomal recessive
LEPR (+601007)	Leptin receptor	Receptor for adipocyte-derived hormone	1p31	3% among severely obese children	Autosomal recessive
MC4R (*155541)	Melanocortin 4 receptor	Receptor for POMC products αMSH and βMSH	18q22	Up to 1/1,000; up to 6% of severely obese children	Autosomal recessive / Autosomal dominant
POMC (*176830)	Pro-opiomelanocortin	Hypothalamic neuropeptide	2p23.3	<1/1,000,000	Autosomal recessive
PC1/3 (*162150)	Prohormone convertase 1/3	Processes pro-peptides (including POMC) to active moieties	5q15-21	<1/1,000,000	Autosomal recessive
BDNF (*113505)	Brain-derived neurotropic factor	CNS development	11p14.1	Unknown	Unknown
NTRK2 (*600456)	Neurotrophic tyrosine kinase receptor type 2	Receptor for BDNF	9q21.33	Unknown	Unknown
SIM1 (*603128)	SIM1 (homologue of Drosophila single minded 1)	Transcription factor necessary for hypothalamic development	6q16.3-21	<1/1,000,000	Unknown

2.2.1 Genes involved in monogenic forms of obesity

LEP

Leptin is a hormone primarily secreted by adipose tissue, and circulating levels are positively correlated with body fat and adipocyte size. Leptin has multiple actions, but importantly it is a key regulator of energy balance through its actions in the hypothalamus. Leptin is a 'starvation hormone' and a lack of leptin signals a state of starvation by stimulating or inhibiting the release of several neurotransmitters. As concentrations increase from very low levels, orexigenic (appetite increasing) neuropeptides are down-regulated, including neuropeptide Y, melanin-concentrating hormone, orexins and agouti-related peptide; anorexigenic (appetite suppressing) neuropeptides are up-regulated, including α-melanocyte-stimulating hormone, which acts on the melanocortin-4 receptor, and corticotrophin-releasing hormone[46].

Mutations in the gene encoding leptin were identified as causing extreme obesity in the ob/ob mouse model in 1994, however it was not until 1997 that two severely obese children from the same family were found to have

very low circulating leptin levels, despite very high body fat mass[47]. Both of these children, who were from a highly consanguineous pedigree, were found to be homozygous for a mutation in the leptin gene, resulting in congenital leptin deficiency. Congenital leptin deficiency is a form of monogenic obesity characterised by severe early onset obesity and marked hyperphagia. It is extremely rare, having been described in less than 30 patients worldwide[48]. Characteristics of congenital leptin deficiency include severe hyperphagia from early infancy, and although birth weight is normal, patients rapidly become obese in early childhood. Additional characteristics include hypogonadism and impaired T-cell mediated immunity. All characteristics are reversed by treatment with recombinant human leptin, with weight loss occurring within a fortnight of commencement of daily therapy[49].

In a sample of five children identified with congenital leptin deficiency, the mean BMI standard deviation score was 6.8±2.1, with a body fat percentage of 52.8±3.2% (normal range 15-25%). These children consumed almost five times as much energy (relative to their lean body mass) as control children[41].

LEPR

A similar phenotype to congenital leptin deficiency is observed in individuals homozygous for mutations of the leptin receptor gene, with hyperphagia from early childhood and early-onset of severe obesity. In these patients, circulating leptin levels were not disproportionately elevated for body fat level, meaning that serum leptin level cannot be used as a marker. Among a cohort of 300 patients with severe early-onset obesity (BMI standard deviation score (SDS) of more than 3 before the age of 10 years), prevalence was found to be 3%[41].

Mean BMI standard deviation score in a sample of patients with *LEPR* mutations was 5.1±1.6, which was significantly lower than those with congenital leptin deficiency (P=0.005), although their percentage body fat was similar, at 58.0±3.5%.[41] Their lean mass was in the normal range for their ages. These patients consumed almost three times the amount of energy consumed by control subjects at a 'free-feeding' *ad libitum* meal, although this was less than the amount consumed by those with congenital leptin deficiency.

Whilst childhood linear growth is normal in patients with *LEPR* mutations, adult height is reduced due to lack of the pubertal growth spurt, and hypogonadism was apparent in all adults studied. Childhood infections were more frequent, particularly of the upper respiratory tract.

POMC

Leptin mediates its anorexigenic effects in part through induction of expression of pro-opiomelanocortin (POMC)-derived melanocortin peptides in the hypothalamus; these activate the melanocortin-4 receptor (MC4R), suppressing food intake.[53] Functional loss of both alleles of the human POMC gene, resulting in POMC deficiency, is a form of monogenic obesity, which result in extreme hyperphagia from the first weeks of life, severe early-onset obesity, adrenal insufficiency, red hair and pale skin[54]. Complete POMC deficiency is transmitted as an autosomal recessive trait and is caused by homozygous or compound heterozygous loss of function mutations in the POMC gene. In addition, a heterozygous missense mutation has been found which is present in 0.9% of children with severe early-onset obesity compared with 0.2% of normal weight subjects.

PC1/3

Prohormone convertase 1/3 is an enzyme involved in the processing of POMC, and numerous other prohormones, including proinsulin and gastrointestinal hormones[55]. Mutations in the prohormone convertase 1/3 (*PC1/3*) gene resulting in PC1/3 deficiency represent the rarest form of human monogenic obesity, with only several cases having been identified[56]. Of three cases described, two of these were compound heterozygotes, and the third homozygous for a loss of function mutation. PC1/3 deficiency is characterised by severe hyperphagia and obesity, with normal birth weight. Severe neonatal-onset diarrhoea (due to improper development of the gastrointestinal tract) has been a characteristic of all three patients. Energy expenditure has been measured in one patient to be in the normal range.

Although PC1/3 has numerous substrates which are known to be involved in energy balance, it is thought to be disrupted POMC processing in the hypothalamus which plays a key role in the development of obesity in PC1/3 deficiency, due to the reduced melanocortin signalling in the hypothalamus[56].

MC4R

MC4R mutations represent the most frequent known monogenic cause of severe obesity, being found in up to 6% of children with this condition[27], and 0.5-1% of obese adults[50]. In the European population, the prevalence of deleterious *MC4R* mutations has been estimated to be 0.5-1 per 1,000[32].

MC4R mutations are characterised by either dominant or co-dominant inheritance, with penetrance ranging from around 30-80%, and varying by age and specific mutation[51, 52]. Homozygous mutations are less frequent and more severe than heterozygous, due to lower residual protein activity. *MC4R* mutations present with hyperphagia and severe hyperinsulinaemia and accelerated linear growth in children.

BDNF

The *BDNF* gene encodes brain-derived neurotrophic factor, a neurotrophin with a fundamental role in development of the central nervous system. It has an important role in the regulation of food intake, with key regulators of appetite including leptin exerting anorexigenic effects through BDNF[57]. *BDNF* mutation has been observed in one obese child with hyperphagia. In animal models, homozygous mutations are lethal as BDNF is required for brain development. BDNF haplo-insufficiency is also associated with the childhood-onset obesity occurring in a subset of patients with WAGR (Wilms' tumour, aniridia, genitourinary anomalies and mental retardation) syndrome, named WAGRO (the 'O' for obesity), and by 10 years of age, 100% of patients with heterozygous *BDNF* deletions studied were obese, compared with 20% of those without these deletions[58].

NTRK2

NTRK2 encodes neurotrophic tyrosine kinase receptor type 2, the receptor for brain-derived neurotrophic factor and neurotrophin 3. Mutation, observed in one obese child, has been associated with severe childhood obesity and with developmental delay, very similar to that seen with *BDNF* mutations[40].

SIM1

SIM1 encodes a transcription factor essential for the development of the supra-optic and paraventricular nuclei of the hypothalamus. Disruption due to chromosomal translocation, observed in one patient to date, has been

associated with severe early-onset obesity, developmental delay and increased linear growth[32]. Rare non-synonymous *SIM1* mutations are enriched in severely obese patients in comparison with lean individuals, and SIM1 haplo-insufficiency has been associated with Mendelian obesity and with a Prader-Willi-like syndrome[42].

16p11.2

Heterozygous deletions of at least 593kb at locus 16p11.2 have been observed as a highly penetrant form of obesity, which is associated with both cognitive impairment and obesity, although the presence in obese subjects without cognitive symptoms suggests a possible direct association of these deletions with obesity distinct from the cognitive phenotype. Evidence suggests an age-dependent penetrance with all teenagers and adults carrying a deletion being obese, but variable penetrance in children. Whilst the causal gene has yet to be confirmed, a likely candidate is *SH2B1*, which is involved in leptin signalling[43].

Although there is a strong correlation between developmental and cognitive impairment and obesity, these deletions have been detected in 0.4% of a cohort of morbidly obese patients. Patients with both phenotypes showed a higher frequency of 2.9%, and those with cognitive impairment in the absence of obesity had a frequency of 0.6%[59]. In a case-control association analysis using sib pairs with lean/normal weight controls, 16p11.2 deletions have been associated with obesity (Odds Ratio (OR) 29.8, P=5.7x10-7) and morbid obesity (OR 43.0, P=6.4x10-8)[59].

Although heterozygous, these deletions are highly likely to be causal and represent the second most frequent genetic cause of obesity after point mutations in *MC4R*. The deletions frequently occur *de novo*, but it is estimated that around 0.4% of all morbidly obese cases are due to an inherited 16p11.2 deletion. The frequent *de novo* occurrence is likely to mean that there is a lack of linkage disequilibrium with any marker variants, meaning that if these are involved in common obesity, they are not likely to be readily detected by GWAS.

2.3 Common obesity

Whilst candidate gene and family-based linkage approaches have proved highly successful in identifying causal genes in the monogenic forms of obesity, these methods have not consistently identified genes contributing to common obesity[33] and only a few of those variants which cause rare monogenic obesity have been found to be sufficiently frequent in the population to explain any measureable proportion of the common obesity cases[34]. Despite a lack of unequivocal results, mounting evidence does suggest that some of the candidate genes identified have some small effect on obesity at the population level. Meta-analyses of candidate gene studies, which have included sample sizes of more than 5,000 have detected associations with variants causing biological changes in the genes encoding melanocortin 4 receptor (*MC4R*), β-adrenergic receptor 3 (*ADRB3*), prohormone convertase 1/3 (*PC1/3*), brain-derived neurotrophic factor (*BDNF*), melanotonin receptor type 1B (*MTNR1B*) genes and for a functional variant near the lactase (*LCT*) gene[34, 38].

As discussed above, genome-wide association studies (GWAS) are a suitable approach for examining the genomic basis of common conditions such as obesity. GWAS have been used to investigate several measures of the level and distribution of adiposity, however the most commonly studied outcome is BMI, which is available in many large cohorts. Associations have also been examined with waist circumference and the waist-to-hip ratio, which are indicative of

central obesity. This report focuses on loci identified as being associated with body weight-for-height, measured as BMI. Several waves of GWAS have been performed, with increasing sample sizes resulting in increasing discoveries with each[38]. To date, these have resulted in the identification of 32 loci robustly associated with common obesity. These studies and the identified loci are summarised in Table 2 and Figure 6. It is important to note that the cohorts studied have largely been populations of European descent, and associations of these loci with BMI in other populations remain to be demonstrated. This must be borne in mind when considering any application of the research.

FTO was the first gene to be robustly associated with common obesity.

In 2007, the first wave of studies identified the *FTO* gene (fat mass and obesity associated gene)[60, 61]. *FTO* was the first gene to be robustly associated with common obesity, in parallel findings from two separate publications. One of these publications identified *FTO* whilst examining associations of common variants with type 2 diabetes, but found that the association disappeared following adjustment for BMI, indicating that the increased risk of diabetes conferred by the *FTO* gene was entirely mediated by its effect on BMI[60].

The second wave of studies in 2008 identified a second loci associated with common obesity as near-*MC4R* (the melanocortin-4 receptor gene). The *MC4R* gene was the most likely biological candidate for this association, due to its known role in the regulation of food intake and frequent implication in monogenic forms of obesity[62]. *MC4R* was identified by using a much larger sample size through meta-analysis, providing increased power to detect the association[62]. This larger sample size was needed as the variant has both a lower frequency and smaller effect size than *FTO*. A second study identified an association of *MC4R* with waist circumference at the same time as this, in a cohort of Indian Asians, which despite being a smaller cohort, had increased power due to higher frequency of the BMI-increasing allele in this population (36%) compared with white Europeans (27%)[62, 63].

The third wave of studies increased sample size still further in 2009, and two large studies increased the number of genetic loci associated with BMI to 12[64, 65]. There was some, but not complete overlap between the discoveries of these two publications, as illustrated in Figure 6.

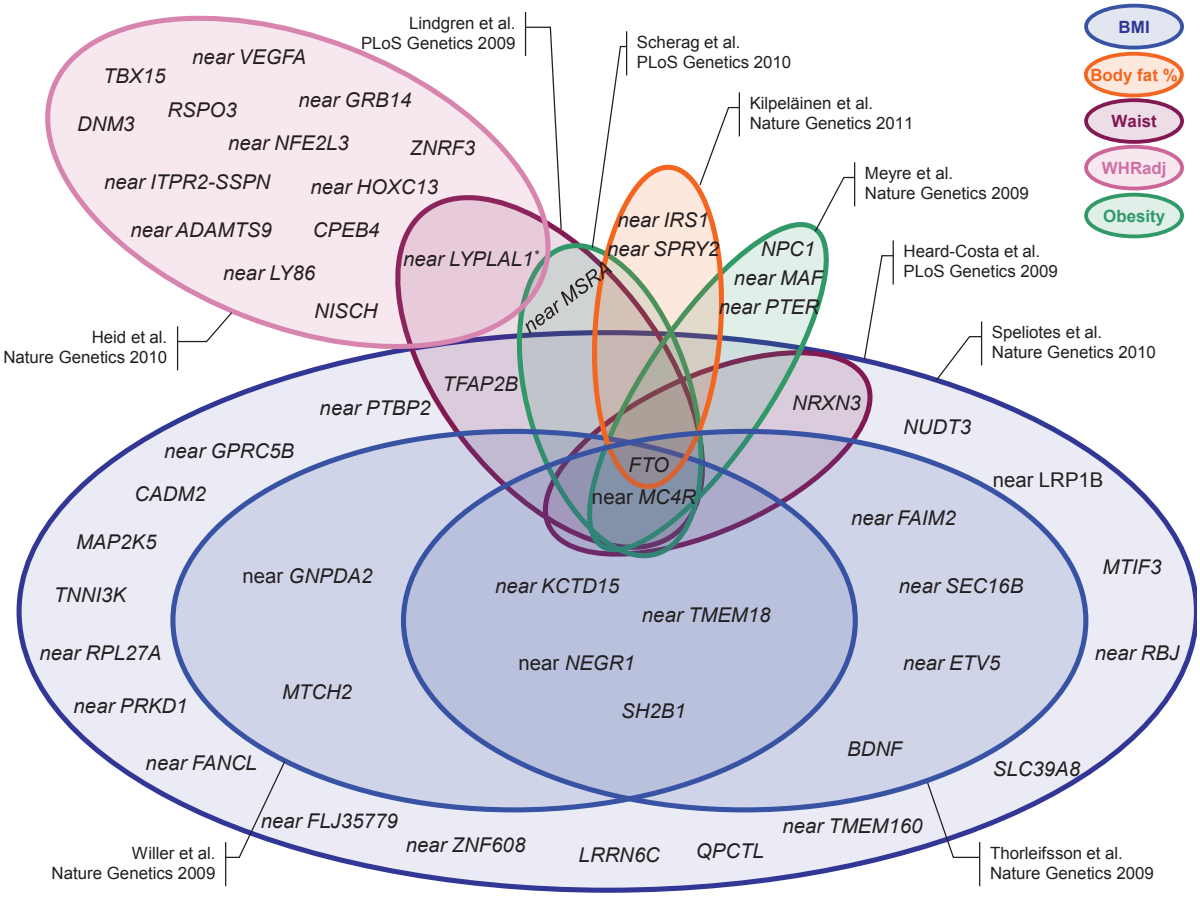
The most recent large GWAS, published in 2010, with a larger sample size still, confirmed all of the previously identified loci, plus two previously associated with waist circumference, and identified a further 18 novel loci[66].

In addition to these population-based cohort studies, two case-control studies have explored loci associated with severe obesity, comparing cases with normal weight controls. In a study of morbidly obese adults compared with normal weight adults controls, associations were found with signals near-*NPC1*, *MAF* and *PTER*[67]. In cases with extreme early onset obesity compared with lean controls, *SDCCAG8* and *TNKS-MSRA* were associated with childhood obesity[68.] These studies are also shown in Figure 6. Investigation of the role of the 32 BMI-associated loci in extreme and early onset obesity has been performed using data from case-control studies. This analysis revealed that 30 of the 32 alleles showed directionally consistent effects on the risk of extreme and early-onset obesity. In addition, 23 of the alleles increased BMI in children and adolescents, and in family-based studies, 24 were over-transmitted to obese offspring[66]. The investigators speculate these studies were too small to have sufficient power to identify all 32 loci. They conclude that their findings show that the effects of the identified obesity susceptibility loci extend to BMI differences throughout the life-course[66].

Table 2. Major GWAS of BMI (adapted from McCarthy, 2010[69])

Reference	Sample Size: GWAS	Replication	Major Ethnic Group	Study Type	Main Findings
Frayling et al, 2007	4,862	38,759	British	GWAS of type 2 diabetes cohort	*FTO* association with BMI, obesity and type 2 diabetes
Scuteri et al, 2007	4,741	3,205	Sardinian	GWAS of large population isolate	*FTO* association with BMI
Loos et al, 2008	16,876	75,981	European	GWAS meta-analysis	Association of common *MC4R* variants with BMI
Willer et al, 2009	32,387	59,082	European	GWAS meta-analysis	*FTO* and near-*MC4R* plus 6 new associations with BMI: *TMEM18, KCTD15, GNPDA2, SH2B1, MTCH2* and *NEGR1*
Thorleifsson et al, 2009	34,416	43,625	Icelandic	GWAS of large population isolate	*FTO* and near-*MC4R* plus 8 new associations with BMI: *NEGR1, TMEM18, ETV5, BDNF, FAIM2, KCTD15, SH2B1* and *SEC16B*
Speliotes et al, 2010	123,865	125,931	European	GWAS meta-analysis	Confirmation of previously identified loci plus 18 new loci associated with BMI including *POMC, GIPR* and *HMGA1*

Figure 7. Common obesity susceptibility loci (figure and accompanying text from Loos, 2012[70])



Obesity-susceptibility loci discovered in four waves of GWAS for BMI (blue), in one genome-wide meta-analysis for body fat percentage (orange), in two waves of GWAS for waist circumference and waist-to-hip ratio (pink), and in two GWAS for extreme and early onset obesity (green). Each Venn diagram represents the loci of one paper, except for papers that discovered only one locus (*i.e. FTO* and near-*MC4R*) for which no Venn diagram has been drawn.

The 32 GWAS-identified loci are listed in Table 3, together with the frequency and explained variance of each, and the odds of overweight and obesity associated with each signal.

Most of these loci are for markers which are not in known genes, meaning that further work is required to elucidate the responsible genes and thereby the functions and pathways involved[34]. However, several of the loci indicate genes that are highly expressed or known to act in the central nervous system, which further emphasises, as in the monogenic forms of obesity, the important role of central regulation in susceptibility to obesity[64, 65]. Loci are illustrated in Figure 8 below. In addition, very few of the loci include obvious or previously studied candidate genes, although several of the loci include or are near to genes which have established connections with obesity, including *MC4R*, *BDNF*, *POMC* and *SH2B1*. Rare variants of each of these have been identified as causing severe monogenic forms of obesity. A number of the key identified genes are discussed in brief below.

2.3.1 Genes at loci associated with common forms of obesity

FTO

The first common obesity gene to be identified was *FTO*, in 2007. Since this time, the finding has been replicated in a wide range of population and age groups[34]. *FTO* is widely expressed throughout the body, but particularly highly in the brain, and animal studies indicate particularly high expression in the hypothalamic nuclei. The risk allele has been associated with increased food intake and decreased satiety in humans.

MC4R

Mutations in the melanocortin-4 receptor gene (*MC4R*) are the commonest identified monogenic cause of obesity, and the identification of association between SNPs close to the *MC4R* gene with BMI and obesity indicate that it also has a measurable role in common obesity at the population level. Variants have been associated with higher overall food intake and higher dietary fat intake[34].

POMC

Pro-opiomelanocortin (POMC) is involved in leptin signalling and *POMC* mutations have been identified as a monogenic form of obesity.

BDNF

Brain-derived neurotrophic factor (BDNF) is involved in leptin signalling and *BDNF* mutations have been identified as a monogenic form of obesity.

SH2B1

SH2B adaptor protein 1 (SH2B1) is implicated in leptin signalling, and *Sh2b1*-null mice are obese[43, 64]. *SH2B1* has also been suggested as a candidate gene behind the association of the large chromosome 16 deletion with extreme obesity.

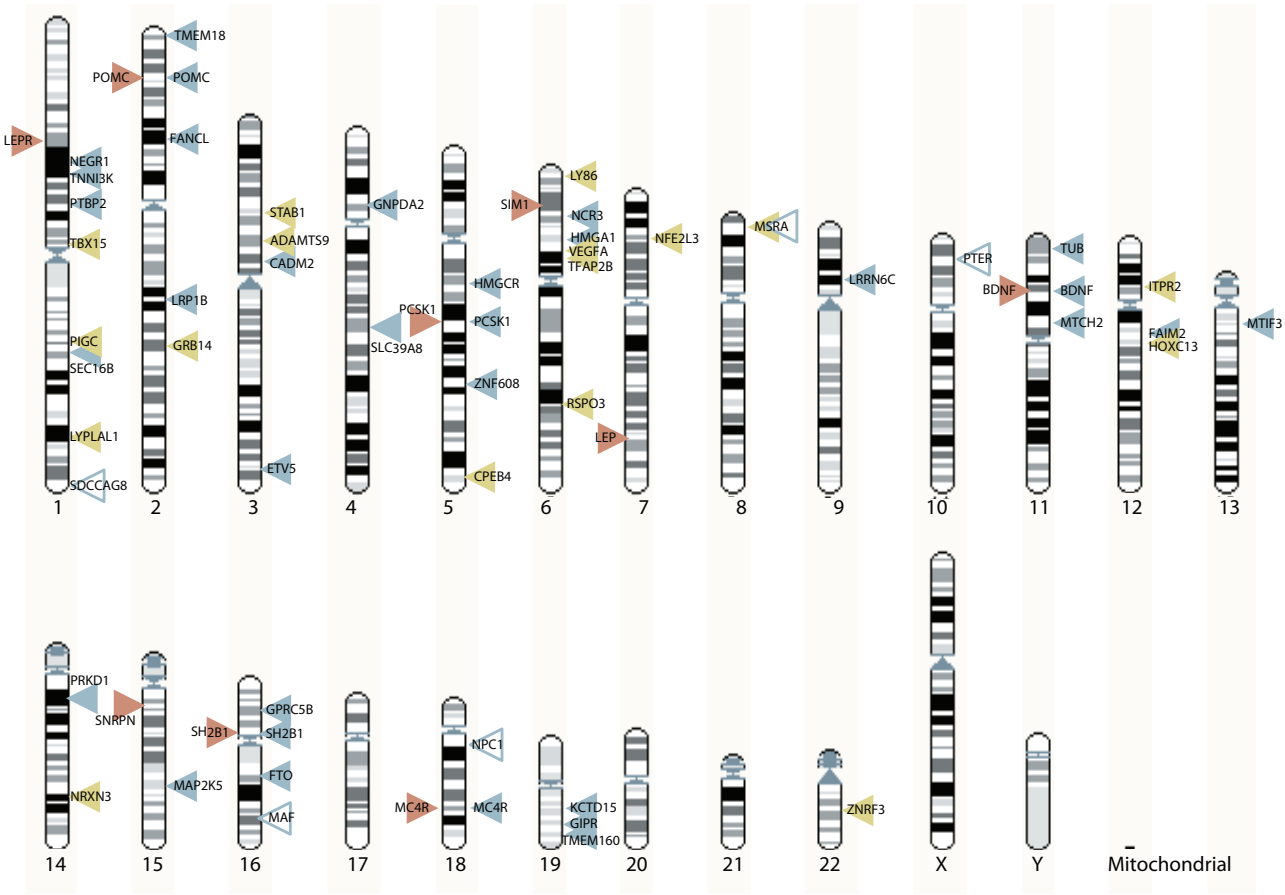
GIPR

A role for peripheral biology is suggested by the proximity of *GIPR* to one of the loci. This encodes a receptor of gastric inhibitory polypeptide (GIP), a hormone that mediates insulin secretion in response to glucose intake.

HMGA1

The HMGA1 protein is a key regulator of the insulin receptor (*INSR*) gene, and individuals with defects in the *HMGA1* gene have decreased insulin receptor expression and increased susceptibility to type 2 diabetes[71].

Figure 8. Genomic locations of proven signals of BMI, obesity and related phenotypes (Figure and accompanying text from McCarthy, 2010[69]).



Signals are shown according to their location on each chromosome. Genes causing monogenic and selected syndromic forms of obesity (red triangles) are shown to the left. Common variants that have significant genome-wide associations with BMI or multi-factorial obesity are shown to the right: loci implicated in BMI or weight variation at the population level (solid blue triangles), additional loci identified in case-control analyses of extreme obesity (open blue triangles), and variants identified primarily because of their association with waist circumference or waist-to-hip ratio (solid yellow triangles). For the variants shown to the right, the genes marked within the triangles are indicative of signal position, but in most instances, formal proof that these are the specific genes responsible for the association is lacking.

Table 3: The 32 SNPs robustly associated with BMI (results from Speliotes *et al* (2010[66].)

Nearest gene to associated SNP (possible candidate)	Region	Context	Frequency (%)	N	P	Per allele change in BMI (95%CI)	Explained variance in BMI (%)	Odds ratio Overweight (95%CI)	Odds Ratio Obesity (95%CI)
FTO	16q12.2	Intron	42	192,344	$4.8x10^{-120}$	0.39 (0.35 to 0.43)	0.34	1.138 (1.114 to 1.164)	1.203 (1.169 to 1.237)
TMEM18	2p25.3	Intergenic	83	197,806	$2.8x10^{-49}$	0.31 (0.25 to 0.37)	0.15	1.119 (1.089 to 1.150)	1.134 (1.095 to 1.174)
MC4R	18q21.32	Intergenic	24	203,600	$6.4x10^{-42}$	0.23 (0.17 to 0.29)	0.10	1.094 (1.068 to 1.121)	1.108 (1.074 to 1.143)
GNPDA2	4p12	Intergenic	43	197,008	$4.8x10^{-31}$	0.18 (0.14 to 0.22)	0.08	1.061 (1.039 to 1.084)	1.075 (1.047 to 1.105)
BDNF	11p14.1	Intron	78	204,158	$4.7x10^{-26}$	0.19 (0.13 to 0.25)	0.07	1.057 (1.031 to 1.084)	1.079 (1.044 to 1.115)
SEC16B	1q25.2	Intergenic	19	179,414	$3.6x10^{-23}$	0.22 (0.16 to 0.28)	0.07	1.072 (1.041 to 1.104)	1.098 (1.059 to 1.138)
NEGR1	1p31.1	Intergenic	61	198,380	$1.6x10^{-22}$	0.13 (0.09 to 0.17)	0.04	1.045 (1.023 to 1.067)	1.061 (1.033 to 1.090)
RBJ (POMC)	2p23.3	Intergenic	47	230,748	$6.2x10^{-22}$	0.14 (0.10 to 0.18)	0.06	1.052 (1.034 to 1.071)	1.069 (1.045 to 1.093)
GPRC5B	16p12.3	Intergenic	87	239,715	$2.9x10^{-21}$	0.17 (0.11 to 0.23)	0.04	1.085 (1.058 to 1.112)	1.078 (1.044 to 1.114)
SH2B1	16p11.2	Near gene	40	204,309	$1.9x10^{-20}$	0.15 (0.11 to 0.19)	0.05	1.041 (1.020 to 1.063)	1.049 (1.022 to 1.077)
TFAP2B	6p12.3	Intron	18	195,776	$2.9x10^{-20}$	0.13 (0.07 to 0.19)	0.03	1.050 (1.023 to 1.078)	1.085 (1.049 to 1.122)
MAP2K5	15q23	Intron	78	227,950	$1.2x10^{-18}$	0.13 (0.09 to 0.17)	0.03	1.045 (1.022 to 1.069)	1.065 (1.035 to 1.096)
ETV5	3q27.2	Intergenic	82	196,221	$1.7x10^{-18}$	0.14 (0.08 to 0.20)	0.03	1.029 (1.001 to 1.057)	1.066 (1.028 to 1.105)
FAIM2	12q13.12	Intergenic	38	200,064	$1.8x10^{-17}$	0.12 (0.08 to 0.16)	0.04	1.044 (1.022 to 1.066)	1.069 (1.040 to 1.098)
QPCTL (GIPR)	19q13.32	Intron	80	194,564	$1.9x10^{-16}$	0.15 (0.09 to 0.21)	0.04	1.055 (1.031 to 1.079)	1.086 (1.054 to 1.119)
TNNI3K	1p31.1	Intron	43	227,900	$8.2x10^{-14}$	0.07 (0.03 to 0.11)	0.02	1.043 (1.024 to 1.063)	1.044 (1.020 to 1.069)
SLC39A8	4q24	Missense	7	245,378	$1.5x10^{-13}$	0.19 (0.11 to 0.27)	0.03	1.062(1.025 to 1.101)	1.098 (1.048 to 1.150)
FLJ35779	5q13.3	Near gene	63	231,729	$2.2x10^{-13}$	0.10 (0.06 to 0.14)	0.02	1.042 (1.023 to 1.061)	1.052 (1.030 to 1.075)
LRRN6C	9p21.1	Intron	31	216,916	$2.7x10^{-13}$	0.11 (0.07 to 0.15)	0.02	1.035 (1.015 to 1.056)	1.040 (1.016 to 1.064)
MTCH2	11p11.2	Intron	41	191,943	$1.6x10^{-12}$	0.06 (0.02 to 0.10)	0.01	1.016 (0.995 to 1.039)	1.016 (0.988 to 1.045)
TMEM160	19q13.32	UTR-3	67	233,512	$1.6x10^{-12}$	0.09 (0.05 to 0.13)	0.02	1.024 (1.005 to 1.045)	1.055 (1.029 to 1.083)
FANCL	2p16.1	Intergenic	29	242,807	$1.8x10^{-12}$	0.10 (0.06 to 0.14)	0.03	1.020 (1.006 to 1.034)	1.051 (1.026 to 1.077)
NRXN3	14q.31.1	Intron	21	183,022	$2.8x10^{-11}$	0.13 (0.07 to 0.19)	0.02	1.054 (1.025 to 1.083)	1.085 (1.049 to 1.123)
CADM2	3p12.1	Intron	20	237,404	$3.9x10^{-11}$	0.10 (0.06 to 0.14)	0.02	1.028 (1.006 to 1.051)	1.027 (0.998 to 1.056)
PRKD1	14q12	Intergenic	4	241,667	$5.8x10^{-11}$	0.17 (0.07 to 0.27)	0.01	1.073 (1.025 to 1.124)	1.102 (1.037 to 1.170)
LRP1B	2q.22.2	Intergenic	18	209,068	$1.4x10^{-10}$	0.09 (0.03 to 0.15)	0.02	1.027 (1.003 to 1.053)	1.048 (1.015 to 1.082)
PTBP2	1p21.3	Intergenic	59	243,013	$3.7x10^{-10}$	0.06 (0.02 to 0.10)	0.01	1.016 (0.999 to 1.033)	1.016 (0.994 to 1.039)
MTIF3	13q12.2	Intron	24	198,577	$9.5x10^{-10}$	0.09 (0.03 to 0.15)	0.02	1.030 (1.004 to 1.055)	1.045 (1.013 to 1.079)
ZNF608	5q23.2	Intergenic	48	241,999	$2.0x10^{-9}$	0.07 (0.03 to 0.11)	0.01	1.031 (1.014 to 1.049)	1.029 (1.006 to 1.052)
RPL27A	11p15.4	Intron	52	249,791	$2.8x10^{-9}$	0.06 (0.02 to 0.10)	0.01	1.013 (0.996 to 1.029)	1.027 (1.005 to 1.049)
KCTD15	19q13.11	Intergenic	67	192,872	$3.0x10^{-9}$	0.06 (0.02 to 0.10)	0.01	1.023 (1.000 to 1.046)	1.017 (0.988 to 1.046)
NUDT3 (HMGA1)	6p21.31	Intron	21	249,777	$3.0x10^{-8}$	0.06 (0.02 to 0.10)	0.00	1.034 (1.013 to 1.056)	1.032 (1.005 to 1.060)

Figure 9 Chart showing frequency of the SNP in the study population (x-axis) against odds ratio of being obese (y-axis) (results from Speliotes et al, 2010[66])

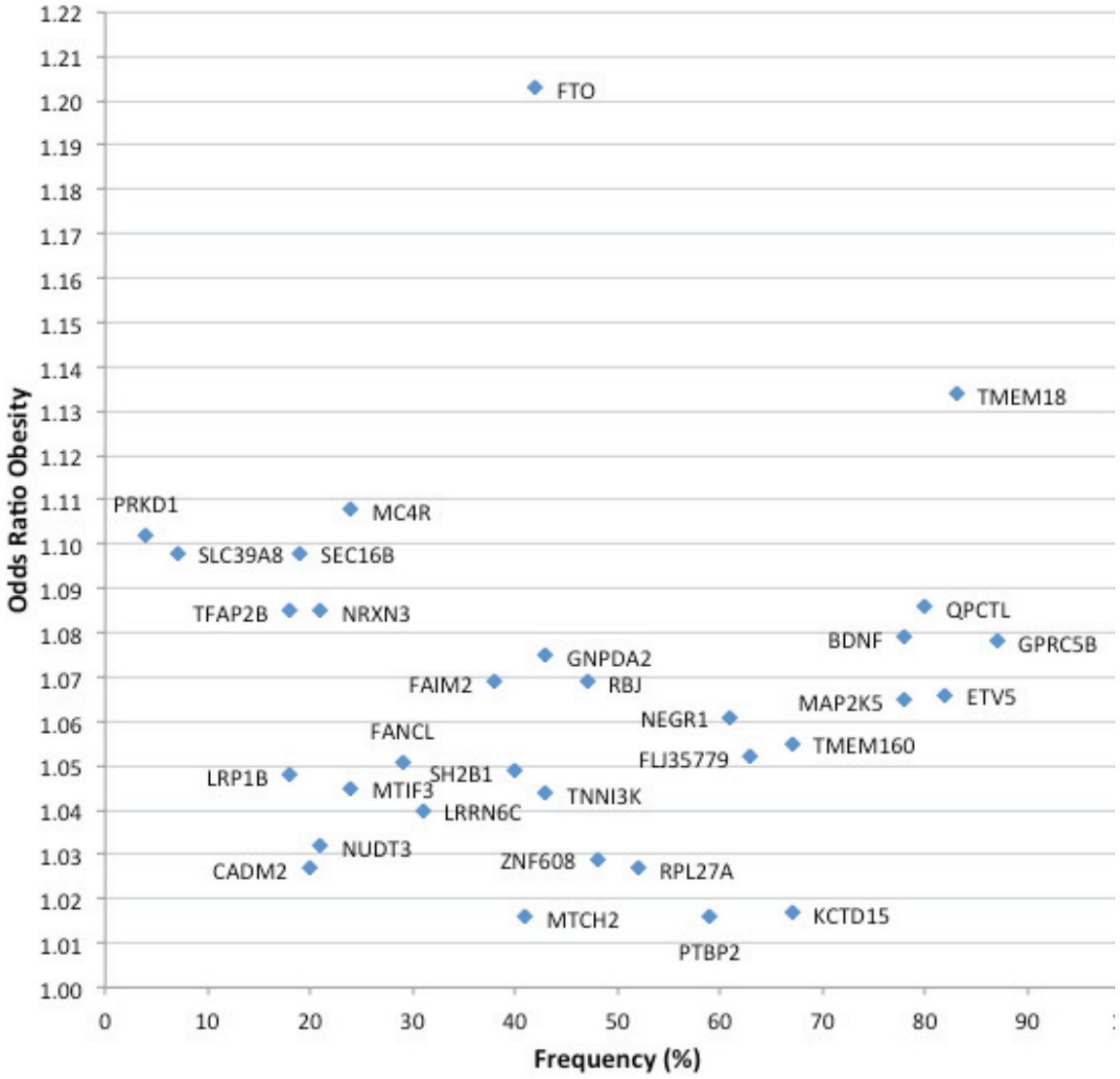
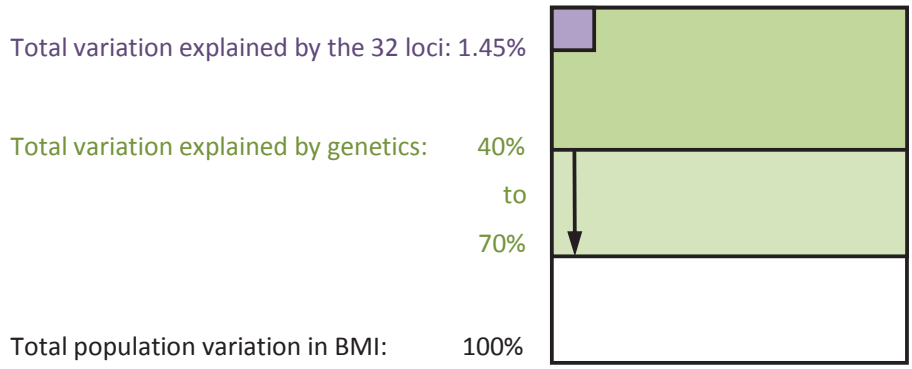


Figure 9 illustrates the frequency of the each of the 32 SNPs associated with BMI in the study population (largely European general populations) against the odds ratio of being obese given the risk allele. This highlights the far bigger effect of *FTO* compared with the other loci. It can also be seen that some of the SNPs are highly frequent in the population, meaning that these variants will not discriminate well between members of the population.

2.4.2 Variability explained and predictive ability of these 32 loci

Taken together, the 32 loci which have been robustly associated with BMI only explain 1.45% of the total variation in BMI within the European population[66]. Given that proportion of the total observable difference in BMI which is due to genetic differences (the heritability of BMI) is 40% to 70%, this means that just 2% to 4% of the heritability is explained by the 32 loci. This is illustrated in Figure 10.

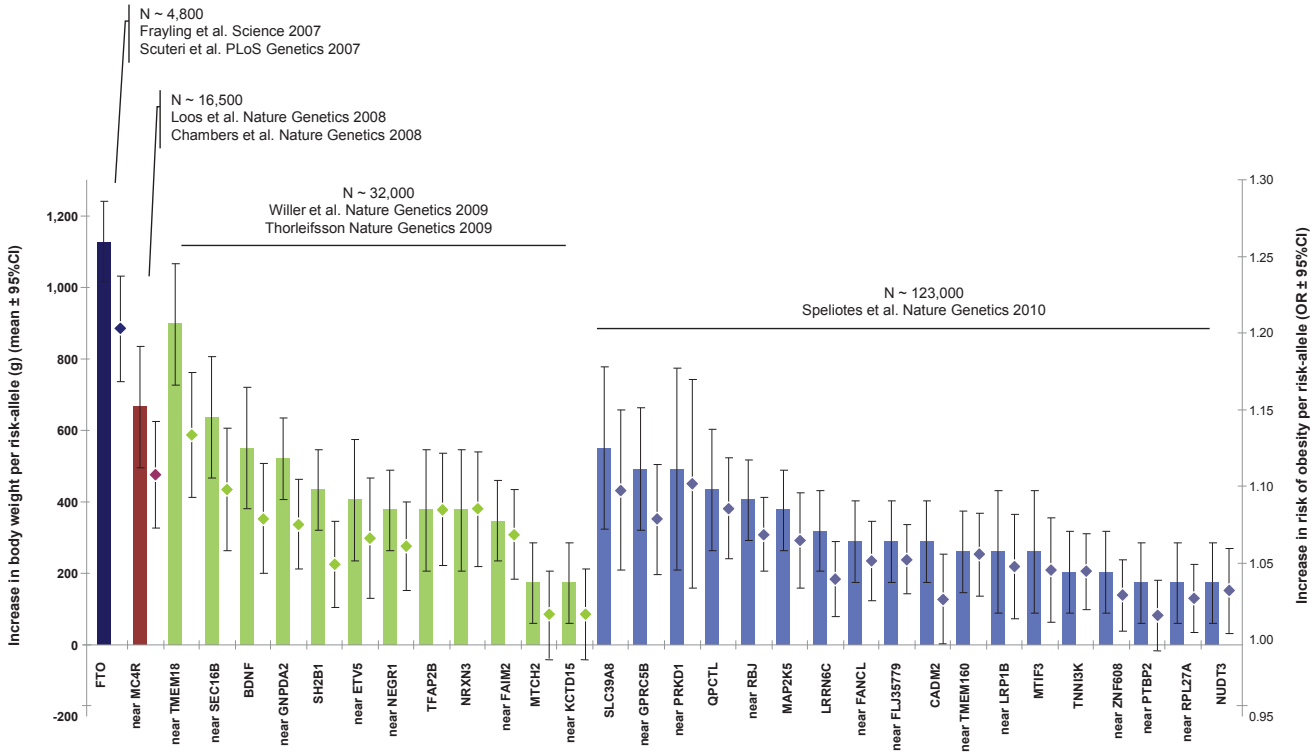
Figure 10. The proportion of population variation in BMI explained by genetics and by the 32 loci



Despite highly significant associations, the effect sizes of these loci on both body weight and risk of obesity are small, as illustrated in Figure 10. *FTO* was the most easily identified locus as its effect size is largest and the BMI increasing allele occurs with greater relative frequency in white European populations[70]. However, this still only explains 0.34% of the total variance in BMI, as given in Table 4, which shows how the amount of variability explained increases with increasing numbers of loci discovered.

The small fraction of variability explained by even the 32 loci together indicates that the combined predictive ability of the alleles is extremely limited. This is an important point as direct-to-consumer genetic tests (DTC) available to consumers include risk of obesity scores, based on selections of these loci. One of the major companies uses 11 loci to determine risk of obesity[72], whilst the global DTC market leader uses only *FTO*[73].

Figure 11. Per-allele effect of BMI-associated loci on body weight (shown as bars with scale on left hand y-axis) and obesity risk (shown as diamonds with scale on right hand y-axis) (Figure and text from Loos, 2012[70])



Loci are sorted by wave of discovery (first wave in dark blue, second in red, third in green and fourth in light blue). Data were derived from Speliotes et al, 2010[66] and additional studies to identify loci are indicated.

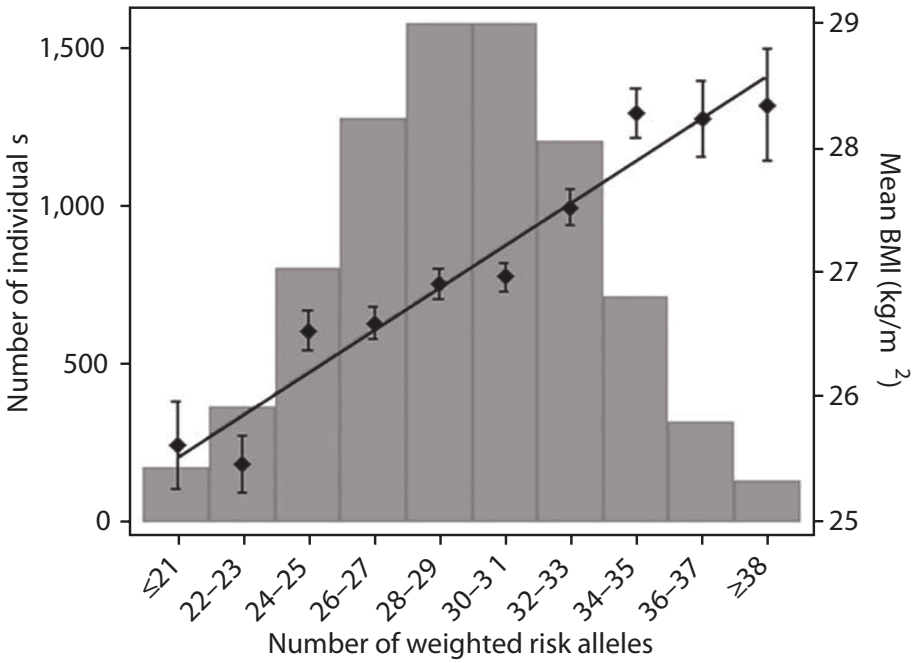
Table 4. Explained variance in BMI by SNPs in BMI-associated loci (adapted from McCarthy, 2010[69])

BMI associated loci included in the model	Explained variance in BMI
FTO	0.34 %
FTO, near-MC4R	0.59 %
11 loci: *FTO*, near-*MC4R*, near-*TMEM18,* near-*SEC16B, BDNF,* near-*GNPDA2, SH2B1*, near-*ETV5*, near-*NEGR1*, near-*FAIM2*, near-*KCTD15*	0.98 %
32 loci identified by Speliotes et al66 (see Table 3 for list)	1.45%

The combined effect of the 32 risk loci has been explored by calculation of a genetic susceptibility score, derived by summing the number of BMI increasing alleles, weighted by their effect sizes[66]. Each unit increase (approximately equal to one additional risk allele) was found to be associated with an increased BMI of 0.17 kg/m^2, or an increased weight of just 435-551 grams in adults 160-180 cm in height, as shown in Figure 12. Those with a high genetic susceptibility score (defined as having ≥38 BMI-increasing alleles across the 32 loci) had a BMI on average 2.7 kg/m^2 higher than those with a low-risk score (≤21 BMI-increasing alleles), equivalent to 6.99-8.85 kg in adults 160-180 cm in height.

However, these groups were the very extremes of the population, comprising just the highest risk 1.5% of the studied population and the lowest risk 2.2%. The 32 risk alleles all showed directionally consistent effects on risk of being overweight or obese, with the increased odds of being overweight ranging from 1.013 to 1.138-fold and the odds of being obese from 1.016 to 1.203 (listed in Table 3)[66].

Figure 12. Combined impact of risk alleles on mean BMI and obesity (figure from Speliotes et al, 2010[66])



The histogram shows the number of individuals (marked on the left hand y-axis) within each risk score category (marked as numbers of risk alleles on the x-axis) and the markers show mean BMI of individuals in each risk category (marked on the right hand y-axis; with error bars indicating standard error of the mean). Individuals were from the Atherosclerosis Risk in Communities (ARIC) study cohort, a population-based sample of US middle-aged adults recruited aged 45-64 years.

2.3.3 *Identifying the missing heritability*

It has been estimated that more than 250 further loci with similar effect sizes to the 32 already identified may exist. However, these would together only explain 4.5% of the phenotypic variation, or 6-11% of the genetic variation. A sample size of almost three quarters of a million participants would be required to detect 95% of these[66].

GWAS identify variants with allele frequencies of 5% or more. The estimation above suggests that these common variants will not account for a large proportion of the genetic contribution to BMI[66]. There is therefore support for a hypothesis that both common and rare variants contribute to common disease, and it is likely that sequencing of all known coding DNA (exomic sequencing) and deep sequencing will identify further variants of interest[34].

Heritable changes in gene expression also occur by mechanisms other than changes in the underlying DNA sequence. These epigenetic effects include functionally relevant modifications of the genome that regulate expression but do not involve a change in nucleotide sequence, and include methylation and histone modification. These changes are preserved when cells divide, and can be passed down through generations. Environmental exposures including nutrition can cause these epigenetic changes, and whilst it is therefore difficult to separate direct effects of the environment on phenotype from effects occurring via epigenetic mechanisms, DNA-methylation-specific microarrays and methylated DNA immuno-precipitation and re-sequencing will further understanding of the role of epigenetic factors[34]. Parent-of-origin effects, suggestive of imprinting, have also been linked to common obesity, and mutations in the form of copy number variants, duplications, insertions, deletions and rearrangements, which are not picked up by analytical methods used in GWAS, may account for up to almost one-fifth of heritable variance in gene expression[34].

2.3.4 *Variable penetrance across the life-course*

Genetic influences on BMI have been shown to vary with age, with heritability estimates becoming progressively stronger during childhood and decreasing into adulthood[74]. In addition, heritability estimates of BMI change appear to be higher in adolescence than young adulthood.

Whilst individual variants may differ in this respect, the combined effect of 11 BMI-associated genetic variants has been used to examine variable penetrance across the life course, by creating a multiple allele obesity risk score (including in/near *FTO, MC4R, TMEM18, GNPDA2, KCT15, NEGR1, BDNF, ETV5, SEC16B, SH2B1, MTCH2*). Longitudinal analysis of how genetic susceptibility to higher BMI (as indicated by this score) influences changes in weight from birth into adulthood has been performed using the 1946 British Birth Cohort Study (n=2537)[74].

The score was found to have a borderline significant association with birth weight (0.019 SDS/allele, P=0.05), but to be associated with higher BMI at all time points between 2-53y. The strongest associations were seen at 11y (0.063 (95%CI 0.043-0.083, $P=1.06x10^{-9}$) SDS/allele) and 20y (0.066 (95%CI 0.046-0.086, $P=8.58x10^{-11}$) SDS/allele). At age 11y, those with ≥14 alleles (n=189) had on average a BMI 1.56 kg/m^2 higher than those with ≤7 (n=161). In longitudinal analysis within individuals, the risk score was only associated with BMI gain between 2-11y (0.005 (95%CI 0.002-0.007) SDS/allele/y, P<0.001). Association with BMI later declined by -0.0005 SDS/allele/y (P=0.001). Growth trajectories by risk score tertile diverged during childhood and converged during later adult life.

Genetic influences on BMI have been shown to vary with age, with heritability estimates becoming progressively stronger during childhood and decreasing into adulthood.

This means that genetic variants predisposing to higher adult BMI are in combination associated with greater gains in weight and BMI up to 11y. However, after this age, they remain heavier, but do not continue to gain weight more rapidly that those with fewer risk alleles. The number of risk alleles is also associated with faster height growth to 7y but no difference in adult height. This is in support of previously established association between faster tempo of childhood growth and adult obesity. Being taller at 7y relative to adult height may therefore indicate genetic susceptibility to a rapid growth trajectory that is associated with later obesity risk.

In summary, the greater gains in weight associated with these loci are achieved in childhood. Once established, differences in BMI continue to track throughout adult life. The findings of this study are consistent with others, but it is possible that penetrance is rising in younger generations, suggesting that the modern obesogenic conditions may allow genetic susceptibility to greater weight gain and adiposity to become more visible.

2.5 Summary

The research described in this chapter highlights how much progress has been made over the past two decades in understanding the genetic basis of obesity, although much remains unknown. It has been an almost consistent finding that the identified genetic causes and contributors increase body mass through central mechanisms driving increased energy intake.

Clear distinction has been made here between monogenic and common genetic causes of obesity. Whilst a number of single genes have been identified as highly penetrant causes of severe early-onset obesity, it is likely that further genes are yet to be discovered, in addition to much heterogeneity of mutations at each gene between individuals. Less still is known about polygenic contributors to common obesity, which not only have small effects but also effects that are complicated due to gene-gene and gene-environment interactions. To date, only 2% to 4% of the heritability of body weight has been explained. As further loci are identified at both ends of this spectrum, it is possible that the clear distinction will no longer be important and a continuum may become apparent, with oligogenic causes of obesity lying between the extremes of the rare monogenic and common polygenic forms. In oligogenic disorders, the phenotype is produced or influenced by two or more genes acting together.

3. Genetic testing in obesity

A key application of the discovery of disease associated genes and variants is that it enables genetic testing of individuals. This chapter discusses the potential utility of this application in obesity.

As described in the previous chapter, the identification of genetic variants that increase risk of obesity has contributed greatly to understanding of the central regulation of body weight and the aetiology of obesity. A key application of the discovery of disease associated genes and variants is that it enables genetic testing of individuals. This chapter discusses the potential utility of this application in obesity. As the genetic contribution and severity of monogenic and common obesity vary markedly, these will be considered separately in light of their ethical, legal and social implications.

Genetic tests are evaluated for analytical validity, the clinical validity, the clinical utility and the ethical, legal and social implications.

A genetic test can be defined as 'a laboratory assay that is used to identify a particular genotype or set of genotypes, for a particular disease, in a particular population, for a particular purpose'[75], where this purpose should be to achieve one or more of the following outcomes[76] : reduction in morbidity or mortality; provision of information salient to the health care of the patient or family members; and/or assistance with reproductive decision-making for patient or family members.

3.1 Evaluation of genetic test

Genetic tests are evaluated using the ACCE framework, in which the Analytical validity, the Clinical validity, the Clinical utility and the Ethical, legal and social implications are assessed and considered[76, 77].

3.1.1 Analytical validity

This relates to how accurately and reliably an assay measures the genotype of interest in the laboratory, and is highly dependent on quality control at all stages from sample collection and processing to the interpretation of the result. It is determined by the analytical sensitivity and specificity of the assay (its ability to correctly identify positive and negative results as to whether the genotype tested for is present, respectively). If the assay is highly sensitive, there will be few false negative results, and if it is highly specific, there will be few false positives.

3.1.2 Clinical validity

In contrast, the clinical validity of a test relates to how accurately it detects or predicts the phenotypic outcome of interest. This requires the outcome to be clearly defined, and relies both on evidence of an association between the gene measured by the assay and the outcome of interest, and on how well the test performs in the clinical setting. In addition to the analytical validity of the assay, the performance of the test is dependent on the clinical sensitivity and specificity of the test (the probability the test will be positive

From the public health perspective, utility is determined by the test's ability to reduce morbidity or mortality at the population level in a cost-effective way.

in those with the phenotype and that it will be negative in those without the phenotype respectively) and the positive and negative predictive values (PPV and NPV) of the test (how likely it is the patient has/ doesn't have the outcome given a positive/ negative test result). The PPV and NPV are influenced by the prevalence of the outcome in the population tested in addition to the clinical sensitivity and specificity of the test, with PPV increasing as the prevalence increases in the test population[78]. As prevalence of genotypes and genetic diseases varies between populations, it is essential that the test is validated clinically in a sample of subjects who are representative of the population the test is intended to be used in.

Clinical validity is also affected by two features of genetic diseases: heterogeneity and penetrance[79]. The same phenotype may result from the different variants within the same gene, or from different genes (heterogeneity). If not all disease-related mutations are known, the clinical sensitivity of a genetic test will be reduced. If penetrance is incomplete, PPV will be reduced even if the assay detects the variant with a high degree of accuracy, since the variant may not lead to the outcome.

3.1.3 Clinical utility

The clinical utility of a genetic test is how likely it is to significantly improve patient outcomes. This is dependent on the natural history of the condition, whether or not there is an effective intervention with the potential to benefit the patient, or if not, whether the information will help reproductive decision making or other members of the family.

There are several perspectives from which to consider utility[80]. Whilst clinical utility is the ability of the test to improve patient outcomes through presenting options for prevention or treatment, from the public health perspective, utility is determined by the test's ability to reduce morbidity or mortality at the population level in a cost-effective way. An additional concept is that of personal utility. This encompasses non-medical and subjective aspects, including the value of the genetic information to the individual, even if no preventive or treatment options exist, for example for planning or motivation for behaviour change. The reaction to genetic information and it's personal utility to an individual will vary between individuals. Here, clinical utility is a subjective interpretation, based on what perspective the evaluation is undertaken from. Whether it is from an individual or a health service provision level will determine the utility attached to different outcomes.

3.1.4 Ethical, legal and social implications

Genetic testing carries unique ethical, legal and social implications. In addition to issues common to other medical testing or screening such as the knowledge that the test will be accurate and will provide information that the individual being tested wants and which will be useful in their clinical care and guiding lifestyle choices, genetic testing raises other quite unique issues.

Genes do not only provide information about existing disease, but in some cases are able to predict possible, or even certain, future disease. Additionally, discovering carriage of a particular variant not only has implications for the individual, but also for their family, and for their future reproductive choices[81]. For these reasons, genetic testing should be preceded by genetic counselling to ensure that the consequences of the result are fully understood before the individual consents to a genetic test. Results should be delivered by a professional able to give tailored advice for that individual according to the

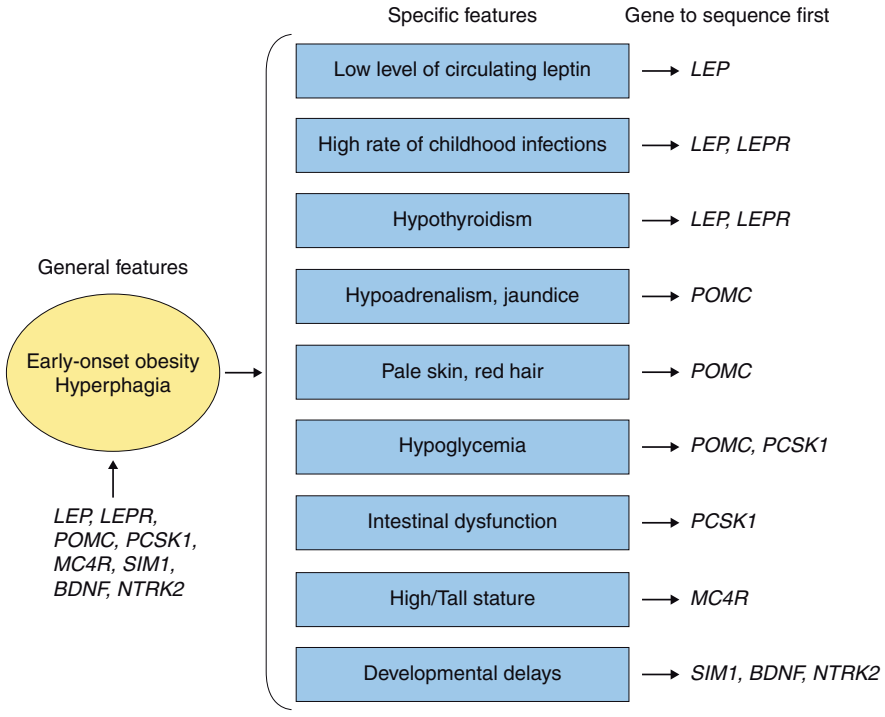
outcome. Further issues to arise from genetic testing may be identification of non-paternity or of incestuous parentage, which can raise difficult ethical and legal issues for the health professional receiving the results[82].

3.2 Genetic testing for monogenic obesity

Although individually the monogenic forms of obesity are rare, those identified to date together account for up to 10% of cases of extreme early-onset obesity[42, 83], with MC4R deficiency alone being present in up to 5% of severely obese children[40]. Among a cohort of over 2000 patients with severe obesity (BMI standard deviation score (SDS) >3) of early onset (<10y; mean BMI SDS 4.5, mean age of onset 5y), the identified causes disrupting the leptin-melanocortin pathway accounted for 7% of cases[84]. However, many of the remaining patients appeared to have inherited their obesity in a Mendelian manner, indicating that further genes remain to be identified. Characterisation of these monogenic forms of obesity has contributed to the understanding of pathways of appetite and satiety, and in the case of leptin deficiency, it has dramatically improved patient outcomes through availability of an effective treatment.

NICE guidance recommends that children who are obese with comorbidities or complex needs (such as learning difficulties) should be referred for secondary care assessment, which should include, among other investigations, assessment of possible genetic causes for their obesity disorders. As obesity is the primary characteristic of a number of the identified monogenic obesity disorders, and metabolic comorbidities may only occur as a result of an extended period of obesity, there may be a case for revision of guidelines for referral to "children with early-onset severe obesity with hyperphagia" alone, with appropriate criteria for age of onset and BMI SDS to be defined by clinical experts. This may aid earlier diagnosis and thus perhaps allow prevention of resulting comorbidities in these patients.

Figure 13. Monogenic gene screening prioritisation during clinical examination (Figure from Choquet and Meyre, 2010[42])



As there are a number of single gene causes of this phenotype, prioritisation criteria have been suggested for order of genetic investigations according to additional specific clinical features, as shown in Figure 13. These additional specific clinical factors can be used to guide choice of which gene should be sequenced first[42].

A future alternative to this approach would be to use a panel test and sequence all of these genes simultaneously. As costs of sequencing reduce with technological progress, this could be both a cost and time-efficient method of identifying single-gene causes of obesity, and hence the need for a series of single gene-by-gene tests would be superseded. This approach would enable more rapid diagnosis and determination of appropriate management and support for the patient.

3.2.1 Analytical validity

If the testing protocol is performed according to guidelines and quality assured, and the assay is performed in an accredited laboratory using validated methods, the analytical validity can be considered to be high.

3.2.2 Clinical validity

The set of eight genes plus the 16p11.2 deletion may explain up to 10% of extreme early-onset obesity. Multiple variants of each of these genes have been identified in obese individuals, and it is therefore likely that more will be discovered in future, in addition to further single-gene causes of obesity. This means that for individuals who receive a negative test result for obesity-causing variants in the identified genes, a causal single gene defect cannot be excluded (*i.e.* the NPV may be low). Due to the high penetrance of these genetic defects however, identification of a susceptibility genotype is highly likely to explain the obese phenotype, or lead to obesity if not already present at the time of testing.

3.2.3 Clinical utility

Primary prevention of obesity in patients with a single gene defect would require very early testing if diagnosis is to be made before the phenotype is expressed. As these genetic tests would currently most frequently be performed as a result of the obese phenotype, the role of genetic testing in primary prevention will be limited under the current referral and care pathways. However knowledge of potentially increased susceptibility to extreme obesity may benefit the management of future siblings or children of the tested individual, enabling hyperphagia to be recognised and managed from very early in life, and primary prevention of obesity to be attempted through education and training of parents.

Secondary prevention of obesity (weight loss and maintenance) is by lifestyle modification, pharmacotherapy or bariatric surgery, or a combination of these. In cases of a genetic cause of leptin deficiency, exogenous leptin administration is a rapidly effective treatment. However, in other monogenic forms of obesity, no such treatment currently exists. This may not be the case in future however, and *in vitro* studies of pharmacological treatment for patients with *MC4R* mutations are promising, although *in vivo* benefits remain to be demonstrated[85].

In the absence of a pharmacological approach, the most effective strategy for treatment of monogenic forms of obesity is stringent restriction of food access. This requires full participation of the parents or carers in the case of

children, and a genetic diagnosis may be important in obtaining support for this approach[85]. Whilst restriction of food access is common to management of obesity regardless of genetic or other cause, the awareness that a child has a greatly increased drive to feed and that there is a biological cause for this could be important in the management of the patient.

Research in patients with *MC4R* and *POMC* monogenic conditions has found that they respond well to lifestyle interventions consisting of either a hypocaloric diet or a multidisciplinary approach including exercise, behaviour and nutrition therapy. However, a study in those with *MC4R* mutations has found failure to maintain weight loss after intervention[85]. This indicates a need for a continued plan of care and monitoring for these individuals, rather than a one-off intervention period. Although these small studies were performed in just two specific monogenic forms of obesity, as all forms identified to date result in obesity through extreme hyperphagia and disruption of appetite and satiety pathways, there may be reason to suspect that the findings may apply to patients with other single gene disorders. As intellectual disabilities accompany obesity in some of these cases, this must be taken into account in tailoring interventions for weight management in these individuals.

Individuals respond very differently to discovering that there is a genetic basis to their obesity.

Evidence is suggestive that awareness of a genetic cause of obesity may be important if bariatric surgery is being considered. Whilst bariatric surgery is the most effective long-term treatment for severe obesity, obesity-susceptibility genes may modify the response to different procedures differentially[85]. Preliminary results from small studies suggest that gastric banding may not be indicated in monogenic hyperphagic patients, but that gastric bypass surgery (Roux-en-Y) may be as effective as in non-carrier controls. These operations are more invasive, but may improve the neuro-hormonal control of satiety better than restrictive operations. Determining whether there is a monogenic cause of obesity may therefore be important in guiding procedure choice in patients being assessed for gastric surgery in future, although further studies are required.

Knowledge of a monogenic cause of obesity may therefore help to guide treatment, even where there is no pharmacological intervention, however more research is needed into the environmental factors which can modulate the penetrance of these causes of obesity, in order that clear guidance can be given in treatment pathways.

3.2.4 Ethical, legal and social issues

Obesity is a highly stigmatising condition and the knowledge of greatly increased susceptibility to the environmental drivers of obesity may lead to a more sympathetic attitude towards people with obesity, and a reduction in discrimination against them[85, 86].

It has also been suggested that knowledge of the genetic basis of a child's obesity may prevent inappropriate action by health or social care, who have in extreme cases occasionally suggested removal of a child from their parents[40].

Consideration must be made of the fact that people respond very differently to discovering that there is a genetic basis to their obesity. Whilst some are reported to feel relief at having a medical cause, others feel depressed at the fact that they have an underlying problem which will not readily be overcome.[86] The consequences of the test results should be explored in full with the individual prior to them consenting to the test.

3.3 Genetic testing for common obesity

In contrast to monogenic obesity, susceptibility to common obesity in the general population is influenced by a great many factors, both genetic and environmental, in addition to interactions between these.

3.3.1 Analytical validity

As above, if tests are performed by accredited laboratories using validated methods, analytical validity can be considered to be high.

3.3.2 Clinical validity

As only a fraction of the genetic variability in obesity in the general population has been accounted for, there is a lack of clinical validity of testing for these SNPs[40]. The ability of the 32 identified loci to predict obesity is very limited and whilst a risk score developed from these loci does slightly (although statistically significantly) increase the predictive ability of age and sex alone, the effect is very limited[66]. Additional factors will need to be considered in developing a method for classifying people at high risk of obesity, importantly environmental exposure, plus possibly also the adipose tissue transcriptome and the epigenome, which can both be influenced by nutritional factors, and additionally the gut microbiome, as the composition of the intestinal microbiota can influence fat storage[42].

Knowledge of increased genetic risk from the 32 BMI-associated loci does not reliably predict that the phenotype will occur in future if it is not already present at the time of testing, just as the phenotype may not be a marker of increased genetic risk. The range of loci currently associated with obesity in the general population only explains 1.45% of the variability in BMI, or 2% to 4% of the heritability, and multiple interactions between genes and the environment add further complexity to the interpretation of genetic results. It is likely that there are many more obesity-susceptibility genes and variants yet to be identified, and a role for more of the monogenic causes in common obesity may be uncovered.

Therefore, as the majority of the heritability of obesity in the general population is not explained, and due to the strong environmental determinants and gene-environment interactions, the positive and negative predictive values of testing for these 32 SNPs will be very low.

3.3.3 Clinical utility

Even if an increased risk score for obesity is discovered, the value of this knowledge is likely to be extremely limited, due to low predictive values (both PPV and NPV). Furthermore, it is likely that at the time a test was taken, an overweight or obese phenotype would already be apparent if the genetic risk was going to be expressed in that individual, and the knowledge of higher genetic risk of obesity would not change the advice given to modify lifestyle to alter energy balance.

It is possible that in future, with further evidence, there may be a role for genetic information about obesity risk in guiding intervention decisions, however this is a fledgling area of research and evidence is not robust yet. *FTO*, as the first and most repeatedly associated susceptibility gene for common obesity has been investigated the most in this respect to date. Consistent with the findings in monogenic obesity, a study of severely obese subjects undergoing obesity surgery found that subjects carrying the *FTO* obesity

predisposing allele lost 3 kg less than those with the common allele. The association was restricted to those undergoing banding surgery, with no significant difference in those undergoing gastric bypass surgery[85]. In addition, there is growing evidence to suggest that obesity-susceptibility genes may interact with dietary composition, with findings of a high fat diet amplifying the effect of *FTO* on obesity risk. Physical activity can also reduce the phenotypic expression of the susceptibility genes, with a number of studies reporting an interaction between *FTO* and physical activity on obesity risk in adolescents and adults, and a high level of physical activity being associated with a 40% reduction in genetic predisposition to obesity, as determined by a risk score of 12 associated SNPs[85]. These findings are all consistent with the hypothesis that obesity susceptibility genes are increasingly expressed in the context of an obesogenic environment.

Interactions also exist with characteristics other than the behavioural ones described above. Age modifies the penetrance of *MC4R* mutations, with the penetrance increasing with age and with the development of the obesogenic environment. In contrast, most of the effect of the *FTO* SNP on BMI gain occurs between childhood and young adulthood, with the increase being maintained although not increased later in life, a finding which has also been made for a risk score of 11 risk SNPs[74, 85]. Ethnicity is also likely to be important, with prevalence and effect of different SNPs varying between ethnic groups. Further research is needed in this area as the majority of the GWAS have been performed in cohorts largely of European descent. In addition, whilst there is a well-known negative association between education and BMI, this is not seen in *MC4R* loss of function mutation carriers, but is seen in the case of *FTO*, with the effect of the SNP on BMI being restricted to those with no university education.

3.3.4 Ethical, legal and social issues

There are conflicting theories as to whether and how knowledge of genetic susceptibility to a condition will influence motivation to change behaviour. On one hand, known higher risk may increase motivation to comply with lifestyle advice, and on the other, it may induce a fatalistic attitude and a feeling of lack of control over outcomes which could de-motivate individuals. It is likely that this effect will vary between individuals, and it is possible that de-motivation may be greatest in more socially-deprived individuals due to lower perception of control. Genetic information as well as general information concerning risk can be difficult to comprehend, and this is likely to be most the case for those with the lowest levels of education.

Whilst well-designed research into the effects of genetic risk information on behaviour change is very limited, there is no evidence to suggest a harmful effect on average. However, neither is there convincing evidence to suggest that receiving these results will motivate people to change their behaviours[87]. Communicating genetic risk information had no effect on physical activity behaviour and only a small effect on self-reported diet and intentions to change behaviour, although there was no evidence identified on actual sustained dietary changes. This is pertinent as whilst there is no suggestion at present of testing for common obesity susceptibility genes within the NHS, direct-to-consumer genetic tests are offering obesity risk scores to consumers.

Whilst consumers receiving information about their risk of obesity were found to initially rate their risk as higher, this perception of increased risk was not apparent after a one year period, and whilst they initially perceived an increase in risk, worry about developing the condition was not significantly increased[88].

Principles for direct-to-consumer tests in the UK are clear that the test provider must not overstate the clinical utility of a genetic test[89].

3.4 Summary

Research into the genetic causes of obesity has increased understanding of the biological mechanisms and aetiology of the condition. However the utility of determining an individual's genetic risk of obesity differs between monogenic and common cases of obesity.

Where a monogenic cause is suspected, knowledge of the causal gene is important. In the case of congenital leptin deficiency, there is an effective treatment. In other cases the knowledge of a genetic cause for the extreme phenotype may be important in addressing the hyperphagia, destigmatising about the condition, and in case of future availability of pharmacological treatment.

However in common or polygenic obesity, there is negligible utility of knowledge of the genotype. This knowledge will not change the approach to management and it is unclear whether awareness of increased risk will increase motivation for behaviour change, and may even decrease this. Regardless of the lack of utility of testing, it is important for public health and health care professionals to understand and be aware that weight loss and maintenance of a healthy weight will be particularly challenging for a significant proportion of the population with an increased genetic susceptibility to obesity.

There remain many more obesity susceptibility genes still to be identified, both rare single gene defects and common variants. Further research to identify these may bring a stratified approach to treatment. This is not yet the case in monogenic obesity, except in leptin deficiency, and is a very long way off in common obesity. However, the prospect remains and there is much research and commercial interest in this. Further research will also increase understanding of the aetiology and may point to potential pharmacological targets as yet undiscovered. Further research may also strengthen evidence for a continuum between monogenic and common obesity, with more of the monogenic genes identified as having a role in obesity in the general population.

4. Conclusions and recommendations

Obesity is an enormous and increasingly important problem worldwide. It causes significant physiological and psychological morbidity and mortality, and the costs to health care and wider society are high.

Obesity is a complex multifactorial condition, with both environmental and genetic determinants. UK guidelines and policy for prevention and management of obesity focus on the environmental causes. Although the heritability of BMI is 40-70%, guidelines make negligible mention of the role of genetics.

Knowledge about the genetic basis of obesity has been building over the past two decades, which has contributed greatly to the understanding of the biological basis of obesity. However it is only in the past few years, with the employment of new technologies, that understanding of the genetic contribution to obesity in the general population has increased.

Eight known genes have to date been implicated in the development of severe, early-onset obesity, in addition to one large deletion. Mutations in these genes are highly penetrant in producing this phenotype, which results from a greatly increased drive to eat from very early in life. Common to all of these genes is a central role in appetite control.

Whilst a pharmacological treatment only exists for one of the known monogenic causes of obesity, knowledge about the other genes provides drug targets for possible future development. In the absence of treatment however, knowledge of a monogenic cause for obesity can still increase understanding of the prognosis and help to ensure appropriate and tailored management for patients that acknowledges the challenges of weight loss in these individuals.

Genome-wide association studies in increasingly large cohorts have robustly associated 32 genomic loci with BMI in the general population, however in contrast to the monogenic forms of obesity, the utility of this knowledge for individuals is extremely limited at present, and these loci only account for 2% to 4% of the heritability of BMI. The growing body of evidence does, however, open up possibilities for future development of novel treatment and prevention strategies.

Further research will expand the discovery of novel genes and variants associated with adiposity, and may also strengthen evidence for a continuum between monogenic and common forms, with more of the monogenic genes identified as having a role in obesity in the general population. This will further improve our understanding of the genetic and biological basis of obesity and may present new opportunities for management.

Recommendations based on the current state of the evidence as synthesised in this review are outlined below. However, given the rapid accumulation of evidence in this area, the application of public health genomics in obesity is likely to expand in the long-term.

This report sets out recommendations based on the current state of evidence. However the application of public health genomics in obesity is likely to expand.

4.1 Recommendations: Polygenic obesity

I. There is currently no utility in testing for common obesity genes.

II. Direct-to-consumer genetic testing for obesity risk should not be recommended.

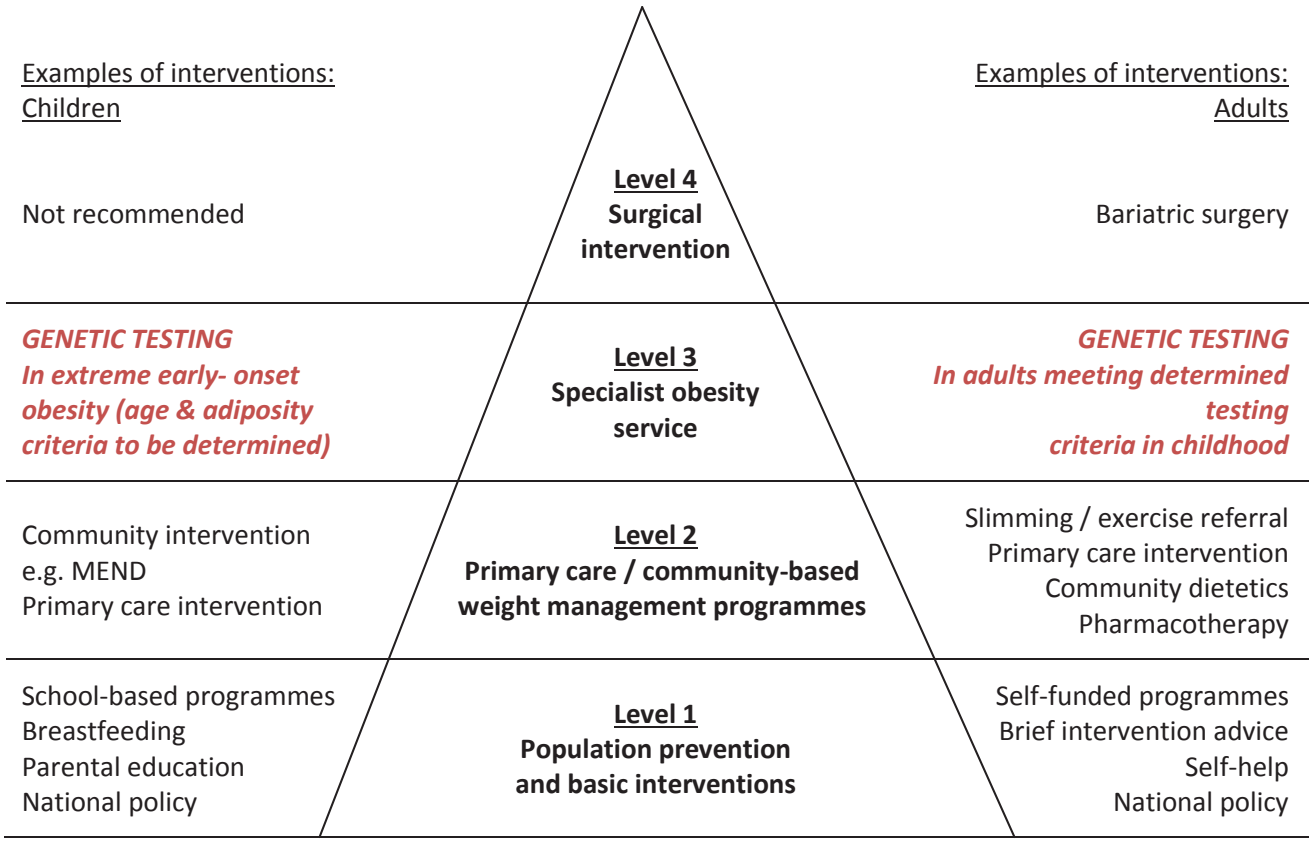
4.2 Recommendations: Monogenic obesity

I. 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 14), 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.

II. 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.

III. 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.

Figure 14. A suggested place for genetic testing in the obesity care pathway



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Appendix

Literature search strategy and results

1. GENETIC **Date: 12 02 17 Results: 2,660,575**

(("genetic"[All Fields]) OR ("gene"[All Fields]) OR ("genotype"[MeSH Terms] OR "genotype"[All Fields] OR "genotypic"[All Fields] OR "genotypes"[All Fields]) OR ("alleles"[MeSH Terms] OR "alleles"[All Fields] OR "allele"[All Fields] OR "allelic"[All Fields]) OR ("genetic variation"[MeSH Terms]) OR ("polymorphism, genetic"[MeSH Terms] OR ("polymorphism"[All Fields] AND "genetic"[All Fields]) OR "genetic polymorphism"[All Fields] OR "polymorphism"[All Fields]) OR ("genomics"[MeSH Terms] OR "genomics"[All Fields]) OR ("Genetic Predisposition to Disease"[All Fields]) OR ("Heritability"[All Fields]) OR ("familial"[All Fields] OR "family"[All Fields]) OR ("inherited"[All Fields] OR "inheritance"[All Fields])(

2. OBESITY **Date: 12 02 17 Results: 574,896**

(("obesity"[MeSH Terms] OR "obesity"[All Fields] OR "obese"[All Fields]) OR ("body weight"[MeSH Terms] OR ("body"[All Fields] AND "weight"[All Fields]) OR "body weight"[All Fields]) OR ("body weights and measures"[MeSH Terms] OR ("body"[All Fields] AND "weights"[All Fields] AND "measures"[All Fields]) OR "body weights and measures"[All Fields] OR "BMI"[All Fields]) OR

("body composition"[MeSH Terms] OR ("body"[All Fields] AND "composition"[All Fields]) OR "body composition"[All Fields]) OR ("body weight changes"[All Fields] OR "body weight change"[All Fields]))

3. GENETICS (AND) OBESITY **Date: 12 02 17 Results: 72,118**

4. (3) ENGLISH ONLY **Date: 12 02 17 Results: 67,595**

5. (4) (AND) ("Review" OR "Meta-analysis") [All Fields] **Date: 12 02 17 Results: 7,753**

(((((("genetic"[All Fields]) OR ("gene"[All Fields]) OR ("genotype"[MeSH Terms] OR "genotype"[All Fields] OR "genotypic"[All Fields] OR "genotypes"[All Fields]) OR ("alleles"[MeSH Terms] OR "alleles"[All Fields] OR "allele"[All Fields] OR "allelic"[All Fields]) OR ("genetic variation"[MeSH Terms]) OR ("polymorphism, genetic"[MeSH Terms] OR ("polymorphism"[All Fields] AND "genetic"[All Fields]) OR "genetic polymorphism"[All Fields] OR "polymorphism"[All Fields]) OR ("genomics"[MeSH Terms] OR "genomics"[All Fields]) OR ("Genetic Predisposition to Disease"[All Fields]) OR ("Heritability"[All Fields]) OR ("familial"[All Fields] OR "family"[All Fields]) OR ("inherited"[All Fields] OR "inheritance"[All Fields])))) AND (("obesity"[MeSH Terms] OR "obesity"[All Fields] OR "obese"[All Fields]) OR ("body weight"[MeSH Terms] OR ("body"[All Fields] AND "weight"[All Fields]) OR "body weight"[All Fields]) OR ("body weights and measures"[MeSH Terms] OR ("body"[All Fields] AND "weights"[All Fields] AND "measures"[All Fields]) OR "body weights and measures"[All Fields] OR "BMI"[All Fields]) OR ("body composition"[MeSH Terms] OR ("body"[All Fields] AND "composition"[All Fields]) OR "body composition"[All Fields]) OR ("body weight changes"[All Fields] OR "body weight change"[All Fields])) AND (English[lang]))) AND (review OR meta-analysis)

Table A1. Pleiotropic obesity syndromes

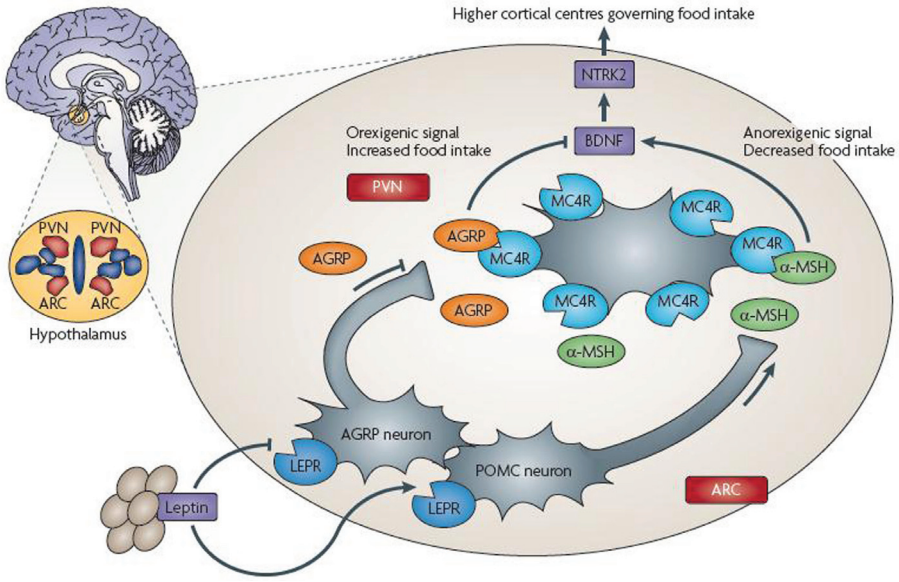
Syndrome	Mechanism of inheritance/ occurrence	Clinical features	Locus	Gene	Population Prevalence
Prader-Willi Syndrome	Majority sporadic; paternal locus absent due to deletion in 75% of cases, or the entire paternal chromosome 15 lost due to presence of two maternal chromosomes 15 in 25% of cases; familial recurrence is rare.	Severe hyperphagia 5-13y; diminished foetal activity; obesity; muscular hypotonia; mental retardation; short stature; hypogonadotrophic hypogonadism; small hands and feet. Syndrome is clinically and genetically heterogeneous.	15q11.2-q13	Deletion of paternal copies of the imprinted SNRPN gene, the necdin (NDN) gene, and possibly others with this region.	1-5/10,000
Fragile X Syndrome	X-linked dominant	Mild to severe intellectual deficit which may be associated with behavioural disorders and characteristic physical features; 30% of adolescents with obesity.	Xq27.3	FMR1	1-5/10,000
Albright hereditary osteodystrophy (Pseudohypo-parathyroidism type Ia)	Autosomal dominant; whether hormone resistance is exhibited is determined by the parental origin of the mutation, with an excess of maternal transmission suggesting genomic imprinting is involved in the expression of the disorder. Full expression of the disorder has been seen maternally transmitted cases, with partial expression in paternally transmitted.	Wide ranging manifestations including multiple hormone resistance; short stature; obesity; rounded face; subcutaneous ossifications and characteristic shortening and widening of long bones in the hands and feet; mental retardation in some patients. Many features associated with pseudo-hypoparathyroidism (resistance to PTH).	20q13.2	Heterozygous loss-of-function mutation in the GNAS1 gene, which is under parental imprinting. This encodes the alpha-stimulatory subunit of the intracellular G protein, which stimulates production of cAMP under certain physiologic conditions.	1-9/1,000,000
Alstrom Syndrome	Autosomal recessive	Multi-systemic ciliopathy characterised by cone-rod dystrophy, hearing loss, obesity, insulin resistance and hyperinsulinaemia, type 2 diabetes mellitus, dilated cardiomyopathy and progressive hepatic and renal dysfunction.	2p13.1	ALMS1	1-9/1,000,000

Table A1 continued overleaf

Syndrome	Mechanism of inheritance/occurrence	Clinical features	Locus	Gene	Population prevalence
Bardet-Biedl syndrome	Autosomal recessive with a modifier of penetrance; oligogenic in some cases (some forms require an additional mutation in a 2nd locus); genetically heterogeneous.	Ciliopathy with multisystem involvement, characterised by a combination of clinical signs: obesity, pigmentary retinopathy, post-axial polydactyly, polycystic kidneys, hypogenitalism, learning disabilities. Clinical expression is variable but most patients manifest the majority of signs during the disease course.	1p35.1	CCDC28B	1-9/1,000,000
			2p15	C2orf86	
			2q31.1	BBS5	
			3q11.2	ARL6	
			3q11.2	ARL6	
			4q27	BBS7	
			4q27	BBS12	
			7p14.3	PTHB1	
			8q22.1	TMEM67	
			9q33.1	TRIM32	
			11q13.2	BBS12	
			12q21.2	BBS10	
			12q21.32	CEP290	
			14q31.3	TTC8	
			15q24.1	BBS4	
			16q12.2	BBS2	
			17q22	MKS1	
			20p12.2	MKKS	
Cohen Syndrome	Autosomal recessive	Obesity, hypotonia, intellectual deficit, characteristic craniofacial dysmorphism and abnormalities of the hands and feet.	8q22-23	COH1	<1/1,000,000
Mehmo Syndrome	X-linked recessive	Severe intellectual deficit, epilepsy, microcephaly, hypogenitalism and obesity.	Xp21.1-22.13	Unknown	<1/1,000,000
Wilson-Turner Syndrome	X-linked recessive	Intellectual deficit, obesity, gynecomastia, speech difficulties, tapering fingers and small feet.	Xp21.1-22	Unknown	<1/1,000,000
Borjeson-Forssman-Lehmann Syndrome	X-linked recessive	Intellectual disabilties, hypogonadism, gynecomastia and obesity.	Xq26-27	PHF6	Unknown
Maternal uniparental disomy chromosome 14	Prader-Willi-like phenotype, symptoms including early onset obesity and reduced adult height.	14	-	Unknown	Unknown

Appendix

Figure A1. The leptin-melanocortin pathway (figure and text from Walley, 2009[34])



Leptin released from adipose tissue binds to leptin receptors (LEPR) on agouti-related protein (AGRP)-producing neurones, and pro-opiomelanocortin (POMC)-producing neurones in the arcuate nucleus (ARC) of the hypothalamus. Leptin binding inhibits AGRP production and stimulates POMC production. POMC then undergoes post-translational modification to generate a range of peptides, including α-, β- and γ-melanocyte-stimulating hormones (MSH). Prohormone convertase 1/3 is involved in this post-translational processing (PC1/3, not shown here). AGRP and α-MSH compete to bind to the melanocortin-4 receptor (MC4R), with AGRP binding suppressing activity and α-MSH binding stimulating MC4R activity. Increased MC4R activity generates an anorexigenic (appetite suppressing) signal, whilst decreased activity stimulates an orexigenic signal (appetite stimulating). Signals from MC4R govern food intake through secondary effector neurones, which lead to higher cortical centres. This process involves brain-derived neurotrophic factor (BDNF) and neurotrophic tyrosine kinase receptor type 2 (NTRK2, also known as tropomyosin-related kinase B, TRKB)

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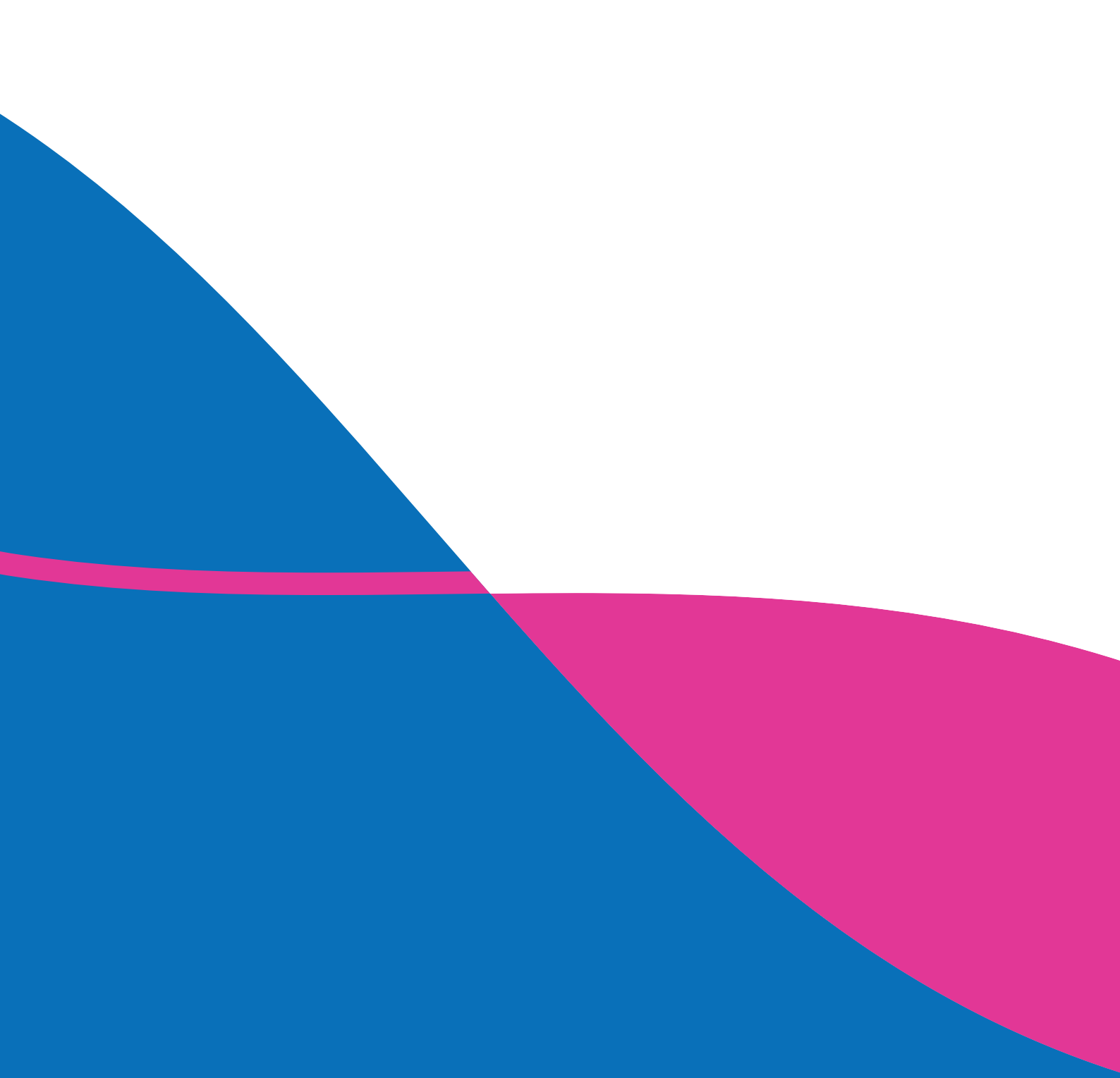

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