The Academy of Medical Sciences

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Diabetes and obesity: getting to the heart of the matter

Report from a joint symposium of the Academy of Medical Sciences and the Royal Society of Edinburgh

January 2011

The Academy of Medical Sciences

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THE ROYAL SOCIETY OF EDINBURGH

Diabetes and obesity: getting to the heart of the matter

Symposium report

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Summary

Rates of obesity and diabetes are increasing globally. The UK has experienced a particularly large rise in obesity prevalence and an associated increase in type 2 diabetes incidence. A similar trend is now emerging in developing countries. On 26 May 2010, the Academy of Medical Sciences and the Royal Society of Edinburgh hosted a joint symposium, 'Diabetes and obesity: getting to the heart of the matter' to: discuss the changing trends, consider contemporary findings in diabetes and obesity research, identify the wider implications for future research directions in the field and explore future opportunities to develop better preventative strategies. This report summarises the themes and issues raised during the event. Key points include:

- **Obesity and diabetes will be responsible for a growing burden of disease in the next 20 years, with the highest increases in developing countries.** The rise in obesity and diabetes already seen in the UK and other developed countries represents a heavy burden for healthcare systems. However, the prevalence of these diseases is now rising in developing countries and the circumstances are complex; for example, increasingly cases of both over- and under-nutrition exist within the same household.
- **Research on genetics and other biological mechanisms is providing new insights, which are expected to lead to better treatments.** Research into genetics, epigenetics and metabolic pathways is beginning to reveal the biological differences between individuals who become obese and those who stay lean in the face of an 'obesogenic' environment. This research offers the opportunity to identify individual risk factors and stratify treatments, increasing efficacy and reducing toxicity.
- **Foetal development is important in establishing a predisposition to disease in later life and there may be critical periods for positive intervention during development.** Identifying the factors that predispose people to obesity and diabetes will be helpful in determining how we might identify individuals who are at risk and develop effective interventions.
- **Determining the most effective management strategies will be central to reducing the incidence of obesity and diabetes. Academia and industry are seeking new, creative approaches to treatment.** For type 2 diabetes patients, current drugs do not consistently offer tight enough control of blood glucose. Developing new drugs with a more durable and accurate effect on blood glucose control will improve the quality of care for these patients.
- **Novel technologies, including imaging, offer promise for understanding the mechanisms of the complications of diabetes and obesity in humans and to speed drug discovery.** Progress is currently being made in molecular imaging techniques, which may in future allow real-time patient monitoring at the bedside and potentially improve diagnostics and drug delivery, guide intervention choices, help to identify new therapeutic targets and enhance drug trials.
- **There is growing evidence to support particular policy interventions that may be helpful in preventing obesity, but better quality evidence is needed.** National strategies should seek to prevent individuals from developing diabetes and obesity, as well as treating patients already diagnosed. Government policy interventions can be made within the

physical, economic, political and socio-cultural environments, and can be directed at entire populations or individuals. Scientific evidence and robust evaluation can help to assess which interventions are most likely to be effective and reach the largest proportion of people, and thus which are worthy of further consideration by policy makers.

- **Comprehensive patient information systems can help improve care and increase participation in clinical trials.** As management strategies improve, translating them into patient benefits should be a central focus for health policy. Using informatics to improve patient monitoring and to increase the availability of data and volunteers for research studies will help to improve the management of risk factors. It will also provide a useful mechanism for assessing the quality and safety of newly introduced management strategies.

The discussions clearly highlighted some important areas for **future research,** which should seek to:

- Refine understanding of the contributions of genetic and epigenetic, early life and adult factors to the development of the obesity-diabetes-metabolic disease continuum and to individual risk in humans.
- Examine mechanisms of pathogenesis, in particular exploiting known and novel pathways revealed by genetic and epigenetic data.
- Consider how findings can be applied to develop effective validated biomarkers of such risk, particularly to define those most likely to develop complications.
- Provide a comprehensive evidence base to define effective interventions for patients affected or at risk.
- Develop evidence-based pragmatic policy interventions to reduce population risk.

1 Introduction

Obesity is a medical condition characterised by an individual having excess body fat caused by a higher energy intake than expenditure. The excess energy must be stored and this is done in the form of adipose tissue, leading to an increase in body mass. The health implications of obesity are significant as it is associated with a number of other conditions, including type 2 diabetes, cardiovascular diseases, cerebrovascular diseases, and certain types of cancer.[1] Obesity is conventionally measured through calculating an individual's body mass index (BMI) (see Box 1).

Diabetes mellitus is a disease that affects the individual's ability to control their blood sugar levels:

- Type 1 diabetes is usually present in children and is characterised by the body's failure to produce insulin, the hormone that causes a fall in blood glucose levels. Insulin is produced and released by the beta cells in the pancreas, but auto-immune destruction of these cells means that they do not function properly in type 1 diabetes patients, thus patients must inject the hormone to control their blood sugar.
- Type 2 diabetes is more common, approximately 90% of diabetes is type 2 and it more often affects adults.[2] Patients gradually become resistant to the effects of insulin, despite maintaining the ability to produce it. They must control their blood sugar through lifestyle changes and possibly drugs. However, as the disease progresses, pancreatic beta cell function diminishes and patients may need to supplement existing treatments with insulin. Obesity is associated with insulin resistance and the subsequent risk of type 2 diabetes, thus the main risk factor for type 2 diabetes is obesity, with 90% of people with type 2 diabetes having a BMI of more than 23 kg/m^2.[3] Type 2 diabetes is a more heterogeneous entity, in terms of its pathogenesis, than type 1. Further types of diabetes also exist, relating to specific genetic mutations affecting beta cells or insulin action.

Both types of diabetes are associated with a substantial risk of serious complications, notably accelerated atherosclerotic heart disease, eye disease, kidney disease, peripheral vascular disease and nerve damage. The incidence of these complications is significantly reduced with successful treatment of the underlying diabetes and obesity.

Box 1 Body Mass Index (BMI)

Body mass index (BMI) measures weight relative to height: an individual's weight (kg) is divided by the square of their height (m^2) to give a value in kg/m^2. A BMI between 18.5 kg/m^2 and 25 kg/m^2 is considered normal, 25-30 kg/m^2 is overweight, 30-40 kg/m^2 is an obese BMI and individuals with a BMI over 40 kg/m^2 are deemed to be morbidly obese. Evidence also suggests that the distribution of adiposity matters, adipose tissue located in the body trunk, especially in the abdomen, engenders much more metabolic disease risk than 'safe stores' in subcutaneous fat depots.

The western world has seen a significant rise in the incidence of obesity and diabetes over the last few decades. This trend is now spreading across the globe and the burden of these conditions and the associated chronic health implications has received attention internationally from governments. The World Health Organisation (WHO) has deemed

1 Kopelman P (2007). *Health risks associated with overweight and obesity.* Obesity reviews **8(s1)**, 13-17.
2 World Health Organisation (2010). *Diabetes.* http://www.who.int/mediacentre/factsheets/fs312/en/
3 Kopelman P (2007). *Health risks associated with overweight and obesity.* Obesity reviews **8(s1)**, 13-17.

the rise in obesity to be a global epidemic, estimating that over 1 billion adults worldwide are overweight and that at least 300 million of these people are obese.[4] Obesity prevalence in the UK is amongst the highest in the world and in 2007, the UK Government Office for Science commissioned Foresight to produce a report on the topic, 'Tackling Obesities: Future Choices'. It estimated that by 2050, 60% of men and 50% of women in the UK could be obese.[5] Such high figures have been challenged, for example, data from the US Centers for Disease Control and Prevention (CDC) suggest that obesity may asymptote at around 30-35% in the West.[6] However, even figures of 30% represent obesity levels that will be accompanied by significant economic impacts. The Foresight report predicted that the cost to the NHS of dealing with overweight and obese people could reach almost £10 billion per year by 2050 and the wider costs to society and business of obesity and associated conditions could reach £49.9 billion per year.

Scotland has a particularly high rate of obesity and is home to an active diabetes and obesity research community.[7] The Scottish Government has paid particular attention to the topic as a national health problem, supporting research and looking for opportunities to utilise promising initiatives in this area. For example, the Government is funding a national database of diabetes patients with the aim of improving the quality of patient care and the availability of data and volunteers for research into the condition. Scotland therefore provided an appropriate location for a one-day symposium to discuss the latest findings of research in this area and its implications, and also provided an opportunity for the Academy of Medical Sciences and the Royal Society of Edinburgh to collaborate on their first joint symposium on a topic of mutual concern.

The symposium featured experts from within Scotland and across the UK and was chaired by Professor Jonathan Seckl FRSE FMedSci. Speakers' presentations and subsequent discussions began by considering the current trends in obesity and the role of genetics, epigenetics and other factors in predisposing individuals to these conditions (Chapters 2 and 3). The focus then moved to management strategies, including the role of exercise and emerging therapies (Chapter 4). Finally, speakers considered how policy interventions might help tackle the obesity epidemic and the role of informatics in enhancing the translation of research into healthcare benefits (Chapters 5 and 6). The meeting was attended by around 170 delegates, including researchers, research funders, and representatives from industry, the NHS, government and professional bodies (see Annexes I and III for the symposium programme and list of delegates).

This report seeks to capture the themes and issues that emerged from the symposium and does not necessarily represent the views of the Academy of Medical Sciences or the Royal Society of Edinburgh. The report will be of interest to researchers, policy makers, research funders, industry, patients and other stakeholders. Key areas covered by the presentations and discussions at the event and included in this report are:

- Trends in diabetes and obesity
- Genetics, epigenetics and beyond
- Emerging management strategies
- Translation and the role of informatics
- Policy interventions and the future

4 World Health Organisation (2010). *Global strategy on diet, physical activity and health: obesity and overweight.* http://www.who.int/dietphysicalactivity/publications/facts/obesity/en/

5 Foresight (2007). *Tackling obesities: future choices. Summary of key messages.* http://www.foresight.gov.uk/Obesity/20.pdf

6 Flegal KM, *et al.* (2010). *Prevalence and trends in obesity among US adults, 1999-2008.* Journal of the American Medical Association **303**, 235-241.

7 In 2008, obesity prevalence in Scotland was 26.0% for men and 27.5% for women, compared to 24% and 25%, respectively, in England. In 2005, the UK averages were 23% and 25%. For more information, see the Scottish Health Survey 2008: http://www.scotland.gov.uk/Resource/Doc/286063/0087158.pdf and the NHS Health Survey for England 2008: http://www.ic.nhs.uk/webfiles/publications/HSE/HSE08trends/Health_Survey_for_england_trend_tables_2008.pdf. For UK prevalence, see: Rennie KL & Jebb SA (2005). *Prevalence of obesity in Great Britain.* Obesity Reviews **6**, 11-12.

2 Trends in diabetes and obesity

Global trends

The western world has seen a significant rise in the incidence of diabetes and obesity over the last 20 years. A number of factors may have contributed towards this trend, including increases in the availability and diversity of food, meaning that diets now consist of more high fat, salt and sugar (HFSS) foods than they did in the 1950s and 1960s. However, there is some evidence to suggest that this increase in obesity and its complications may in fact be reaching a plateau. The great concern for the next 20 years is the rising levels of these conditions in developing countries.

At the meeting, Professor Nishi Chaturvedi, Professor of Clinical Epidemiology at Imperial College London, summarised the predicted future trends in diabetes and obesity. In the West, the number of people with diabetes in the United States was forecast to rise from 17 million in 2000 to an estimated 30 million by 2030 and these predictions appear to be holding up, with an estimated 20 million adult cases reported in 2006.[8,9] In the UK, the figure was estimated to rise from 1.8 to 2.7 million over the same period.[10] Many western countries saw a two-fold increase in childhood obesity between the 1980s and the turn of the millennium, but there is evidence that this rise may be reaching a plateau in the UK, even declining slightly amongst girls.[11,12] Such trends have also been observed in the US, where adult obesity rates may also be beginning to plateau as prevalence, particularly amongst women, does not appear to be increasing at the same rate as previously.[13]

There is, however, a marked difference in this trend between different socioeconomic groups, with the manual social classes having a greater projected prevalence than the non-manual social classes. The precise reasons for this gap are unclear. It may be because higher socioeconomic groups tend to follow health advice and recommendations (for which there may be several reasons: these groups may respond more positively to the messages or their circumstances might mean that they are more able to respond).[14] Alternatively, it might be that the stabilisation in obesity prevalence is taking longer to occur among children from manual households than non-manual. The data do not currently allow a clear conclusion to be drawn.[15]

Professor Chaturvedi emphasised that the greatest future burden of diabetes and obesity will be in developing countries such as India and China. Demographic trends, ethnic susceptibility, and the intrinsic link between rising obesity levels and type 2 diabetes incidence are all contributing to worrying rises in diabetes and obesity in these countries. The percentage of obese individuals in China increased from 16.1% to 23.2% between 1992 and 2002, across both rural and urban areas.[16] It had been estimated that there would be 42 million cases of diabetes in China by 2030, but this figure has already been surpassed, with an estimated 92 million diabetic adults in the country in 2007.[17,18]

In India, predictions suggest that the number of people with diabetes is set to more than double to almost 80 million by 2030.[19] However,

8 Wild S, *et al.* (2004). *Global prevalence of diabetes: estimates for the year 2000 and projections for 2030.* Diabetes Care **27**, 1047-1053.
9 Cowie CC, *et al.* (2010). *Prevalence of Diabetes and High Risk for Diabetes Using haemoglobin A1C Criteria in the U.S. Population in 1988–2006. Diabetes Care* **33**, 562-568.
10 Wild S, *et al.* (2004). *Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030* (Appendix: Number of people with diabetes). Diabetes care **27**, 1047-1053.
11 Ebbeling CB, *et al.* (2002). *Childhood obesity: public-health crisis, common sense cure.* The Lancet **360**, 473-482.
12 Stamatakis E, *et al.* (2010). *Time trends in childhood and adolescent obesity in England from 1995 to 2007 and projections of prevalence to 2015.* Journal of Epidemiology and Community Health **64**, 167-174.
13 Flegal KM, *et al.* (2010). *Prevalence and trends in obesity among US adults, 1999-2008.* Journal of the American Medical Association **303**, 235-241.
14 Adler NE, *et al.* (1994). *Socioeconomic status and health: the challenge of the gradient.* American Psychologist **49**, 15-24.
15 Stamatakis E, *et al.* (2010). *Time trends in childhood and adolescent obesity in England from 1995 to 2007 and projections of prevalence to 2015.* Journal of Epidemiology and Community Health **64**, 167-174.
16 Wang Y, *et al* (2007). *Is China facing an obesity epidemic and the consequences? The trends in obesity and chronic disease in China.* International Journal of Obesity **31**, 177-188.
17 Wild S, *et al.* (2004). *Global prevalence of diabetes: estimates for the year 2000 and projections for 2030.* Diabetes Care **27**, 1047-1053.
18 Yang W, *et al.* (2010). *Prevalence of diabetes among men and women in China.* New England Journal of Medicine **362**, 1090-1101.
19 Wild S, *et al.* (2004). *Global prevalence of diabetes: estimates for the year 2000 and projections for 2030.* Diabetes Care **27**, 1047-1053.

Professor Chaturvedi warned that this figure may also prove to be too modest, with significant rises already evident in both urban and rural communities of India.[20] A further concerning phenomenon is the degree of co-existence of over- and under- nutrition within a single household in the developing world.[21] This trend adds to the challenge of managing the epidemic as strategies cannot simply target weight loss treatment and advice to entire households because underweight individuals may inadvertently be affected. Undernourishment may also further compound the problem of diabetes and obesity because individuals with a low birth weight, perhaps as the result of under-nutrition during development, have an increased risk of diabetes later in life, particularly if they also become obese.[22] The WHO reports that almost 80% of diabetes deaths occur in low- and middle- income countries and a WHO joint initiative with the International Diabetes Federation, 'Diabetes action now', is designed to support the development of effective surveillance, prevention and control of diabetes in these countries.[23]

The implications of these trends

Increasing rates of diabetes and obesity will add to the global burden of disease, particularly cardiovascular and cerebrovascular disease. Mortality in the UK from heart disease has fallen by 50% since 1980 and almost 60% of this decline can be attributed to reductions in cardiovascular risk factors, principally smoking, hypertension and high cholesterol.[24] Professor Chaturvedi warned that the rise in obesity and diabetes incidence may arrest this decline. For example, one study indicated that for individuals admitted to hospital with acute coronary syndromes, those with a higher fasting glucose level (which is associated with lower insulin sensitivity and eventually diabetes) had a significantly increased risk of dying in hospital or during the 6 months after discharge, irrespective of whether the individual had a history of diabetes.[25] Although levels of diabetes and obesity in the developed world may be levelling off (the reasons for which need to be explored), the worrying divergence in obesity rates with socio-economic status has further implications for the future burden of cardiovascular and cerebrovascular diseases in these countries.

Given the predicted trends in diabetes and obesity in developing countries, cardiovascular and cerebrovascular diseases are a major concern here and the environments are complex. There is increasing evidence that development in the womb can create permanent change in organ and tissue structure that can predispose infants to chronic diseases such as type 2 diabetes, cardiovascular disease and certain types of cancer in later life.[26] A study in India gave nutritional supplements to pregnant and breast-feeding mothers and children up to 6 years old.[27] It found that providing supplements to this undernourished population was associated with lower risks of cardiovascular disease later in life, specifically in adolescence and concluded that '*improved maternal and child nutrition may have a role in reducing the burden of cardiovascular disease in low income and middle income countries'.* This evidence suggests that there may be critical periods during development that determine future risk and may therefore be good targets for influencing disease risk. However more data are needed to establish whether or not this is the case and to determine when the critical points for intervention are. Aside from this, further research is required to design effective interventions to address the epidemic of diabetes and obesity in the developing world.

20 Ramachandran A, *et al.* (2008). *High prevalence of diabetes and cardiovascular risk factors associated with urbanisation in India.* Diabetes Care **31**, 893-898.
21 Doak CM, *et al.* (2005). *The dual burden household and the nutrition transition paradox.* International Journal of Obesity **29**, 129–136.
22 Whincup PH, *et al.* (2008). *Birth weight and risk of type 2 diabetes: a systematic review*. Journal of the American Medical Association **300**, 2886-2897.
23 For more information on this initiative see http://www.who.int/diabetes/actionnow/en/DANbooklet.pdf
24 Unal B, *et al.* (2004). *Explaining the decline in coronary heart disease mortality in England and Wales between 1981 and 2000.* Circulation **109**, 1101-1107.
25 Sinnaeve PR, *et al.* (2009). *Association of elevated fasting glucose with increased short-term and 6-month mortality in ST-Segment Elevation and Non–ST-Segment Elevation Acute Coronary Syndromes.* Archives of Internal Medicine **169**, 402-409.
26 Martin-Gronert MS, *et al.* (2010). *Mechanisms linking suboptimal early nutrition and increased risk of type 2 diabetes and obesity*. Journal of Nutrition **140**, 662-666.
27 Kinra S, *et al.* (2008). *Effect of integration of supplemental nutrition with public health programmes in pregnancy and early childhood on cardiovascular risk in rural Indian adolescents: long term follow-up of Hyderabad nutrition trial.* British Medical Journal **337**, a605.

3 Genetics, epigenetics and beyond

Genetics

Genetics of obesity

The increased prevalence of obesity seen over the last few decades has been caused by environmental factors, rather than genetics. However, evidence suggests that there is a biological difference between individuals who develop obesity and those who stay slim in the face of an environment where increased food availability and diversity means that we are now consuming more high fat, salt and sugar (HFSS) foods than before, and are arguably less active. Genes play an important role in producing this variation.

Body weight is continuously distributed across societies and the distribution shifts due to environmental factors, for example falling during times of war or famine, or rising during periods of relative affluence. Within any environment, the concept of 'heritability' provides an estimate of the proportion of the difference between any two people in that distribution that is attributable to genetically inherited factors (rather than their environment, either shared or unique). Studies over many decades have consistently shown that between 60% and 80% of adiposity (body fat composition) is inherited. For example, identical twins separated as children have remarkably similar body shapes in adulthood, despite growing up in different environments.[28] The majority of genes influencing human obesity appear to be predominantly expressed in the brain, rather than in the adipose tissue. Thus, control over energy intake, rather than energy expenditure, appears to be the dominant genetic factor in human obesity.

Professor Stephen O'Rahilly FRS FMedSci, Professor of Clinical Biochemistry and Medicine at the University of Cambridge, reported at the meeting that genetic disorders that result in obesity often involve disruption of brain satiety mechanisms. Genetic analysis of children with extreme cases of either obesity or insulin resistance has led to the discovery of a number of novel disorders involving one gene (monogenic), the causative genes of which are highly expressed in the brain and tend to influence food intake. One such gene controls the hormone leptin, which is released by adipose tissue and contributes towards regulating food intake in the brain. In the absence of leptin, appetite is uncontrolled and children with this defect consume more food than their body needs. The genes identified by studying these monogenic disorders also point towards genes that may contribute to polygenic disorders, responsible for the cases of obesity that lie between the extreme monogenic examples studied. However, further work is needed to establish the polygenic factors of obesity susceptibility, as much of this variation is still unaccounted for. What genetic studies to date do suggest is that in the future, obesity might be considered a neuro-behavioural disorder that is highly sensitive to environmental factors, rather than a metabolic disease.

Genetics of diabetes

Major advances have been made in understanding the genetic components of type 2 diabetes in recent years. More than 35 variants have now been identified that are associated with the condition and most appear to result in impaired pancreatic beta cell function (the cells in the pancreas that produce and release insulin in response to high blood glucose). With age, all individuals gain weight and see a fall in the sensitivity of their tissues to insulin. The result is a need to increase insulin secretion, but the ability to compensate in this manner varies between individuals and it is those with a low capacity to increase insulin production who develop diabetes. These are also the individuals who carry the genetic variants identified for type 2 diabetes. Despite

28 Stunkard AJ, *et al.* (1990). *The body-mass index of twins who have been reared apart.* New England Journal of Medicine **323**, 1483-1487.

recent progress in understanding, Professor Leif Groop, Professor of Endocrinology at Lund University in Sweden, told the meeting that variants identified to date account for only 15% of the total inherited risk. The genetic architecture involved is complex. For example, the impact of some genetic alleles on diabetes development can be higher if the individual also has an elevated BMI.

Genome wide association studies, and the sequencing and quantifying of RNA expressed in key tissues will be crucial to making progress in understanding the genetics of both type 2 diabetes and obesity. This could subsequently support the development of reliable genetic analysis methods that might help to predict individual risk to these diseases and improve our ability to tailor treatments to the individual.

The link between obesity and type 2 diabetes

It will also be important to reveal the mechanisms by which obesity progresses to insulin resistance. This is characterised by the incapacity of beta cells to compensate for the increased insulin demand described above, which is associated with energy imbalance, as well as the natural ageing process. Higher energy intake than expenditure leads to accumulation of adipose tissue mass and defective insulin signalling in liver and muscle. The most prevalent view is that the increased volume of fat tissue causes this defective signalling through altered production of secreted factors, generally termed adipocytokines. However, Professor O'Rahilly presented two alternative hypotheses that might explain the connection:

- It could be that increased adipose tissue does not cause defective insulin signalling, but that adipose cells are merely an 'innocent bystander' in a system where the two phenomena co-occur.
- Alternatively, adipose cells might play a protective role in delaying the onset of diabetes in a model where body mass expands to absorb the disproportionate energy intake, meaning that the liver and muscles are only affected once the adipose tissue can no longer compensate for the excess energy.

The precise mechanisms are unclear and understanding adipose cell biology will be crucial in making progress in this area. Greater knowledge and understanding of the molecular circuitry that is disrupted in obesity will lead to more effective treatments.

A role for the epigenome?

As well as determining the genetic basis of susceptibility to diabetes and obesity, the role of epigenetics in regulating gene expression is also important. The environment experienced in early life can have an important impact on adult development. For example, low birth weight is linked to a greater risk of diabetes and other metabolic disorders in later life.[29] During the Dutch famine from 1944 to 1945, babies born to mothers who had experienced famine were underweight and at highest risk of developing diabetes in later life.[30] This phenomenon of early life programming is an adaptive, biological process; it appears to have developed for specific reasons, but these are not yet fully understood.

Low birth weight indicates that a neonate experienced a challenging environment before birth. Possible mechanisms linking this kind of environment to adult diseases include genetics, environmental factors (e.g. uterine size) and maternal factors (e.g. maternal nutrition). These variables may in turn be influenced by epigenetic factors, which influence gene expression by changing the genome, for example via histone modification and DNA methylation, without altering the underlying DNA. For example, in genetically identical

29 Whincup PH, *et al.* (2008). *Birth weight and risk of type 2 diabetes: a systematic review.* Journal of the American Medical Association **300**, 2886-2897.
30 Heijmans BT, *et al.* (2008). *Persistent epigenetic differences associated with prenatal exposure to famine in humans.* Proceedings of the National Academy of Sciences of the USA **105**, 17046-17049.

mice, maternal diet can influence offspring coat colour.[31] If the diet is high in methyl donors (molecules that donate methyl groups to others), it causes altered DNA methylation at a gene that influences coat colour, changing the expression of this gene.

Research has begun to identify possible epigenetic risk factors for diabetes and obesity in humans. Insulin-like growth factor II (IGF2) is an imprinted gene which is important in early human growth and development. It is expressed exclusively from the paternal allele and DNA methylation plays a key role in regulating gene expression. Altered methylation at this locus may therefore impact on gene expression. Changes in IGF2 methylation are associated with higher BMI in adults aged 40 and individuals exposed to the Dutch famine *in utero* continue to have altered IGF2 methylation six decades later.[32,33] The alterations in methylation in these studies are small, but may be of significance since methylation differences in the order of 10-20% are associated with profound effects on growth and development as seen in the overgrowth and growth retardation disorders, Beckwith-Wiedemann and Silver-Russell syndromes.[34] Dr Amanda Drake, MRC Clinician Scientist at the University of Edinburgh, therefore suggested at the symposium that smaller variations in such methylation could affect disease risk, e.g. for obesity, in the wider population.

The effects of epigenetic influences on early life programming are not limited to first-generation offspring, they can be multigenerational. Human and animal studies have demonstrated that a tendency to glucose intolerance can be transmitted from a parent to the first and second generation offspring, but transmission stops by the third and there is evidence that some multigenerational effects are sex-specific to the male line.[35,36] Moreover, other such programmed effects might be transmissible beyond the second generation.[37] The underlying mechanisms for the transmission of programmed effects across generations are unclear, but developing our understanding of them could have significant implications for improving human health. For example, we may be able to develop interventions that reduce the negative effects of early life programming and to subsequently target them to critical developmental periods, during which they are likely to have the greatest effect.[38] However, designing such interventions will be a complex process as the results will not be consistent across all communities, thus research and careful evaluation will be crucial to devising effective strategies for multiple populations.

Metabolism

Although the brain and the pancreas have been highlighted as the main sites that determine susceptibility to obesity and diabetes, much of the residual variance in risk, and the potential for modifying risk, may lie in peripheral metabolic tissues such as the adipose tissue and liver. Many of the individual metabolic pathways involved in obesity and diabetes have been identified, but studies must now explore how these pathways are integrated, so that we can understand the wider physiology of metabolic processes and how they might contribute to disease development.

Current knowledge of complex peripheral metabolic pathways and systems is based largely on genetically modified mouse models, the findings of which cannot necessarily be

31 Waterland RA & Jirtle RL (2004). *Early nutrition, epigenetic changes at transposons and imprinted genes, and enhanced susceptibility to adult chronic diseases.* Nutrition **20**, 63-68.
32 Drake AJ & Reynolds RM (2010). Currently unpublished.
33 Heijmans BT, *et al.* (2008). *Persistent epigenetic differences associated with prenatal exposure to famine in humans.* Proceedings of the National Academy of Sciences of the USA **105**, 17046-17049.
34 Murrell A, *et al* (2008). *Distinct methylation changes at the IGF2 locus in congenital growth disorders and cancer.* PLoS ONE **3**, e1849.
35 Drake AJ, *et al.* (2005). *Intergenerational consequences of fetal programming by in utero exposure to glucocorticoids in rats.* American Journal of Physiology: Regulatory, Integrative and Comparative Physiology **288**, R34-R38.
36 Pembrey ME, *et al.* (2006). *Sex-specific, male-line transgenerational responses in humans.* European Journal of Human Genetics **14**, 159-166.
37 Benyshek DC (2006). *Glucose metabolism is altered in the inadequately-nourished grand-offspring (F3 generation) of rats malnourished during gestation and perinatal life.* Diabetologia **49**, 1117-1119.
38 Drake AJ & Liu L (2010). *Intergenerational transmission of programmed effects: public health consequences.* Trends in Endocrinology and Metabolism **21**, 206-213.

extrapolated to humans. Many human studies focus on individuals with extreme phenotypes, so a further challenge is to understand the physiology of the wider population, who lie between these extremes. Studying integrated pathways and extrapolating between model species and humans presents substantial technological challenges.

These challenges were illustrated at the symposium by Professor Brian Walker, Professor of Endocrinology at the University of Edinburgh, using the example of 11ß-hydroxysteroid dehydrogenase type 1 (11ß-HSD1), an enzyme that amplifies intracellular glucocorticoid concentrations. In mice, this enzyme responds to nutritional and inflammatory states. Inhibiting it protects mice from metabolic syndrome, and increasing enzyme activity causes obesity and metabolic syndrome. Studying 11ß-HSD1 in humans has required extensive methodological development, including novel stable isotope tracers, imaging tools, genetic analyses and bio-markers. The results have contributed to successful translation of findings in mice into novel 11ß-HSD1 inhibitors that are effective in humans, and allow prediction and monitoring of individual patient's responses to treatment. However, the resources required to dissect each pathway at this level of detail are very substantial, and prioritising pathways worthy of investment is a key challenge for the future.

4 Emerging management strategies

The role of physical activity

Management strategies aim to reduce body mass and improve patients' overall health, including susceptibility to, and development of, diabetes. A combination of dieting and increased physical activity has been the principle approach to date and this remains the primary strategy, even though a selection of drugs are now on the market. A healthy diet is agreed to be an effective method of controlling and reducing body mass. However, more debate exists around the extent to which increasing exercise levels can specifically help to reduce body mass.

Professor John Speakman FRSE FMedSci, Director of the Institute of Biological and Environmental Sciences at the University of Aberdeen, outlined this debate at the symposium, reporting that the body's ability to maintain a healthy body weight may have been underestimated. He suggested that the obesity epidemic has not been caused by sustained small increases in energy intake over time or by small reductions in physical activity, as is commonly suggested. He believes that the view that small differences in energy balance are sufficient to drive large increases in body mass is based on a flawed model, which assumes fat is only a passive recipient of the stored energy. However, deposited adipose tissue not only stores excess energy, but both burns energy and requires an individual to use more energy in transporting it around, leading to increases in lean tissue mass, which burns even more energy. Thus a small increase in energy intake also leads to a small increase in expenditure, resulting in a new balance between the two. When individuals are in positive energy balance, body mass will rise slightly, but only until the new balance is established, which is generally only a small increase if the original imbalance is also small. Thus, minor changes in diet or exercise do not have the significant effects on weight that it is often suggested they do and much larger changes in energy balance are required to become obese.

Professor Speakman also challenged the notion that physical activity has significantly decreased over the time course of the epidemic. There have undoubtedly been changes in the way we lead our lives over the past few decades, with large rises in car ownership and in sedentary activities such as watching television. Such changes in lifestyle may have had a relatively small effect on our overall energy expenditure levels because the activities that have declined have been replaced by other activities that burn similar amounts of energy. For example, television viewing has increased tremendously since the 1950s, but it is mostly performed at a time when people were previously sedentary anyway: either listening to the radio or reading or, before the invention of the electric light, sleeping. Thus, Professor Speakman suggested that what appear to be large lifestyle changes do not necessarily translate into the large differences in energy expenditure that are necessary to cause obesity. A study in the Netherlands that compared people over the period between 1983 and 2005 found no change in physical energy expenditure levels.[39] During this period, obesity rates in the Netherlands rose from 4% to 10%.[40] The USA saw a larger increase in obesity rates from 20% to 32% over a similar period, but Professor Speakman reported that US physical activity levels were still unchanged

39 Westerterp KR & Speakman JR (2008). *Physical activity energy expenditure has not declined since the 1980s and matches energy expenditures of wild mammals.* International Journal of Obesity **32**, 1256-1263.
40 Schokker DF, *et al.* (2007). *Prevalence of overweight and obesity in the Netherlands.* Obesity Reviews **8**, 101-107.

over this timescale.[41,42,43] The increase in the prevalence of obesity was already underway in the 1980s and there is no accurate method of comparing current data on physical activity with that from before the epidemic began in the West. Comparing activity levels to those in non-westernised rural societies of developing countries is the closest comparison that can be made to the western lifestyle before the epidemic began. Comparing such data with that from the USA and the Netherlands still reveals no difference in levels of energy expenditure.[44]

Professor Speakman suggested that the level of exercise required to significantly lower body mass and therefore to reduce an obese BMI to a more healthy one is large and, in most cases, incompatible with today's lifestyle; for example, four hours of walking or two hours of cycling each day. He proposed that moderating food intake should be the primary strategy for treating obesity.

The session prompted much discussion amongst delegates and Professor Speakman emphasised that whether or not physical activity impacts body mass, there is no doubt that exercise offers many other health benefits, including reducing the risk of developing heart disease and type 2 diabetes. One of the mechanisms for such benefits is through activation of AMP activated protein kinase (AMPK). Professor Grahame Hardie FRS FRSE FMedSci, Professor of Cell Signalling at the University of Dundee explained that AMPK is activated in rats after 5 minutes on a treadmill, an effect that is prolonged following cessation of the activity.[45] AMPK is a cellular energy sensor with multiple functions; activating it stimulates glucose uptake and breakdown (and thus reduces circulating glucose), increases fatty acid uptake and inhibits synthesis of glucose, fatty acids, cholesterol and triglycerides. Thus, drugs that activate AMPK may be good therapeutic strategies for treating or preventing type 2 diabetes and obesity. Metformin has been used to treat diabetes since the 1960s and is now the most prescribed drug for the disease, with more than 120 million patients using it worldwide. Metformin's mechanism of action involves activating AMPK.[46,47]

AMPK may also play a role in cancer, which could explain the finding that diabetes patients treated with metformin have a 30% lower incidence of cancer than those on other medications.[48] Activated AMPK in tumour cells appears to inhibit cell growth and the cell cycle and clinical trials on the use of metformin to treat cancers, including breast cancer, are underway. Although AMPK-activating drugs such as metformin could play an important role in both diabetes and cancer treatment, Professor Hardie emphasised that the best way of activating AMPK is through exercise rather than drugs.

Monitoring disease progress

Management strategies would be significantly improved by more effective methods of monitoring disease progress and Dr Kev Dhaliwal, Clinical Lecturer in Respiratory Medicine at the University of Edinburgh told the meeting that imaging techniques can play a central role here. The first imaging techniques (e.g. x-ray) provided anatomical information.

41 Ogden CL, *et al.* (2006). *Prevalence of overweight and obesity in the United States, 1999-2004.* Journal of the American Medical Association **295**, 1549-1555.
42 Flegal KM, *et al.* (2002). *Prevalence and trends in obesity among US adults, 1999-2000.* Journal of the American Medical Association **288**, 1723-1727.
43 Westerterp KR & Speakman JR (2008). *Physical activity energy expenditure has not declined since the 1980s and matches energy expenditures of wild mammals.* International Journal of Obesity **32**, 1256-1263.
44 Westerterp KR & Speakman JR (2008). *Physical activity energy expenditure has not declined since the 1980s and matches energy expenditures of wild mammals.* International Journal of Obesity **32**, 1256-1263.
45 Winder WW & Hardie DG (1996). *Inactivation of acetyl-CoA carboxylase and activation of AMP-activated protein kinase in muscle during exercise.* American Journal of Physiology: Endocrinology and Metabolism **270**, E299-E304.
46 Zhou G, *et al.* (2001). *Role of AMP-activated protein kinase in mechanism of metformin action.* Journal of Clinical Investigation **108**, 1167-1174.
47 Hawley SA, *et al.* (2010). *Use of cells expressing gamma subunit variants to identify diverse mechanisms of AMPK activation.* Cell Metabolism **11**, 554-565.
48 Evans JMM, *et al.* (2005). *Metformin and reduced risk of cancer in diabetic patients.* British Medical Journal **330**, 1304-1205.

Functional imaging methods have since been introduced (e.g. that measure blood flow), but in the future, developments in molecular imaging offer the potential to observe, define and track the way molecules function and change inside the body. Instead of collecting small amounts of data from images taken at particular time points, molecular imaging could make it possible to study disease processes in real time, *in vivo in situ.*

A particularly valuable imaging technique has been positron emission tomography (PET) scanning. The technique is versatile and potentially highly applicable because the technology can be used to trace the biological pathway of virtually any compound in the human body, provided it can be radio-labelled. However, it is also expensive and thus not likely to be widely available in the near future, and there are additional concerns about exposing patients to radiation. Alternative, smaller scale techniques are therefore preferable. Monitoring diseases would be enhanced in the future by developing hand-held scanners that could be used at the bedside to observe processes inside the body. Monitoring patients at the bedside means that real time data can more easily be collected over longer time periods or at particular times of day, as well as offering more flexible medical care and monitoring to patients who are not in hospital. For example, standard optical imaging devices can detect particular types of radiation, e.g. Cerenkov radiation, from radioisotopes and these devices could be developed into hand-held scanners. Fibre optic probes have already been developed that can penetrate deep into tissues and imaging probes that can be ingested or placed in the body could generate images of many potential locations.

Such techniques are opening up new possibilities in monitoring and managing diabetes and obesity, such as imaging fat metabolism, pancreatic inflammation and screening drugs for effects at the target tissue or for other side effects elsewhere. Research, commercial involvement and investment in infrastructure over the next decade will help to capitalise on technological developments and bring benefits to patients. In the future, bedside or near patient imaging could improve diagnostics and drug delivery, guide intervention, help to identify new therapeutic targets and enhance drug trials.

Emerging therapeutics for type 2 diabetes

Dieting and physical activity is the primary therapy for obesity and diabetes. Maintaining consistent and safe blood sugar levels (glycemic control) is very important in managing type 2 diabetes, thus these patients need to pay particular attention to their diet. However, patient compliance with this healthy lifestyle advice is often poor, meaning that effective drugs are often an important part of managing the disease. Tight control of the condition, in particular of blood glucose levels, is an essential function of any antidiabetic medicine. Adequate glycemic control not only improves the patient's diabetes, but also reduces their risk of cardiovascular events including heart attack.

Beta cells are central to the pathology of type 2 diabetes. Current drugs include metformin, which decreases glucose synthesis and increases peripheral utilisation of glucose, and thiazolidinediones (e.g. rosiglitazone), which reduce peripheral insulin resistance. Metformin offers good glycemic control, but does not improve insulin sensitivity sufficiently to decrease the demand for insulin secretion from pancreatic beta cells. Consequently, these cells decline in function, meaning that the drug's effects are not durable. Thiazolidinediones are longer lasting than metformin, but they have a number of side effects and their effectiveness ultimately still falls. Thus, patients must currently alter their medication when a drug becomes ineffective. Maintaining

beta cell function by achieving tight glycemic control is the aim of novel drugs for type 2 diabetes and Dr Tim Rolph, Vice President and Chief Scientific Officer of the Cardiovascular, Metabolic and Endocrine Disease Research Unit at Pfizer, told the meeting that he believes that we can look forward to the introduction of drugs with novel mechanisms to the market in the near to mid term.

Two of the key targets for new drug design are a) to more effectively reverse peripheral insulin resistance and b) to increase non-insulin dependent glucose disposal. Both of these mechanisms which will reduce demand on beta cells to secrete insulin and lower blood glucose and lipids, all of which accelerate the decline in beta cell function. There are some promising molecules for increasing glucose disposal in the pipeline:

- *Sodium-glucose co-transporter 2 (SGLT2) inhibitors.* SGLT2 in the kidneys reabsorbs filtered glucose into the bloodstream. Inhibiting this transporter therefore increases the disposal of glucose in the urine, lowering blood glucose via a non-insulin dependent mechanism. This allows for tight glycemic control that can be maintained using the same drug. These drugs also promote weight loss and appear to have a modest effect on reducing blood pressure. SGLT2 inhibitors could potentially be used in combination with other drugs, possibly as a second line therapy for obese diabetics once metformin has ceased to be effective.
- *Hepato-selective glucokinase (GK) activators.* GK regulates hepatic glucose uptake and production. Its activity is reduced in diabetics, leading to less uptake and more production of glucose. Thus activating GK in diabetic patients offers an alternative, non-insulin dependent mechanism for glucose disposal, which could potentially be used in combination with metformin or as a first line therapy in patients intolerant to metformin.

5 Translation and the role of informatics

Translating research discoveries into clinical practice and implementing new products or approaches is an important component of medical research, but achieving effective translation remains a challenge. This is compounded by changes facing the pharmaceutical industry, where fewer drugs are reaching the market, meaning that companies face greater demand to improve the return on their investments. Professor Andrew Morris FRSE FMedSci, Professor of Medicine at the University of Dundee told the meeting that informatics (specificall y, informatics tools that improve the acquisition, storage, retrieval and use of information for health and medicine purposes) will be a key component of improving translation. Until now, informatics has played a minor role but Professor Morris believes it has the potential to act as a catalyst for translation. In 2007, the UK's Council for Science and Technology judged e-health to be in the top six priorities for development, *'in which a larger-scale focus by Government could accelerate the real returns for the UK within a five-year timeframe',* in terms of commercial or social benefits.[49] The report warned that investing in e-health does not guarantee substantial rewards, but Professor Morris believes that Scotland's use of informatics in diabetes management, as a vehicle to support world class clinical care and clinical trials, provides a good example of the potential of informatics.

Improving patient care

Scotland has adopted a clinical information system for diabetes known as the Scottish Care Information: Diabetes Collaboration (SCI-DC), which records all patient data on a single register that is available to healthcare providers nationwide. The database now has 220,000 registered type 2 diabetes patients: 95% of all people with diabetes in Scotland.[50] Development began in 2002 following the success of the Lanarkshire Diabetes System (LDS) and the Diabetes Audit and Research in Tayside Scotland (DARTS) systems. The aim was to underpin well-managed and integrated diabetes care with effective information technology systems. It is now being used to monitor the quality of care provided across Scotland by listing patient histories and enabling more effective health tracking, screening, and recruitment to research and clinical trials. Evidence from the annual Scottish Diabetes Survey indicates that since the introduction of SCI-DC, the number of patients achieving the recommended targets for glucose control, blood pressure and cholesterol levels is improving year on year, although improvements can still be made, particularly in helping patients to reach the targets on all risk factors.[51]

Diabetic retinopathy, which results from changes in the blood vessels of the retina, is a danger of diabetes and is common among diabetes patients, particularly those who have lived with the condition for a long time. With time, this background retinopathy may become more severe and develop into maculopathy, in which a patient's central vision gradually worsens. Since the introduction of SCI-DC, the Tayside region of Scotland has seen a 43% reduction in the number of type 2 diabetes patients being treated for maculopathy, despite an increase in the prevalence of diabetes and a greater effort to identify affected individuals through screening. The success has been in slowing disease progress through earlier detection of type 2 diabetes and improved risk factor control.[52] Consequently, diabetes is no longer the most common cause of blindness in people of middle age in Scotland. Improved

49 Council for Science and Technology (2007). *Strategic decision making for technology policy.* http://www.cst.gov.uk/reports/files/strategic-decision-making.pdf
50 For more information on SCI-DC see http://www.scotland.gov.uk/Publications/2003/01/16290/17641
51 Data from the annual Scottish Diabetes Survey: http://www.diabetesinscotland.org.uk/Publications.aspx?catId=3
52 Vallance JH, *et al.* (2008). *Diabetic retinopathy: more patients, less laser. A longitudinal population-based study in Tayside, Scotland.* Diabetes Care **31**, 1126-1131.

patient care and monitoring following the introduction of the database has also been accompanied by a 40% reduction in the incidence of major lower extremity amputation in the Tayside region, of which diabetes was previously one of the most common causes.[53]

Improving research and clinical trials

Such improvements are encouraging, but the focus must not only be on type 2 diabetes and obesity: similar risks exist for those with type 1 diabetes. Patients with type 1 diabetes experience an elevated risk of cardiovascular disease and Professor Morris warned that there is a need to address the current under-use of existing therapies in patients with the condition.[54] For example, although the risk of a cardiovascular event is seven times higher for women with type 1 diabetes, only 16% of these individuals are currently prescribed statins.[55]

The Scottish Diabetes Research Network (SDRN), established in 2006, uses SCI-DC data in research and clinical trials.[56] Epidemiological studies are carried out using nationwide anonymised data. For example, it has helped to show lower cancer rates in diabetic patients treated with the type 2 diabetes drug, metformin.[57,58,59]

Enhanced recruitment to clinical trials is also possible with the database. Every patient who registers on the SCI-DC system can give their consent to take part in clinical trials. This has resulted in an increase in the number of both academic and clinical trials in Scotland, for example by 40% between 2007 and 2009, and the country is now the top recruiter in four global studies.[60] The regulations around the licensing of antidiabetic drugs have become more stringent since research found that the type 2 diabetes drug rosiglitazone may be associated with an increased risk of heart attack.[61] This incident led to an alteration in the US Food and Drug Administration (FDA) guidelines, which now advise that *'to establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk'.*[62] Professor Morris advised that this will likely require clinical trials involving up to 5000 patients to establish cardiovascular safety of any new diabetes drug and that routinely collected patient information in databases such as SCI-DC could be used to run pharmacovigilance studies that assess associations between drug exposure and adverse outcomes. SCI-DC has already been used to analyse prescribing data and cancer rates for over 200,000 patients on insulin glargine over a four year period. The study concluded that the drug did not increase cancer risk.[63] These kinds of informatics systems can also play an important role in increasing our understanding of the genetics of diabetes and in exploring how pharmacogenetics may help to more effectively target drugs to patients in the future.[64]

53 Schofield CJ, *et al.* (2009). *Decreasing amputation rates in patients with diabetes: a population-based study.* Diabetic Medicine **26**, 773-777.
54 Donnelly LA, *et al.* (2008). *Long-term adherence to statin treatment in diabetes.* Diabetic Medicine **25**, 850-855.
55 SDRN Epidemiology group (in preparation).
56 For more information on SDRN see http://www.sdrn.org.uk/
57 Evans JMM, *et al.* (2005). *Metformin and reduced risk of cancer in diabetic patients.* British Medical Journal **330**, 1304-1205.
58 Huang X, *et al.* (2008). *Important role of the LKB1-AMPK pathway in suppressing tumorigenesis in PTEN-deficient mice.* Biochemical Journal **412**, 211-221.
59 Libby G, *et al.* (2009). *New users of metformin are at low risk of incident cancer.* Diabetes Care **32**, 1620-1625.
60 Scottish Diabetes Research Network (2009). *Scottish diabetes research portfolio: November 2008-October 2009.* http://www.sdrn.org.uk/files/Portfolio%20Report%20-%20SDRN%20-%202009.pdf
61 Nissen SE & Wolski K (2007). *Effect of Rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes*. New England Journal of Medicine **356**, 2457-2471.
62 US Food and Drug Administration Center for Drug Evaluation and Research (2008). *Guidance for industry: diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes.* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf
63 Colhoun HM (2009). *Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group.* Diabetologia **52**, 1755-1765.
64 Zhou K, *et al.* (2010). *Loss-of-function CYP2C9 variants improve therapeutic response to sulfonylureas in type 2 diabetes: A Go-DARTS Study.* Clinical Pharmacology & Therapeutics **87**, 52–56.

The large number of patients in the NHS and initiatives such as biobanking mean that the UK is well placed to perform this kind of research. Since the symposium, the UK government has expressed a desire to improve the availability of anonymised data for research and to provide greater patient access to studies, in its 2010 Health White Paper.[65] There are complex challenges inherent in the kind of informatics system described into the NHS, and to making it work. However, Professor Morris argued that the NHS is going to have to increase its productivity in the tough new economic climate and that informatics can make a major contribution to driving forward improvements in patient care and greater efficiency. Further, such a system is not only applicable to diabetes, but could be implemented in other major conditions such as cancer and stroke to create a national research platform for these diseases.

Effective translation of research to applications and patient benefits is essential to optimise the care of obese and diabetic patients. Using informatics to improve patient monitoring, data availability and recruitment into trials will not only improve the management of complications such as diabetic retinopathy, but also provide a useful mechanism for assessing the quality and safety of newly introduced drugs and other management strategies.

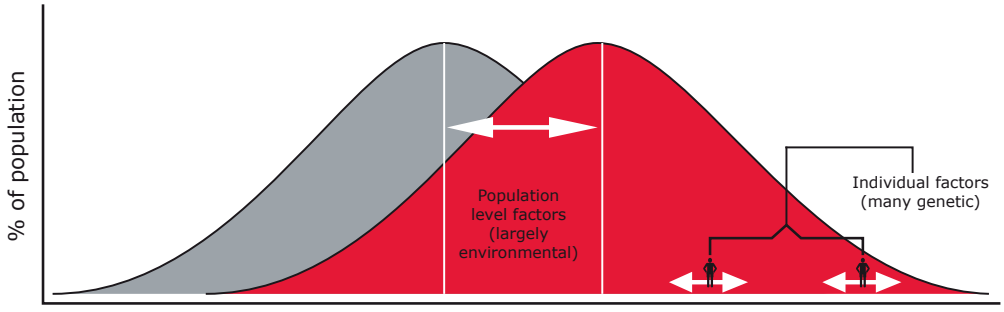
65 Department of Health (2010). *Equity and excellence: Liberating the NHS.* http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_117794.pdf

6 Policy interventions and the future

Implementing effective policy interventions

A major part of managing the obesity epidemic is the search for effective policy interventions. The epidemic has progressed quickly, but will not be quick or easy to reverse and this is complicated by its association with other diseases. The relationship between obesity levels and the associated risk of clinical consequences can be represented on a bell curve. The obesity epidemic has caused the entire bell curve to shift to the right, meaning that individuals at the same point along the curve now are now at a higher risk of clinical consequences (Figure 1). Research by Rose highlighted the importance of using population-based measures to control disease incidence.[66] Before the causes of particular diseases and their rising frequency are identified, management strategies can only target those individuals who are clearly at a particularly high risk of disease. However, if the causes of a disease are known, then management strategies can be designed to target these factors at a population level, rather than only in individuals (Figure 1). For obesity and its associated clinical conditions, the rise in disease incidence in individuals with a low risk, relative to the whole population, strengthens the need to target the wider population. A number of environmental causes of obesity have been identified, allowing us to seek to tackle the rising prevalence of obesity with population-based measures. Thus overall, interventions should influence both the wider population (the macro-environment, which determines overall obesity prevalence) and the individual (the micro-environment, which determines whether or not individuals are obese), and should do so across multiple types of environment: physical, economic, political and socio-cultural.[67]

Figure 1 The implications of a right-shift of the risk factor bell curve [68]



66 Rose G (1985). *Sick individuals and sick populations.* International Journal of Epidemiology **14**, 32- 38.
67 Egger G & Swinburn B (1997). *An 'ecological' approach to the obesity pandemic.* British Medical Journal **315** 477-480.
68 Rose G (1985). Sick Individuals and Sick Populations. International Journal of Epidemiology **14**, 32- 38.

The UK Government Office for Science's 2007 Foresight report, 'Tackling Obesities: Future Choices', recognised the complex nature of efforts to tackle the obesity epidemic and concluded that reducing obesity levels requires *'whole societal change with cross governmental action and long term commitment.'* [69] One of the difficulties in identifying the most effective interventions is the lack of good quality evidence applicable to the UK. There are many observational studies from the US and Australia, for example, but it cannot be assumed that the findings of this research can simply be applied to the UK because of differences in culture and environment. The Academy of Medical Sciences has previously highlighted the importance of ensuring that policy interventions are well evidenced and supported by rigorous piloting.[70] Professor John Frank, Professor of Public Health Research and Policy at the University of Edinburgh, reported to the meeting the findings of a review of policy interventions, summarised in the remainder of this chapter, which was intended to identify promising strategies that could help to inform Scottish public health policy.[71]

The physical environment

Physical activity can be separated into recreational or 'active travel' (e.g. commuting). There is evidence that features of the environment in which people live can influence their habits and their health. For example, a study in Portland, Oregon showed that individuals in 'high-walkability' neighbourhoods (i.e. those in which walking was easier or more pleasant), who took advantage of this by increasing their levels of physical activity, experienced a mean weight loss of 1.2kg and a decrease in waist circumference of 1.57cm over a one year period.[72] However, it is hard to extrapolate this kind of research to a UK context given the differences in residential environments between the two countries and the fact that physical activity levels in different countries can vary considerably. In fact, recent research findings in Scotland would tend to suggest that environmental factors are of relatively minor importance with regard to variation in physical activity when compared to individual/personal factors (e.g. age, car access).[73] One significant exception was easy access to local amenities, which was associated with increased physical activity levels. A very limited range of variability in a number of relevant behaviours in Scotland, most notably in rates of active travel, also makes it difficult to measure any impact of the external built environment. More insightful comparisons however can be made with some Northern European neighbours with similar climates and comparable resources. The Netherlands and Denmark for instance have high rates of cycling, a trend which appears to relate to road safety. Car use in the Netherlands rose rapidly during the 1950s and 1960s, as did the number of cyclist fatalities. This led to a sharp decline in the number of cyclists on the roads. However, since the 1970s, there has been considerable investment in the Netherlands into cycling infrastructure and reducing car use, which has been accompanied by both a reduction in fatalities and an increase in cycling.[74]

Within the micro-environment, studies, including one in a Glasgow underground station, suggest that 'point of decision prompts', such as motivational signs placed in the vicinity of stairwells and escalators to encourage individuals to use nearby stairs, can increase the number of people choosing the more active option.[75] The initial marked increase diminished after a few weeks in Glasgow, but settled at a higher level than before the signs had been introduced. An international review from the US Centers for Disease Control and Prevention concluded that overall, *'sufficient evidence shows that point-of-decision prompts are*

69 Foresight (2007). *Tackling obesities: future choices. summary of key messages.* http://www.foresight.gov.uk/Obesity/20.pdf
70 Academy of Medical Sciences (2007). *Identifying the environmental causes of disease.* http://www.acmedsci.ac.uk/p48prid50.html
71 Mooney J, *et al.* (2010). *Environmental scan of potential policy interventions to tackle obesogenic aspects of the adult environment.* Edinburgh: Scottish Collaboration for Public Health Research and Policy. (In preparation, Sept. 2010: www.scphrp.ac.uk).
72 Li F, *et al.* (2009). *Built environment and 1-year change in weight and waist circumference in middleaAged and older adults.* American Journal of Epidemiology **169**, 401-408.
73 Ogilvie D, *et al.* (2008). *Personal and environmental correlates of active travel and physical activity in a deprived urban population.* International Journal of Behavioral Nutrition and Physical Activity **5**, 43.
74 Pucher J & Buehler R (2008). *Making cycling irresistible: lessons from The Netherlands, Denmark and Germany.* Transport Reviews **28**, 495-528.
75 Blamey, *et al.* (1995). *Health promotion by encouraged use of stairs.* British Medical Journal **311**, 289-290.

effective in increasing levels of physical activity, as measured by an increase in the percentage of people choosing to take the stairs rather than an elevator or escalator'. It also reported that tailoring prompts by specifying particular health benefits or targeting them to specific populations can increase the effectiveness of the intervention.[76]

The physical environment also includes nutritional aspects and within the macro-environment, access to healthy or unhealthy foods can exert an impact. The Portland study outlined above also found that individuals in neighbourhoods with a high density of fast food outlets, who visited these outlets on a regular basis, experienced a mean weight gain of 1.4kg and an increase in waist circumference of 2.04cm over a one year period.[77] At the local level, the environment within a restaurant might also influence our choice of food. Fast food outlets, for example, more often encourage large portions and overeating, but are also more likely to provide nutrition information and to highlight healthy menu options than sit-down restaurants.[78]

The economic environment

Within the macro-environment, taxation is a common method of altering the economic environment. The rationale for introducing taxes on soft drinks, snack foods and fast foods is manifold.[79] Firstly, there is evidence that increased consumption of these products is linked to the obesity epidemic and its implications, including type 2 diabetes.[80] For example, one large follow-up study in the US found that, over a four year period, women who increased their soft drink consumption from one or fewer drinks a week to one or more experienced greater weight gain and an increased risk of type 2 diabetes.[81] Evidence indicates a relationship between obesity levels and implementation of such taxes,[82] but taxing high calorie food and drink will only be beneficial if it can be established that increasing price helps to reduce consumption. There is evidence that increasing the price of sugary drinks by 10% reduces consumption by 7.8%.[83] Further, public support for such a move has steadily increased over recent years, especially if the extra revenue gained is channelled back into obesity prevention.[84] However, Professor Frank warned that any such move will be strongly resisted by the food and drink industry, meaning that any intervention will require a strong evidence base and detailed preparation. Further motivation for taxing certain foods and drinks comes from the perception that the level of information available to consumers and producers is asymmetric (e.g. because advertising has distorted consumers' understanding of a healthy diet).[85] The current cost of obesity to society and the projected increases based on current trends also make investment in prevention an economic imperative.

76 Kahn EB, *et al.* (2002). *The effectiveness of interventions to increase physical activity: A systematic review.* American Journal of Preventive Medicine **22(4S)** 73-107.
77 Li F, *et al.* (2009). *Built environment and 1-year change in weight and waist circumference in middle-aged and older adults.* American Journal of Epidemiology **169**, 401-408.
78 Saelens BE, *et al.* (2007). *Nutrition environment measures study in restaurants (NEMS-R). Development and evaluation.* American Journal of Preventive Medicine **32**, 273-281.
79 Kim D & Kawachi I (2006). *Food taxation and pricing strategies to 'thin out' the obesity epidemic.* American journal of Preventative Medicine **30**, 430-437.
80 Vartanian LR, *et al.* (2007). *Effects of soft drink consumption on nutrition and health: a systematic review and meta-analysis.* American Journal of Public Health **97**, 667-675.
81 Schulze MB, *et al.* (2004). *Sugar-sweetened beverages, Weight gain, and incidence of type 2 diabetes in young and middle-aged women.* Journal of the American Medical Association **292**, 927-934.
82 Kim D & Kawachi I (2006). *Food taxation and pricing strategies to 'thin out' the obesity epidemic.* American journal of Preventative Medicine **30**, 430-437.
83 Brownell KD & Frieden TR (2009). *Ounces of prevention: the public policy case for taxes on sugared beverages.* New Engl& Journal of Medicine **360**, 1805-1808.
84 Brownell KD, *et al.* (2009). *The public health and economic benefits of taxing sugar-sweetened beverages.* New England Journal of Medicine **361**, 1599-1605.
85 Kim D & Kawachi I (2006). *Food taxation and pricing strategies to 'thin out' the obesity epidemic.* American journal of Preventative Medicine **30**, 430-437.

The political environment

The majority of control measures within the political environment are based on introducing an obligation to provide information, rather than attempts to restrict specific food items, e.g. through trade barriers, which can be hard to establish. In the UK, food labelling has received a lot of attention and is governed by the Food Labelling Regulations (1996). The UK Food Standards Agency (FSA) attempted to improve the consistency of labelling and the ease of information access for consumers through a 'traffic-light' food labelling system, which makes the relative contents of particular constituents of food, e.g. salt and saturated fat, readily available to the consumer. The initiative was met with uneven industry support, but evidence suggests that this could be a useful strategy. Shoppers are five times more likely to identify healthier foods when this kind of labelling is in use and it is particularly helpful to individuals in lower socioeconomic groups.[86]

The socio-cultural environment

At the macro scale, the media can play a significant role in consumer behaviour, including influencing diet and physical activity levels. Concern over the advertising of less healthy foods to children led the UK's independent regulator of communications industries, Ofcom, to prohibit the promotion on television of HFSS foods to children from 2007. This led to an estimated 34% fall in children's exposure to HFSS advertising in 2007/8 compared to 2005.[87]

Media campaigns can also attempt to promote particular behaviours. These have had mixed results, but there are some successful examples. For example, the US Centers for Disease Control and Prevention instigated a multimedia campaign aimed at children that used commercial marketing methods to promote physical activity. The campaign improved children's attitudes towards, and levels of, physical activity, with children who were exposed to the campaign at least once week choosing to take part in 4 free-time activity sessions per week, compared to those exposed less than once a week, who took part in 2.8 sessions.[88]

Choosing an intervention

Measurable population impacts are feasible with the kinds of policy interventions described above. As highlighted in the Foresight report, 'Tackling Obesities: Future Choices', the most effective approach is to aim interventions at several diverse drivers of obesity and diabetes. Box 2 outlines the ways in which different interventions might be compared. The most desirable policy interventions will have a high certainty of effectiveness on a large proportion of the population, but other effective interventions may have a high certainty in a small number of people, or low certainty in a high proportion of the population.[89] Professor Frank believes that ranking interventions in this way will aid decisions and that all stakeholders should be involved in a discussion about which ones are acceptable, affordable and sustainable.

86 Kelly B, *et al.* (2009). *Consumer testing of the acceptability and effectiveness of front-of-pack food labelling systems for the Australian grocery market.* Health Promotion International **24**, 120-129.
87 Ofcom (2008). Changes in the nature and balance of television food advertising to children: A review of HFSS advertising restrictions. http://stakeholders.ofcom.org.uk/binaries/research/tv-research/hfssdec08.pdf
88 Huhman ME, *et al.* (2007). *Evaluation of a national physical activity intervention for children.* American Journal of Preventive Medicine **32**, 38-43.
89 Swinburn B, *et al.* (2005). *Obesity prevention: a proposed framework for translating evidence into action.* Obesity reviews **6**, 23-33.

Box 2 Comparing interventions

Swinburn et al. (2005) designed a portfolio matrix for categorising the promise of potential interventions, based on the potential population impact and the certainty of effectiveness of each intervention.[90] Potential population impact incorporates efficacy (impact under ideal conditions), reach, and uptake; various different measurements can be used, such as effectiveness or cost-effectiveness. Certainty of effectiveness is based on the *'quality of the evidence, the strength of the programme logic, and the sensitivity and uncertainty parameters in the modelling of the population impact.'* By using such a matrix, interventions can be judged on their promise and decisions made about whether the idea represents a viable policy option.

		Potential population impact		
		LOW	MODERATE	HIGH
Certainty of effectiveness	Quite High	**Moderate Promise**	**High promise**	**Most promise**
	Medium	**Low promise**	**Moderate Promise**	**High promise**
	Quite Low	**Least promise**	**Low promise**	**Moderate Promise**

Professor Frank and colleagues have considered what a portfolio matrix for categorising interventions for obesity within the economic and political environment might look like, presented below. The 'grid-allocations' for the sample interventions shown are not intended to be definitive, as the evidence base around obesity prevention continues to evolve.

		Potential population impact		
		LOW	MODERATE	HIGH
Certainty of effectiveness	Quite High	**Local price incentives**	**Trade restrictions; Tariffs**	**Sugared beverage tax**
	Medium	**Financial incentives for physical activity; Exercise referral**	**Food labeling; Workplace rules**	**Agricultural frameworks**
	Quite Low	**Purely information based campaigns**	**Workplace rules and regulations**	**Subsidised public transport**

Developing effective treatments for individuals diagnosed with obesity or diabetes is key, but national strategies should also be implemented that seek to prevent individuals from developing these conditions to begin with. Government policy interventions can be made within the physical, economic, political and socio-cultural environments, and can be aimed at entire populations, local community areas or individuals. Assessing which particular mix of interventions would offer the greatest certainty of effectiveness and reach the largest proportion of people will help to establish which offer the most potential and warrant the attention of policy makers.

90 Swinburn B, *et al*. (2005). *Obesity prevention: a proposed framework for translating evidence into action.* Obesity reviews **6** 23-33.

Annex I: Symposium programme

Welcome and introduction

Professor Jonathan Seckl FRSE FMedSci, Moncrieff-Arnott Professor of Molecular Medicine and Director of Research, College of Medicine and Veterinary Medicine, University of Edinburgh

Plenary I **Human metabolic disease: lessons from experiments of nature**

Professor Stephen O'Rahilly FRS FMedSci

Professor of Clinical Biochemistry and Medicine, University of Cambridge

Session I **From Populations to Genes**

Chair: Professor Jonathan Seckl FRSE FMedSci

Trends in diabetes and obesity: implications for public health

Professor Nishi Chaturvedi, Professor of Clinical Epidemiology, Imperial College London

Genetics of type 2 diabetes: are we getting any closer?

Professor Leif Groop, Professor of Endocrinology, Lund University, Sweden

Session II **Molecules to Evolution**

Chair: Professor John Connell FRSE FMedSci

Why exercise is good for you: activating AMPK via exercise and via drugs

Professor Grahame Hardie FRS FRSE FMedSci, Professor of Cellular Signalling and Head of Division, College of Life Sciences, University of Dundee

Obesity and exercise: where do we go now?

Professor John Speakman FRSE FMedSci

Director, Institute of Biological and Environmental Sciences, University of Aberdeen

Session III **Mechanisms**

Chair: Professor Stephen O'Rahilly FRS FMedSci

Metabolism: future horizons

Professor Brian Walker, Professor of Endocrinology and Head, Centre for Cardiovascular Science, University of Edinburgh

Diabetes and obesity: a role for the epigenome?

Dr Amanda Drake, MRC Clinician Scientist, University of Edinburgh

Session IV **Technologies and Therapies**

Chair: Professor Irene Leigh OBE FRSE FMedSci

Opening the optical toolbox to see inflammation

Dr Kev Dhaliwal, Clinical Lecturer in Respiratory Medicine, University of Edinburgh

Emerging therapeutics for type 2 diabetes

Dr Tim Rolph, Vice President and Chief Scientific Officer, Cardiovascular, Metabolic & Endocrine Disease Research Unit, Pfizer

Environmental Policy and Programme Interventions for Obesity Control in Adults

Professor John Frank, Professor of Public Health Research and Policy, University of Edinburgh and Director, Scottish Collaboration for Public Health Research and Policy

Plenary II **Opportunities for translation in an epidemic of diabetes**

Professor Andrew Morris FRSE FMedSci, Professor of Medicine of Diabetic Medicine and Director, Biomedical Research Institute, University of Dundee

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Head, College of Medicine, Dentistry and Nursing, University of Dundee

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Ms Nahid Aslam
Mrs Sandra Bacon, University of Dundee
Mrs Jane Banks, Cels Business Services Ltd
Mr Lawrence Barton
Mrs Pam Baxter
Dr Craig Beall, University of Dundee
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Dr Giovanna Bermano, Robert Gordon University
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Mr Robert Brennan, University College Cork
Mr Kevin Byrne, University College Cork
Mrs Mary Cameron
Dr Karen Chapman, Reader, University of Edinburgh
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Professor Francine Cheater, Glasgow Caledonian University
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